Int J Adv Life Sci Res. Volume 7(2) 17-40
https://doi.org/10.31632/ijalsr.2024.v07i02.003

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Review Article

Chemotherapy Resistance in Cancer: Mechanism and Roadmap to Evade Exploring Apoptosis

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Abstract

Chemotherapy resistance indicates the non-responsiveness of cancer cells to the cytotoxic and inhibitory effects of chemo drugs attributed to either intrinsic or extrinsic resistance mechanisms in cancer cells. Studies so far indicate that drug resistance can be triggered by a multitude of factors such as the over-expression of drug efflux pumps, DNA repair mechanisms, modifications in the drug target such as point mutations and gene amplification, over-expression of anti-apoptotic proteins and down-regulation of pro-apoptotic signals, presence of cancer stem cells and immune-suppressive cells, excessive cytokine production, tumor heterogeneity, epigenetic changes, activation of alternate pro-survival signaling pathways, etc. Both host and tumor-related factors can contribute to therapy resistance. Currently, chemo resistance poses the foremost setback in the successful treatment of cancer, and it exerts significant stress on the available medical resources. Besides the costs associated with the treatment, patients go through severe emotional and physical trauma. Chemotherapy resistance is also a major contributor to accelerated metastasis and invasion. Dose-escalation is not always practical since the associated side effects may increase apart from increasing the treatment costs. Several studies are ongoing to address this issue productively, such as therapeutic molecules designed to restore the apoptotic machinery. Site-specific delivery of pro-apoptotic agents such as small molecules, antibodies, peptides, etc. targeting the apoptosis pathway is also thoroughly studied. Moreover, the efficacy of combination strategies is also a topic of research.

Keywords:-*Apoptosis, Cancer, Chemotherapy, Drug resistance, Mechanisms*

Introduction

Despite the advances so far, cancer remains a global health priority as indicated by the estimated 30 million newly diagnosed cancer cases by 2040. The highest incidence is predicted to occur in low- and middle-income countries(*World Cancer Day 2023*, n.d.). Cancer starts with the abnormal proliferation of cells, which acquire several molecular features over time and ultimately spread to other organs of the body (metastasis). It is the second most common cause of mortality globally after cardiovascular diseases. Cancer caused approximately 10 million deaths globally in 2020, and the number of cancer-associated deaths is increasing at an alarmingly high rate(Sung *et al.*, 2021). Although several modalities for managing cancer have been discovered so far, chemotherapy has remained the backbone of cancer treatment for more than 70 years. Chemotherapy is the use of certain drugs to inhibit the proliferation of cancer cells so that the invasion and metastasis can be prevented(Delou *et al*., 2019). Conventional chemotherapeutic agents interfere with the synthesis of nucleic acids and proteins(Berdis, 2017).Certain other drugs inhibit the formation of mitotic spindles(Solon *et al*., 2022). So far, United States Food and Drug Administration (US-FDA) has approved more than 100 types of chemotherapeutic drugs including cytotoxic agents and biologically targeted small molecule inhibitors(de la Torre & Albericio, 2023; Liu *et al*., 2022; Sun *et al.*, 2017).

Received on :20th January 2024; Revised version received on :1st March 2024; Accepted: 31st March 2024

Resistance to chemotherapy drugs poses a serious and complex problem in the therapy of cancer. Apart from poor response to treatment, it is the pivotal cause of disease relapse both in hematological malignancies and solid tumors(D'Alterio *et al*., 2020; Z.-W. Zhang *et al.*, 2023). Cancer drug resistance can generate considerable mental, physical, and financial stress on the patients and medical resources(Papadopoulou *et al.*, 2022). This is a significant global health concern and unless addressed in time, chemo resistance can be highly deleterious. The crisis is more pronounced in low and middle-income countries due to the inaccessibility of quality diagnostic and treatment measures(Walker *et al*., 2021). Gathering the shreds of evidence so far, it is understood cancer cells exhibit chemo resistance via a multitude of mechanisms, which can be generally classified into intrinsic and acquired(Cadamuro*et al., 2017;* Comandatore*et al., 2022;* Hu & Chen*, 2021;* Luo*et al., 2023;* Ozcan*, 2023;* Palamaris*et al., 2021;* Ren & Yu*, 2018;* Tune*et al., 2022;* Wang*et al., 2022;* Yeldag*et al.*, 2018; Zhu *et al.*, 2023).

Among the various mechanisms of chemotherapy resistance studied so far evasion of apoptosis remains a major sought-after topic of research(Campbell & Leung, 2021; Chen *et al.*, 2018; Mohammad *et al*., 2015; Neophytou *et al.*, 2021). Apoptosis is an intricate process that is crucial for the growth and development of any organism. Evasion of apoptosis is a crucial hallmark of cancer cells(Hanahan, 2022). Deregulation of apoptosis can occur at any stage of the apoptotic pathway not only causing oncogenic transformation of the affected cells, but also invasion, metastasis, and therapy resistance(Novikov *et al.,* 2021; Roth *et al*., 2011). The balance between pro- and anti-apoptotic molecules is crucial for maintaining cellular homeostasis(Giacomini *et al*., 2023). However, this balance is considerably perturbed during malignant transformation and deficits in the apoptotic pathway are observed in tumor cells when they exhibit therapy resistance(Shoshan-Barmatz *et al*., 2023). Several studies are ongoing that focus on restoring the apoptotic machinery to circumvent chemotherapy resistance in cancer cells. This review discusses the significance of chemotherapy resistance and the relevance of apoptosis evasion mechanisms in chemo resistance.

Brief epidemiology and severity of drug resistance in cancer

As discussed earlier, the epidemiology of chemotherapy resistance is quite complex. Genetic and epigenetic alterations in proteins such as those associated with apoptosis can cause chemo resistance("Epigenetic Basis of Cancer Drug Resistance," 2020; Lønning & Knappskog, 2013). Genetic changes comprise point mutations, chromosomal relocations and rearrangements, deletions, etc(Hasty &Montagna, 2014). Recent studies indicate that genetic heterogeneity and subsequent chemo resistance can be attributed to the presence of miRNAs, circular RNAs and long non-coding RNAs (Liu *et al.*, 2020; Ren & Yu, 2018; Wang *et al*., 2022). Recent report by Wang *et al* indicates the significance of circular RNAs in gastrointestinal cancer(Wang *et al*., 2022). Li *et al*. have shown that circular RNAs have regulatory roles in the expression of genes by acting as miRNA sponges controlling splicing thus promoting drug resistance(Li *et al*., 2021). A similar mechanism is presumed to be active in the chemo resistance of gastrointestinal cancer.

The up regulation of miR-21 and down regulation of miR-34a have been found to influence evasion of apoptosis in cancer(Buscaglia & Li, 2011; Tao *et al*., 2020). Circular RNAs that act as miRNA sponges regulate the miRNA activity(Li *et al.*, 2021). Long non-coding RNAs can influence gene expression at transcriptional, post-transcriptional, and epigenetic levels and identified as regulators of chemo resistance(Statello *et al*., 2021). Pancreatic ductal adenocarcinoma is one of the aggressive types of cancer with poor prognosis and Ren and Yu reported that miRNAs play crucial roles in the chemo resistance of pancreatic ductal adenocarcinoma(Ren & Yu, 2018). The presence of cancer stem cells can also cause unresponsiveness to therapy, especially in hard-to-treat cancers such as glioblastoma(Lathia *et al*., 2015).Tumor stromal factors(growth factors and cytokines), exosomes, cancer-associated fibroblasts, hypoxia, presence of tumor-associated macrophages, etc. can cause intrinsic drug resistance(Cadamuro *et al*., 2017; Comandatore *et al*., 2022; Ozcan, 2023; Zhao *et al*., 2023). Certain alterations in the drug-binding proteins, alterations in plasma protein binding, lipid metabolism etc. can negatively affect drug binding and activity(Roberts *et al*., 2013; Yang *et al*., 2022). Point mutations can change the conformations of the target protein and this is implicated very severely in drug resistant chronic myeloid leukemia(Patel *et al*., 2017). Similarly, the presence of ABC drug transporters and drug efflux proteins can prevent the intracellular transport and retention of the drug(Emran *et al*., 2022; Engle & Kumar, 2022). Among the several types of ABC transporters, the Multidrug Resistance (MDR) protein P-glycoprotein (P-gp) is one of the most studied proteins that has been found to efflux a wide variety of structurally unrelated drug molecules causing their reduced intracellular concentrations(Nanayakkara *et al*., 2018; Robey *et al*., 2018). Normally the expression of P-gp is observed in the epithelial cells lining the liver, intestine, kidney, blood-brain barrier, etc.(Juvale

et al., 2022). However, its expression is high in certain tumor tissues as well which causes both intrinsic as well as acquired drug resistance(Karthika *et al*., 2022; Nanayakkara *et al*., 2018). Other studied classes of multidrug resistance proteins include Multidrug Resistance-Associated Proteins (MRPs) and Breast Cancer Resistance Protein (BCRP or ABCG2), responsible for efflux of the drugs from the cells(Sjöstedt *et al*., 2017; Sodani *et al*., 2012). Furthermore, alternate signaling mechanisms become activated that resist the cytotoxic effects of chemotherapeutics(Nussinov *et al*., 2017).

Currently, drug resistance in cancer is a critical health issue since it has emerged as a rate-limiting factor influencing the availability of chemotherapeutic drugs. It has been reported that more than 90% of mortality reported among cancer patients receiving conventional chemotherapeutics is due to chemotherapy resistance(Bukowski *et al*., 2020). There is a plethora of studies that throw light on the mechanisms of chemo drug resistance in cancer which are discussed below.

Mechanisms of Drug Resistance in Cancer

Mechanisms of chemotherapy resistance can be broadly categorized into intrinsic and acquired. The difference between the two mechanisms and the factors contributing to the same are discussed below, and briefly depicted in Figure. 1.

Intrinsic drug resistance

Intrinsic drug resistance is the inherent/pre-existing resistance exhibited by cancer cells without prior treatment and negatively affects the treatment response(X. Wang *et al*., 2019). It can be caused by genetic and epigenetic alterations, tumor micro environmental factors, tumor heterogeneity, the presence of cancer stem cells, etc.("Epigenetic Basis of Cancer Drug Resistance," 2020; Hasty & Montagna, 2014; Lathia *et al*., 2015; Marusyk *et al*., 2020; Yeldag *et al*., 2018).

Acquired Drug Resistance

Acquired resistance is the resistance acquired by cancer cells during the treatment, after having an initial response("Mechanisms of Acquired Tumor Drug Resistance," 2019). This occurs primarily due to the activation of alternate signaling mechanisms, point mutations in the drug target that prevent the drug binding, alterations in the tumor microenvironment, over-expression of genes causing multi-drug resistance, epithelial-mesenchymal transition, etc.(Nussinov *et al*., 2017; Palamaris *et al*., 2021; Yeldag *et al*., 2018).

Factors contributing to drug resistance

The factors contributing to drug resistance can be classified into host-associated, tumor-associated, and tumor-host interacting factors as indicated below.

Host-related/systemic factors:

The major host-associated factors influencing chemotherapy resistance are absorption of the drug, its distribution, metabolism, and interactions with other drugs(Alfarouk *et al*., 2015). Under certain circumstances, host-associated factors can influence the pharmacokinetics of the drug causing its failure in reaching the target site at therapeutic concentrations such as follows:

1. Alterations in drug absorption:

(i) Absorption of drugs affected by food intake: Certain components in the food can alter drug absorption and its bioavailability. Some drugs undergo fast absorption in the presence of high-fat diet whereas certain others have delayed absorption. Moreover, food can also influence the stomach pH, which may further influence the absorption of orally administered drugs. Similarly, food components can hinder the activity of enzymes required for drug metabolism thus interfering with the activity of the drug. Some of the studies also show that food can also influence the gastrointestinal retention time of certain drugs(Barboza *et al*., 2018; Segal *et al*., 2014).

(ii) Absorption of drugs affected by drug efflux proteins: The absorption of drugs is significantly influenced by the activity of multidrug drug resistance protein/P-glycoprotein (P-gp) at the site of cellular absorption, the expression of which can also increase with continuous drug administration. P-gp is a drug efflux protein belonging to the family of ATP-binding cassette (ABC) transporter, and its primary function is to efflux toxins from the cells (Lin & Yamazaki, 2003). The activity of P-gp in the small intestine can negatively affect the absorption of anticancer drugs especially orally administered ones(Chan *et al*., 2004).

(iii) The reduction in drug absorption can also occur due to poor drug binding at the target site and also a reduced number of drug transporters(Terada & Hira, 2015).

2. Alterations in drug distribution:

To exhibit desired therapeutic effects, the drug must undergo favorable *in vivo* distribution and reach the target site. Undesirable drug distribution is cited as one of the reasonsfordrug resistance. Drug distribution is in turn influenced by blood flow to the target site, vascular permeability of the tissues, physicochemical characteristics of the drug, plasma protein binding, drug binding interactions in the tissues, drug formulation, etc.(Stylianopoulos *et al*., 2018; Wang *et al*., 2021b).

3. Alterations in drug metabolism:

Undesirable drug metabolism can also cause chemotherapeutic resistance. Many cancer drugs exert their cytotoxic activity via metabolic conversions, while some others lose their cytotoxic potential when converted into their metabolites. Genetic alterations in metabolizing enzymes such as cytochrome P450 can significantly affect the therapeutic potential of chemotherapeutics(Alzahrani & Rajendran, 2020; Bertholee *et al*., 2017). Similarly, drug-drug interactions can also affect the metabolism of individual drugs(Leeuwen *et al*., 2015).

Tumor-related factors:

Apart from the host-associated factors, tumor-associated factors also contribute to chemotherapy resistance, especially acquired resistance as indicated below.

Tumor heterogeneity:

Tumors can be highly heterogenous and complex since they harbor different populations of cells and extracellular matrix components which influence the activity of the drug at the target site(Marusyk *et al*., 2020).Moreover, these cells have various genetic and epigenetic heterogeneity, and significantly contribute to the tumor microenvironment(Guo *et al*., 2019).

Multi-drug resistance (MDR) and alteration of drug retention in cancer cells:

The proteins contributing to multi-drug resistance belong to the family of ABC transporters and are called Multidrug resistance proteins (MRPs). There are 13 types of MRPs, among which MRPI to MRP9 are the major contributors of drug resistance in cancer, which are responsible for pumping out drugs from the cells which in turn cause poor drug retention(Sodani *et al*., 2012). The over expression of these proteins and their enhanced activity via genetic mutations and amplifications can confer resistance to therapy as reported by Rahman *et al.,* 2020.

Cancer stem cells (CSCs):

Studies so far show that CSCs have crucial roles in chemotherapy resistance(Lathia *et al*., 2015; Phi *et al*., 2018). CSCs can remain quiescent for long periods and escape the effects of chemo drugs. Moreover, they also have high levels of efflux protein expression, and DNA repair mechanisms which help them to overcome the damaging effects of chemotherapeutics. It is difficult to target the CSCs by conventional chemotherapeutics because of their high phenotypic plasticity and self-renewal capability(*Characteristics of the Cancer Stem Cell Niche and Therapeutic Strategies | Stem Cell Research & Therapy | Full Text*, n.d.).

Microenvironmental resistance:

Tumor microenvironment can significantly influence the activity of chemotherapy drugs(Yeldag *et al*., 2018). Tumors often have regions of low vascularization and oxygen supply and hence it is difficult for the chemodrugs to reach the interior of tumors and induce ROS-induced cytotoxicity(Matuszewska *et al*., 2021). The acidic tumor microenvironment can also reduce the effectiveness of certain drugs(Bogdanov *et al*., 2022). The cellular and non-cellular components of the extracellular matrix (ECM) such as stromal cells, cancer associated fibroblasts, cancer stem cells, immune suppressive cells, ECM proteins, etc. can impart therapy resistance(Kozlova *et al*., 2020). Collagen in the ECM can affect drug penetration since it can act as a barrier affecting drug diffusion in the tumor. Moreover, it can also trigger various signaling pathways responsible for cell survival and cancer stemness. Similarly, fibronectin in the ECM can interact with integrins, and enhance the adhesive properties of the cancer cells(Henke *et al*., 2020). CAFs have several roles in cancer progression and therapy resistance. They promote Epithelial-Mesenchymal Transition (EMT), secrete several growth factors, cytokines, etc. responsible for chemoresistance. Moreover, they also over-express drug efflux proteins on the cell surface which causes poor drug retention in the tumor(Joshi *et al*., 2021).

Similarly, immune suppressive cells such as MDSCs and Tregs inhibit the activity of cytotoxic immune cells (T cells and NK cells) and initiate survival signaling pathways via interleukins and TGF-β. MDSCs have been shown to enhance invasive properties of tumors by ECM remodeling primarily by secretion of matrix metalloproteinase (Tie *et al*., 2022).

Role of ATP and glucose metabolism in chemoresistance:

Apart from being a crucial promoter of cell survival and proliferation, ATP has a critical role to play in the activity of efflux pumps. Moreover, DNA repair machinery also heavily relies on ATP supply(Pote & Gacche, 2023). Extracellular ATP has been shown to induce chemoresistance in breast cancer as reported by Yang*et al*.(2022a). Cancer cells also exhibit altered glucose metabolism which has been found as a promoter of cancer drug resistance. The metabolic adaptation of cancer cells wherein they rely on Warburg effect or aerobic glycolysis for energy production has been shown to play a major role in chemoresistance. The metabolic intermediates provided via aerobic glycolysis pathway fuel the proliferation of cancer cells and this effect is more pronounced in drug resistant cancer cells(Icard *et al*., 2018). The Warburg effect is in turn responsible for the acidic pH of the tumor because of the excess secretion of lactate which prevents the activity of certain drugs(de la Cruz-López *et al*., 2019). Altered glucose metabolism also triggers pro-survival signaling cascades such as PI3K/Akt/mTOR pathway which is very sensitive to the glucose levels(Lin *et al*., 2020a).

Inhibition of apoptosis :

Since most of the anti-cancer drugs act by inducing apoptosis, suppression of apoptotic machinery can cause drug resistance in cancer cells, since the cancer cells can accumulate mutations with prolonged cell survival(Wolf, 2021). Upregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1, etc.) and down-regulation of pro-apoptotic proteins (Bax, Bak, Bid, and Bad) have been observed in cancer cells(Campbell & Tait, 2018; Qian *et al*., 2022).Furthermore, mutations in pro- and anti-apoptotic proteins can modulate their activity causing apoptosis evasion(Shahar & Larisch, 2020). Activation of PI3K/Akt and MAPK/ERK cell survival pathways can also cause evasion of apoptosis(Bahar *et al*., 2023; Liu *et al*., 2020a). Phosphatidylinositol (3,4,5)-triphosphate (PIP3) generated from PI3K recruits Akt to the cell membrane and the phosphorylation at Thr308 and Ser473 residues inhibit pro-apoptotic protein Bad, caspase-9, Forkhead Box O (FoxO) transcription factor(Datta *et al*., 1997; Jeong *et al*., 2008; Zhang *et al*., 2011). The phosphorylation of FoxO causes its inactivation due to cytoplasmic sequestration, that in turn causes transcriptional inhibition of pro-apoptotic target genes(Zhang *et al*., 2011). Akt-mediated activation and translocation of NF-κBto the nucleus activates cell survival pathways(Tang *et al*., 2016). Akt also regulates the expression of XIAP (X-linked inhibitor of apoptosis protein), Mdm2 (murine double minute 2),and GSK-3β (glycogen synthase kinase 3 beta)(Chibaya *et al*., 2021; Gagnon *et al*., 2008; Lin *et al*., 2020). Similarly, MAPK/ERK activation can lead to the inhibition of pro-apoptotic Bad and Bim(Chakraborty *et al*., 2013). Increased expression of anti-apoptoticBcl-2 and Bcl-xL inhibit apoptosis by blocking the cytochrome c release(Tashker *et al*., 2002). Similarly, MAPK/ERK pathway can cause the upregulation of IAP and subsequently inhibit the activity of caspase and thus evade apoptosis(Lee *et al*., 2020).

Alterations in drug target :

Mutations in the target protein can cause alterations in the drug binding site, which in turn affects the affinity of the drug. Gefitinib or Erlotinib resistance in non-small cell lung cancer (NSCLC) can be triggered by mutations in the EGFR that can affect the drug binding(Zou *et al*., 2018). Most often, the mutations in the drug binding site can cause conformational changes that negatively affect the drug binding. Imatinib resistance in BCR-ABL positive chronic myeloid leukemia (CML) is caused by reduced binding affinity due to point mutations-induced conformational in the BCR-ABL kinase domain(Chandrasekhar *et al*., 2019). Furthermore, certain gain-of-function point mutations also enhance the activation of alternative signaling pathways(Du & Lovly, 2018).

Enhanced DNA repair :

Chemotherapy drugs usually act by inducing DNA damage in the cancer cells. However, over time cancer cells overcome chemotherapy-induced DNA damage by overexpression of DNA damage repair proteins such as DNA polymerases, ligases, and helicases. Moreover, gain of function mutations in the DNA repair genes can enhance their activity which in turn cause resistance to chemo drugs (Jurkovicova *et al*., 2022).

Gene amplification :

Increased target gene expression and anti-apoptotic proteins can enhance cell proliferation and circumvent the inhibitory effects of the chemo drugs by activating downstream signaling cascades. Moreover, the enhanced activity of the target protein can also increase intra-tumoral heterogeneity(Jim Yen *et al*., 2006; Mahgoub *et al*., 2023; Matsui *et al*., 2013).

Epigenetic alterations :

Epigenetic modifications such as hypermethylation of promoter regions of tumor suppressor genes can inhibit their expression(Lakshminarasimhan & Liang, 2016). Moreover, acetylation, and methylation of histones can also affect the expression of oncogenes, tumor suppressor genes and genes involved in the apoptotic machinery. Recent studies also indicate that cancer cells exhibit significant epigenetic modulations compared to that of normal healthy cells that enable them to overcome the inhibitory effects of chemo drugs termed as epigenetic plasticity(Audia & Campbell, 2016; Rajan *et al*., 2020;Yang *et al*., 2020).

Cytokine-mediated regulation:

Cytokines can significantly affect the response of cancer cells to chemotherapeutics. This is mainly due to activation of cell survival pathways (JAK/STAT and PI3K/Akt) by cytokines such as interleukins and tumor necrosis factor-alpha (TNF-α)in several cancers, both solid tumors and hematological malignancies(Jones *et al*., 2016). Cytokines can also regulate the activity and/or expression of drug efflux proteins, DNA repair and apoptotic proteins(Ashino *et al*., 2023; Centurione & Aiello, 2016). Moreover, remodeling of tumor microenvironment is also affected by the secretion of cytokines that in turn contribute to chemoresistance(Kartikasari*et al*., 2021).

MicroRNAs and long non-coding RNAs:

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) also play a major role in apoptosis evasion since miRNA-mediated suppression of pro-apoptotic genes such as PTEN have been reported in the case of miR-21(Liu *et al*., 2020a; Meng *et al*., 2020). Similarly, miRNAs can also upregulate the expression of anti-apoptotic genes as in the case of miR-15 and 16 upregulating the expression of anti-apoptotic Bcl-2(Pekarsky *et al*., 2018). Moreover, high expression of oncogenic miRNAs and reduced expression of tumor suppressive miRNAs have been observed in chemoresistance(Magee *et al*., 2015; Pavlíková *et al*., 2022).MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1), HOTAIR (HOX Transcript Antisense Intergenic RNA), H19, UCA1 (Urothelial Carcinoma Associated 1), etc. are some of thelncRNAs involved in drug resistance of cancers (Angelopoulou *et al*., 2020; He *et al*., 2018; Li *et al*., 2021; Wu *et al*., 2021).

Tumor-host interacting factors:

Physical, mechanical,and regional factors affect the efficacy of the drug. The distribution and diffusion kinetics of the drug is affected by the composition of the body such as presence of adipose tissue, muscle mass, morphology of the vasculature, site of the tumor, surface area of the body, presence of physiological and cellular barriers (blood-brain barrier/BBB, blood-testis barrier, etc.), composition of the extracellular matrix, pressure of interstitial fluid, pH and tumor heterogeneity, presence of hypoxic regions in the tumor, etc.(Gouju & Legeay, 2023; Matuszewska*et al*., 2021; Ozcan, 2023; Sriraman *et al*., 2014).

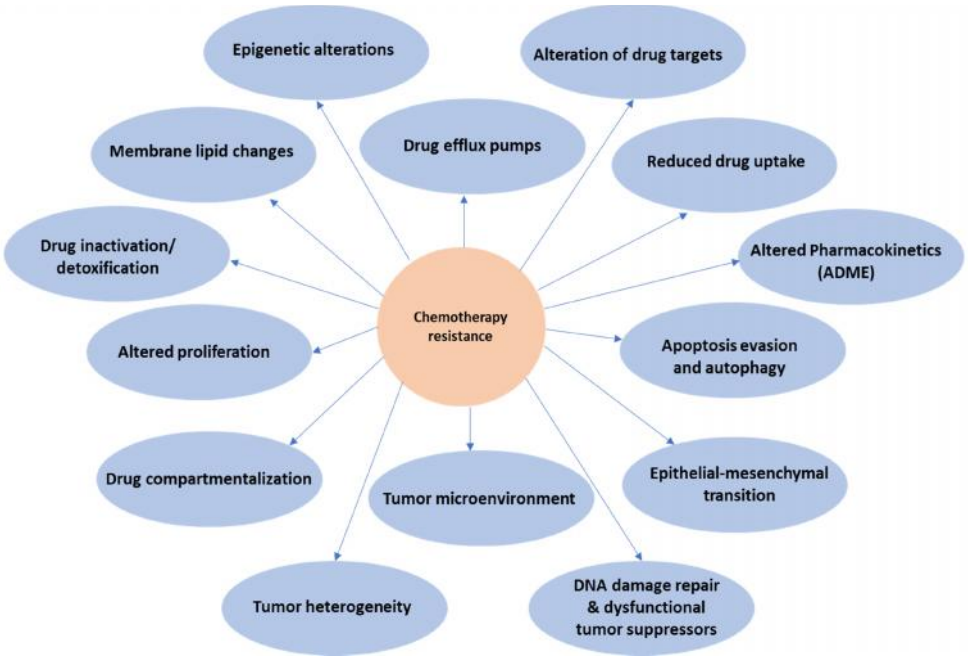

Figure 1. Factors contributing to chemoresistance in cancer

Role of apoptosis in cancer progression

Figure 2 shows the intrinsic and extrinsic pathways of apoptosis. Cancer cells tend to rewire the apoptosis process, by resisting pro-apoptotic signals and enhancing the effects of anti-apoptotic signals, despite the presence of the stimuli, as indicated in Figure 3(Mohammad *et al*., 2015).

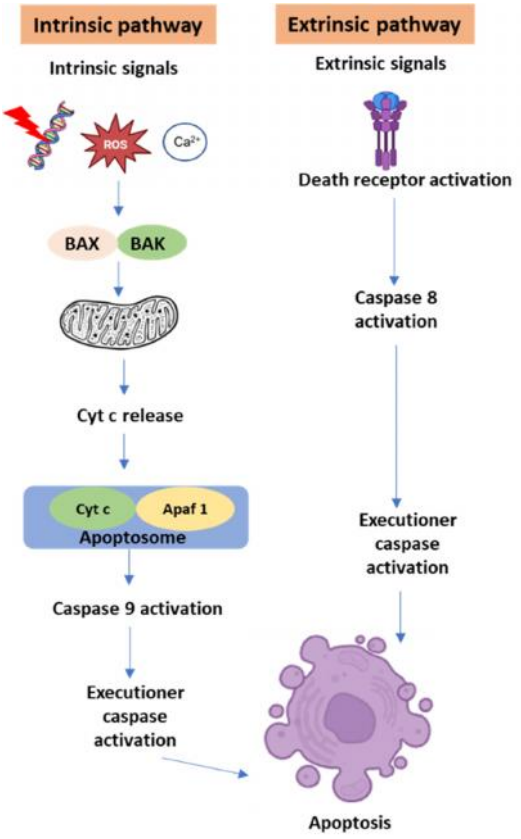

Figure 2. Intrinsic and extrinsic pathways of apoptosis.

The intrinsic apoptosis pathway is initiated by stress or injury that happens within the cells such as hypoxia, DNA damage, nutrient deprivation, high intracellular Ca2+, etc. The tumor suppressor protein p53 activates the intrinsic pathway by activating pro-apoptotic proteins of the Bcl2 family such as BAX and BAK. This leads to the destabilization of the mitochondrial membrane potential and the release of cytochrome c which ultimately forms an apoptosome with Apaf 1. The apoptosome activates the initiator caspase, Caspase 9 which in turn activates the executioner caspases. The protease activity of the caspases leads to structural changes in the cell marking apoptosis. Extrinsic pathway is initiated by signals outside the cell, that lead to the activation of death receptors. The receptor dimerization causes the activation of caspase 8, which further activates the executioner caspases and further morphological changes in the cell.

Cancer cells resist pro-apoptotic signals and enhance anti-apoptosis signals

Cancer cells circumvent apoptosis pathway via several mechanisms such as downregulation of death receptors and ligands of death receptors, loss-of-function mutations in pro-apoptotic proteins, upregulation of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL), activation of alternate cell survival pathways (e.g., JAK/STAT, NF-κB,PI3K/mTOR/Akt), dysfunctional tumor suppressors (e.g., p53, PTEN), etc(Artykov*et al*., 2021; Devanaboyina *et al*., 2022; Dong *et al*., 2021; Mengie Ayele *et al*., 2022; Twomey *et al*., 2015).Moreover, in certain cancer types (e.g., breast cancer), mislocalization or lack of surface death receptors appears to correlate with therapy resistance as reported by Chen *et al.* (2012).

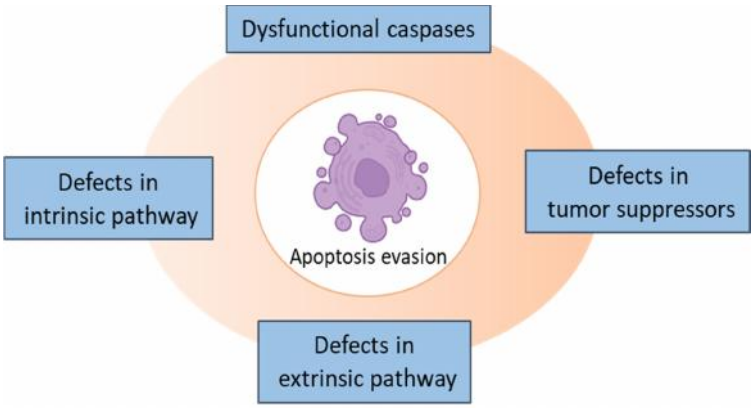

Figure 3. Apoptosis evasion in cancer progression and resistance

Role of the intrinsic pathway of apoptosis:

The intrinsic pathway of apoptosis or mitochondrial pathway is regulated by intracellular signals. Chemotherapeutics-induced DNA damage trigger intrinsic pathway of apoptosis(Stefanski *et al*., 2019). However, its dysregulation has been observed in several cancers causing drug resistance(*Regulated Cell Death (RCD) in Cancer: Key Pathways and Targeted Therapies | Signal Transduction and Targeted Therapy*, n.d.). B-cell lymphoma-2 (Bcl-2) family of proteins consisting of both pro- and anti-apoptotic proteins regulate the intrinsic pathway of apoptosis. Bax, Bak, etc are the major pro-apoptotic proteins whereas Bcl-2, Bcl-xL, etc. are the major anti-apoptotic proteins(Chota *et al*., 2021). However, a down regulation or reduced expression of pro-apoptotic proteins and an enhanced activity and/or over-expression of anti-apoptotic proteins have been observed in the case of drug resistant tumors(Bou Antoun & Chioni, 2023). Most of the chemo drugs induce mitochondrial outer membrane potential (MOMP) that lead to the release of cytochrome c into the cytoplasm. However, certain drugs fail to induce MOMP causing therapy unresponsiveness. Under certain circumstances formation of apoptosome (complex formed by cytochrome c and apoptotic protease-activating factor 1 (Apaf-1))is negatively affected causing blockade in caspase 9 activation(Bahar *et al*., 2022). Recent report by Guan *et al*., throws insights into the role of mitophagy or mitochondrial in chemoresistance(Guan *et al*., 2021). Furthermore, cancer cells exhibit metabolic reprogramming, especially deregulated glucose metabolism which affects the normal mitochondrial function (Icard *et al*., 2018).

Role of the extrinsic pathway of apoptosis:

The extrinsic pathway of apoptosis is triggered by death receptors, and its dysregulation has been observed in cancer progression and chemotherapy resistance(Chen *et al*., 2018). Tumor necrosis

factor (TNF) receptor superfamily of proteins play significant roles in the extrinsic pathway of apoptosis, which has a crucial role in immune surveillance(Sonar & Lal, 2015). There are several therapeutic molecules that induce extrinsic pathway of apoptosis in cancer cells. Ligands of death receptors such as recombinant TRAIL and agonistic monoclonal antibodies have been thoroughly studied both in preclinical and clinical settings(Thapa *et al*., 2020). However, in therapy unresponsive cancer types, reduced activity and expression of ligands and death receptors have been reported(Je *et al*., 2021). Moreover loss-of-function mutations can also negatively affect extrinsic pathway of apoptosis(Bin *et al*., 2007). Loss of function mutations of TRAILR1 and TRAIL-R2 have been identified in several cancers both sporadic and familial origin such as those of head and neck cancer, NSCLC, hepatocellular carcinoma (HCC), breast cancer, etc. (Lee *et al*., 1999). Missense, splice-site, nonsense, and missense mutations have been identified. These tumors were also found to be aggressive in nature with a tendency to spread to the lymph nodes(Lee *et al*., 1999)

Therapeutic implication of targeting apoptosis in cancer

Since apoptosis is a fundamental property of cells, selectively activating apoptosis machinery can kill cancer cells without affecting normal healthy cells. Chemodrugs exert their therapeutic potential by inducing DNA damage, cell cycle arrest, inhibiting or suppressing the expression of oncoproteins, etc. All these mechanisms ultimately trigger the apoptotic machinery(De Zio *et al*., 2013; Godwin *et al*., 2021; Li *et al*., 2018). However, cancer cells evolve different mechanisms of resistance because of prolonged exposure of chemodrugs(Campbell & Leung, 2021). Direct effects on apoptotic proteins are also observed such as over expression of anti-apoptotic proteins and down regulation of pro-apoptotic signals(Chota *et al*., 2021). It is significant to understand the intricate crosstalk between the mechanisms of chemoresistance and different pathways of apoptosis to achieve maximum therapeutic benefits and disease-free survival. Targeted inhibition of anti-apoptotic proteins and activation of pro-apoptotic signals have already exhibited promising benefits both in preclinical and clinical settings(D'Aguanno & Del Bufalo, 2020). Moreover, apoptosis-inducing compounds can be combined with existing chemodrugs to induce synergistic toxicity in cancer cells(Lim *et al*., 2019). However, it is important to have deeper insights into the molecular mechanisms underlying apoptosis and evasion of apoptosis to design novel therapeutic strategies.

Targeting apoptosis inhibition to overcome drug resistance

Selective induction of apoptosisis an attractive therapeutic strategy to improve the therapeutic outcomes of chemotherapy, targeted therapy, or immunotherapy. There are several molecules, synthetic or biologic, that are aimed at restoring the apoptosis signaling, that can act alone or in combination with conventional chemotherapeutics(Pfeffer & Singh, 2018).

Therapeutic strategies targeting intrinsic pathway of apoptosis

Therapeutic strategies targeting the intrinsic pathway of apoptosis primarily focus on activating or restoring the apoptotic machinery.

(i) BH3 mimetics: Among the several strategies BH3 mimetics are one of the most researched ones. There are small molecules that mimic the activity of BH3-only proteins, by binding to anti-apoptotic Bcl-2 family of proteins such as Bcl-xL, Bcl-2, Mcl-1, etc. and inhibiting their activity such as venetoclax (ABT-199) and navitoclax (ABT-263)(Townsend *et al*., 2021).

(ii) Inhibition of IAPs: Inhibitor of apoptosis proteins (IAPs) suppress the activity of caspases thus inhibiting programmed cell death. IAP inhibitors such as LCL161, birinapant, AT-406, etc. Have been shown to induce apoptosis by relieving the inhibition on apoptosis machinery(Ferris *et al*., 2023).

(iii) Direct targeting of Bcl-2 family proteins: Anti-apoptotic molecules such as Mcl-1 and Bcl-2 can be directly targeted using rationally designed inhibitors such as Venetoclax (ABT-199), Navitoclax (ABT-263), Sabutoclax (BI-97C1), A-1331852, A-1155463, etc.(Roberts *et al*., 2013).

(iv) Targeting p53: p53 tumor suppressor plays a crucial role in intrinsic pathway of apoptosis. There are several strategies to modulate and restore the activity of p53 in tumor cells such as small molecule inhibitors targeting MDM4, p53-reactivating peptides, gene therapy using viral vectors, targeting the downstream effectors of p53 such as Puma, Bax, Noxa, and Fas(Nishikawa & Iwakuma, 2023).

(v) Targeting mitochondrial metabolism: Mitochondrial metabolism is intricately associated with apoptosis and there are several strategies to induce mitochondrial stress and induce apoptosis such as (i) inhibition of oxidative phosphorylation (OXPHOS) using metformin, phenformin, and inhibitors of mitochondrial complex I such as IACS-010759, (ii) disruption of mitochondrial membrane potential, (iii) induction of mitochondrial ROS production using compounds such as menadione or mitochondrial-targeted antioxidants (e.g., MitoQ), (iv)activation of mitochondrial fission using small molecule Drp1 inhibitors, such as Mdivi-1, (v) targeting mitochondrial metabolism-related proteins using small molecule inhibitors of mitochondrial pyruvate carrier (MPC), such as UK5099, isocitrate dehydrogenase (IDH) inhibitors, etc., and (vi) induction of mitochondrial autophagy using mTOR inhibitors or AMPK activators(Janzer *et al*., 2014; Jeena *et al*., 2019).

(vi) Inducing Endoplasmic Reticulum stress: ER stress can induce intrinsic pathway of apoptosis. Proteasome inhibitors and also compounds that affect the protein folding can exert significant stress on the ER(Rudzińska *et al*., 2021; Sano & Reed, 2013).

(vii) Pro-apoptotic peptides: Peptides developed from the BH3 domain of pro-apoptotic proteins, such as Bid or Bim mimic the BH3-only proteins and have been shown to activate caspases and induce apoptosis in cancer cells. They act by inducing mitochondrial outer membrane permeabilization (MOMP)(Sun *et al*., 2019).

(viii) Procaspase activators: Small molecules that directly activate procaspases, the inactive precursor forms of caspases, have been developed as potential apoptosis-inducing agents. These molecules promote the autocatalytic cleavage and activation of procaspases into active caspases, thereby initiating the caspase cascade and inducing apoptosis. E.g., Apoptin(Malla *et al*., 2020).

(ix) Gene therapy: Pro-apoptotic genes and siRNAs can be delivered to cells using viral vectors to induce caspase activation. Adenoviral vectors expressing pro-apoptotic genes such as Bax or TRAIL to trigger caspase-dependent apoptosis in cancer cells(Jia *et al*., 2012; Pathak *et al*., 2023; Rieger *et al*., 2015).

Therapeutic strategies targeting extrinsic pathway of apoptosis

Therapeutic strategies targeting the extrinsic pathway of apoptosis activate death receptors that further lead to activation of caspases. The following are the approaches to target extrinsic pathway of apoptosis.

(i) Agonistic antibodies targeting death receptors: Death receptors (tumor necrosis factor receptor 1 (TNFR1), Fas (CD95), or TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1 or DR4) and TRAIL-R2 (DR5)) can be activated by agonistic antibodies that leads to activation of caspases. Eg: TRAIL-R1 activated by mapatumumab and lexatumumab and TRAIL-R2 activated by drozitumab and conatumumab(Dine *et al*., 2016; Y. Liu *et al*., 2022; von Pawel *et al*., 2014; X. Zhao *et al*., 2017).

(ii) Recombinant death receptor ligands: Ligands such as tumor necrosis factor (TNF), Fas ligand (FasL), or TNF-related apoptosis-inducing ligand (TRAIL) can bind to the death receptors and activate extrinsic pathway of apoptosis. Eg: Recombinant human TRAIL also known as dulanermin(Snajdauf*et al*., 2021).

(iii) Inhibition of decoy receptors and anti-apoptotic proteins: Small molecule inhibitors against decoy receptors or Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (c-FLIP) a master regulator of apoptosis, (e.g., birinapant and SM-164), sensitize cancer cells to apoptosis(Lei *et al*., 2020; Song *et al*., 2022).

Therapeutic strategies targeting inhibitors of apoptosis

In addition to IAP inhibitors, Bcl-2 inhibitors and BH3 mimetics, there are also small molecule inhibitors targeting Mcl-1 anti-apoptotic protein to overcome chemoresistance. S63845 is a Mcl-1 inhibitor that binds to BH3-binding groove and induces apoptosis in cancer cells(Wang *et al*., 2021). There are also combined strategies for simultaneously suppressing the activity of inhibitors of apoptosis. The efficacy of epigenetic modulators is also being investigated. Targeted inhibition of histone deacetylases and DNA methyltransferases have been shown to sensitize cancer cells to apoptosis by overcoming chemoresistance(Castro-Muñoz *et al*., 2023). Table 1 shows the list of agents that target the apoptotic machinery for treating cancer.

Table 1. Therapeutic agents targeting apoptosis.

Class of molecules	Names/examples	Mechanism	Reference
IAP (Inhibitor of Apoptosis Protein) inhibitors	Birinapantand ASTX660	block the anti-apoptotic activity of IAP proteins	(Song *et al*., 2022; Ward *et al*., 2018)
SMAC mimetic	LCL161	promotes the degradation of cIAP proteins	(Yang *et al*., 2019)
Bcl-2 inhibitors	venetoclax (ABT-199), navitoclax (ABT-263) Sabutoclax (BI-97C1), A-1331852, A-1155463	inhibit anti-apoptotic Bcl-2causing disruption of interaction between pro-survival and pro-apoptotic Bcl-2 proteins causingMOMP and release of apoptotic factors	(Hu *et al*., 2018; Nor Hisam *et al*., 2021; Teh *et al*., 2023)
	AT-101 (Gossypol)	inhibits anti-apoptotic Bcl-2 family proteins	(Gao *et al*., 2010)
	Obatoclax (GX15-070)	-do-	(Cournoyer *et al*., 2019)
TRAIL receptor agonists	conatumumab drozitumab	Activate TRAIL-R1 (DR4) TRAIL-R2 (DR5)	(Dine *et al*., 2016; Y. Liu *et al*., 2022)
	Theralizumab (TGN1412)	monoclonal antibody agonist of CD95 (Fas) activating apoptosis	(Brown, 2018)
BH3 mimetics	A-1331852 (Bcl-xL inhibitor), A-1155463 (Bcl-xL inhibitor)	small molecules that mimic the action of BH3-only proteins	(Townsend *et al*., 2021)
Mcl-1 inhibitors	S63845, AMG 176 AZD5991, A-1210477	Inhibition of anti-apoptotic Mcl-1	(Wang *et al*., 2021)
Caspase-based drug therapy	(i) Apoptin	proline-rich protein capable of inducing apoptosis	(Malla *et al*., 2020)
Caspase-based gene therapy	(i) Human caspase-3 gene therapy (ii) Gene transfer of constitutively active caspse-3 (iii) Recombinant adenovirus carrying caspase 3	Restores caspase activity	(Pathak *et al*., 2023)
Proteasome inhibitors	Bortezomib (Velcade)	inhibit 26S proteasome, causing accumulation of misfolded or damaged proteins, ER stress and apoptosis	(Alwahsh *et al*., 2023)
	Carfilzomib (Kyprolis)	irreversibly inhibits the chymotrypsin-like activity of the 20S proteasome, leading to the accumulation of proapoptotic proteins and induction of apoptosis	(Groen *et al*., 2019)
	Ixazomib (Ninlaro)	inhibits the chymotrypsin-like activity of the 20S proteasomeand induces apoptosis in cancer cells by disrupting protein homeostasis	(Muz *et al*., 2016)
MDM2 Inhibitors	Nutlin-3	binds to the p53-binding pocket of MDM2 and prevents its interaction with p53	(Yee-Lin *et al*., 2018)
	Idasanutlin (RG7388)	-do-	(Konopleva *et al*., 2022)

	AMG 232	-do-	(Gluck *et al*., 2020)
p53 Reactivators	PRIMA-1 and PRIMA-1Met (APR-246)	restores wild-type conformation of p53	(Rangel *et al*., 2019)
	Cyclic Penta-peptides	Peptides that restore the transcriptional activity of mutant p53	(Ramadhani *et al*., 2022)
Electron Transport Chain Inhibitors	Metformin	suppresses the activity of complex I of the mitochondrial electron transport chain, leading to alterations in mitochondrial metabolism and induction of apoptosis in cancer cells.	(Janzer *et al*., 2014)
	IACS-010759	induces apoptosis in cancer cells by disrupting mitochondrial metabolism and generating oxidative stress.	(Yap *et al*., 2023)
Mitochondrial Permeability Transition Pore (MPTP) Modulators	Cyclosporine A	modulate the opening of the mitochondrial permeability transition pore (MPTP), causing apoptosis	(Han *et al*., 2018)
Mitochondrial Fission/Fusion Regulators	Mdivi-1	inhibitor of mitochondrial fission protein Drp1	(Zhang *et al*., 2023)
Hexokinase Inhibitors	Lonidamine	Inhibits hexokinase enzyme	(Huang *et al*., 2020)
Pro-apoptotic peptides	D-(KLAKLAK)2	synthetic peptide that disrupts mitochondrial membrane integrity	(Ko *et al*., 2009)
	Cationic Antimicrobial Peptides (CAPs)	Synthetic peptide with pro-apoptotic activity	(Baxter *et al*., 2017)
	TAT-Bim BH3 Peptide	cell-penetrating peptide fused to the BH3 domain of the pro-apoptotic protein Bim	(Kashiwagi *et al*., 2007)
TRAIL Receptor agonists	Mapatumumab	monoclonal antibody targeting TRAIL-R1	(von Pawel *et al*., 2014)
	Lexatumumab (HGS-ETR2)	A monoclonal antibody targeting TRAIL-R2	(X. Zhao *et al*., 2017)
CD95 (Fas) Agonists	APG101 (Asunercept)	fusion protein combining extracellular domain of CD95 and the Fc region of human immunoglobulin G (IgG), to induce CD95-mediated apoptosis	(Krendyukov & Gieffers, 2019)
TRAIL mimetics	Dulanermin (recombinant human TRAIL or rhTRAIL)	mimic the action of endogenous TRAIL ligands, binding to death receptors and induce apoptosis	(Soria *et al*., 2010)
Histone Deacetylase (HDAC) Inhibitors	Vorinostat (SAHA)	inhibits class I and II HDACs	(Wawruszak *et al*., 2021)
	Romidepsin (Istodax)	inhibits class I HDACs	(Pojani & Barlocco, 2021)
DNA Methyltransferase (DNMT) Inhibitors	Decitabine (5-aza-2'-deoxycytidine)	reversing aberrant DNA methylation patterns and reactivating tumor suppressor genes	(Traube *et al*., 2022)
Bromodomain and Extra-Terminal (BET) Protein Inhibitors	JQ1	downregulating the expression of anti-apoptotic genes	(Jiang *et al*., 2020)
Sirtuin (SIRT) Inhibitors	Sirtinol	Inhibits SIRT1 and SIRT2	(Hu*et al*., 2014)

Need for new anticancer drugs to overcome resistance especially those targeting apoptosis

Several studies are ongoing to precisely target the apoptosis pathways and overcome the mechanisms of resistance(Kumar *et al*., 2019). These include accurate targeting of apoptosis-inducing drugs in a cell-specific manner, so that healthy cells are spared. Studies also show the potential of new therapeutic strategies targeting transforming growth factor-β (TGF-β), PI3K-Akt, FOXO transcription factors, annexins etc.(Kumar *et al*., 2019). Moreover, several combination strategies are also being studied, wherein apoptosis inducing molecules are combined with existing clinically approved drugs(Rudzińska *et al*., 2021). The goal is to eliminate the residual cancer cells so that disease relapse with a resistant phenotype is addressed. The crosstalk of apoptosis pathways with autophagy signaling in chemotherapy resistance is also a focus of research(Guan *et al*., 2021). Recent studies also indicate the need for personalized targeting since 'one-size fits all' approach may not be sufficient to overcome drug resistance(Hoeben *et al*., 2021). Cell-directed delivery of anti-apoptotic drugs can be achieved by using nanoparticles, which hold great promise because improved drug dissolution and stability can be achieved using nanoparticle-mediated drug delivery. Moreover, nanoparticles enable delivery of multiple drugs simultaneously coupled with real-time monitoring features both actively and passively in the tumor tissues(Chu & Stochaj, 2020; Hassanin & Elzoghby, 2020; Ulldemolins *et al*., 2021). Studies are ongoing to optimize the formulations, improve the drug release kinetics, and for improving safety and efficacy.

Conclusion

Apoptosis is a complex process regulated by an intricate network of proteins. One advantage of targeting apoptosis to overcome resistance is that since apoptosis is a fundamental process, cell death can be induced irrespective of the resistance mechanisms in cancer cells. Several agents, both biological and synthetic origin capable of eliciting desired therapeutic effects and that can enhance the clinical outcomes of conventional treatment strategies by sensitizing the cancer cells have been studied. The preclinical and clinical results so far are indeed promising and insightful and targeting apoptosis pathways indeed provide an alternative strategy to prevent the emergence of resistant clones thereby reducing the chances of disease relapse. Furthermore, unlike the previous approaches, several studies focus on personalizing the treatment approaches to tailor the treatment for better clinical outcomes, by mapping the unique genetic and molecular features contributing to the drug resistance. However, deeper insights into the activation of alternate signaling mechanisms in drug resistant cancer cells must be studied in suitable *in vitro* and *in vivo* models, and patient populations. Although several studies hold promise in this direction, in-depth research is warranted to optimize the efficacy of these strategies across various cancer types.

Acknowledgement

I would like to extend my heartfelt appreciation to the Principal of Brahmananda Keshab Chandra College for her invaluable support in providing seamless access to the various facilities within the institution. The assistance rendered in terms of departmental resources, the library, laboratory facilities, and internet access has played a pivotal role in enhancing our overall experience. I am sincerely grateful for the logistical support, which has greatly contributed to my academic endeavors and success within the college environment.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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