Molecular Biology Reports
https://doi.org/10.1007/s11033-023-08568-1

REVIEW

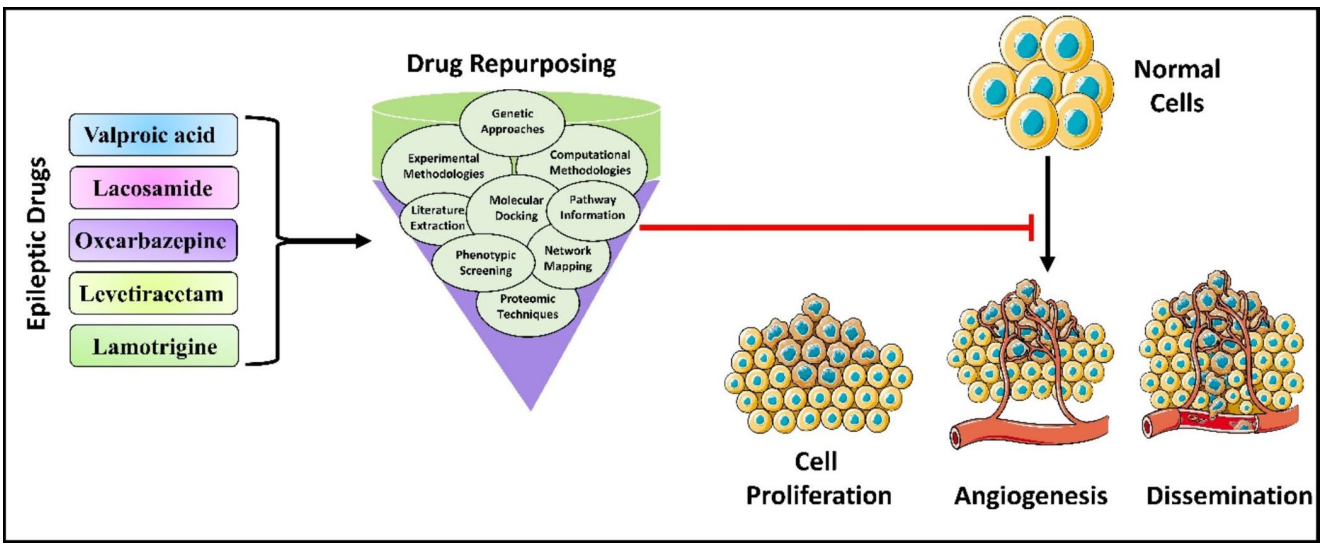
The evidence for repurposing anti-epileptic drugs to target cancer

Mir Aroosa[1] · Jonaid Ahmad Malik[2,3] · Sakeel Ahmed[4] · Onur Bender[5] · Nafees Ahemad[6] · Sirajudheen Anwar[7]

Received: 22 February 2023 / Accepted: 31 May 2023
© The Author(s) 2023

Abstract Antiepileptic drugs are versatile drugs with the potential to be used in functional drug formulations with drug repurposing approaches. In the present review, we investigated the anticancer properties of antiepileptic drugs and interlinked cancer and epileptic pathways. Our focus was primarily on those drugs that have entered clinical trials with positive results and those that provided good results in preclinical studies. Many contributing factors make cancer therapy fail, like drug resistance, tumor heterogeneity, and cost; exploring all alternatives for efficient treatment is important. It is crucial to find new drug targets to find out new antitumor molecules from the already clinically validated and approved drugs utilizing drug repurposing methods. The advancements in genomics, proteomics, and other computational approaches speed up drug repurposing. This review summarizes the potential of antiepileptic drugs in different cancers and tumor progression in the brain. Valproic acid, oxcarbazepine, lacosamide, lamotrigine, and levetiracetam are the drugs that showed potential beneficial outcomes against different cancers. Antiepileptic drugs might be a good option for adjuvant cancer therapy, but there is a need to investigate further their efficacy in cancer therapy clinical trials.

Graphical Abstract



Keywords Breast cancer · Antiepileptic drugs *for cancer* · Drug repurposing · Cancer treatment · Antiepileptic drugs

Introduction

Cancer is among the leading reasons of death globally. Increasing understanding of human neoplastic illnesses and technological advancements make it possible to develop novel antineoplastic agents to reduce cancerous deaths [1–4]. A recent example that completely changed cancer

Mir Aroosa, Jonaid Ahmad Malik and Sakeel Ahmed contributed equally.

Extended author information available on the last page of the article

Published online: 07 July 2023

perception is PD1, blocked by dostarlimab [5]. Drug development requires a long period for exploration and manufacture, with medications requiring up to 15 years to enter the therapeutic or clinical space and financing from corporate or scientific organizations [6]. Screening the safety and efficacy of drugs in human participants in a clinical trial (CT) [7].

Furthermore, most innovative drugs/molecules failed to institute safety and efficacy in clinical trial and, as a result, failed to access the therapeutic or clinical space: the rate of success is < 10%. Many organizations are reanalyzing commercially licensed pharmaceuticals from a drug repurposing standpoint as a unique strategy for overcoming these constraints [6]. Drug repositioning ("creative innovations for old medications") is a strategy to explore new indications for approved or experimental drugs that go beyond the primary medical indication [8, 9]. The main advantages of this technique are that the pharmacodynamic, pharmacokinetic, and toxicity profiles of medications have been extensively documented in preclinical and Phase-1 trials. Hence, these medications might promptly advance through Phase-2/3 of clinical trials, and developmental costs could be greatly lowered. Thus, drug repurposing can result in a lower risky business model with reduced developmental costs, notably if new drug failures during research and development are avoided (Fig. 1) [3, 10, 11]. The first productive descriptions of drug repurposing were primarily the consequence of coincidental innovations.

In contrast, resultant comprehensive methodologies for identifying non-oncology drugs that could presumably be repurposed in cancer therapy originated (Fig. 1). They can be divided into computational and experimental methodologies [12]. Computational ones depend on high throughput screening and bioinformatics tools such as molecular docking or network mapping.

In contrast, experimental depends on assays that are based on activity such as proteomic techniques or chemical genetic approaches to recognize pertinent relationships between novel targets and defined drugs, or cell-based phenotypic screening focused on the classification of prevalent phenotypic criteria (e.g., proliferation, exosome biogenesis modulation, cell cycle profiling) without previous knowledge of the target [13]. Several applicant drugs have been under investigation, from non-cancer to cancer therapy. Some examples include celecoxib, primarily used for arthritis treatment, which is under investigation for lung, colorectal, and breast cancers (NCT01695226); aspirin in colorectal cancer; valproic acid, which is an antiepileptic drug that has been under investigation for leukemia (NCT00530907); metformin, an anti-diabetic drug is under investigation for breast, prostate and colorectal cancers (NCT00897884), angiotensin receptor blockers, which include losartan, primarily used for the treatment of hypertension, has been under investigation for breast and pancreatic cancer (NCT01821729) [14]. Disulfiram, initially authorized as an anti-alcoholism drug, has displayed antitumor effects in many preclinical studies, most recently on several types of human cancer such as; lung, breast, prostate, pancreatic, and melanomas. Moreover, has a viable advancement in the intervention of non-small cell lung cancer and glioblastoma [15]. All drugs employed in clinical treatment can approach multiple targets [16, 17]. As a result, if the targets of these medications are extremely consistent with cancer, there is a good chance that those with similar targets will be therapeutic for additional cancer patients. Historically, drug repurposing has been mostly opportunistic and fortuitous [18, 19]. It is worth mentioning that the repurposing strategy necessitates the systematic assimilation of research data from various disciplines, including synthetic chemistry, in silico modeling, systems pharmacological approaches, in vitro screens, clinical studies, and in vitro and in vivo functional assays [20]. As evidenced by a huge body of data through in vitro and in vivo investigations or clinical trials, several novels recognized non-oncology medications repurposed for cancer therapy function by suppressing proliferation and promoting cell death.

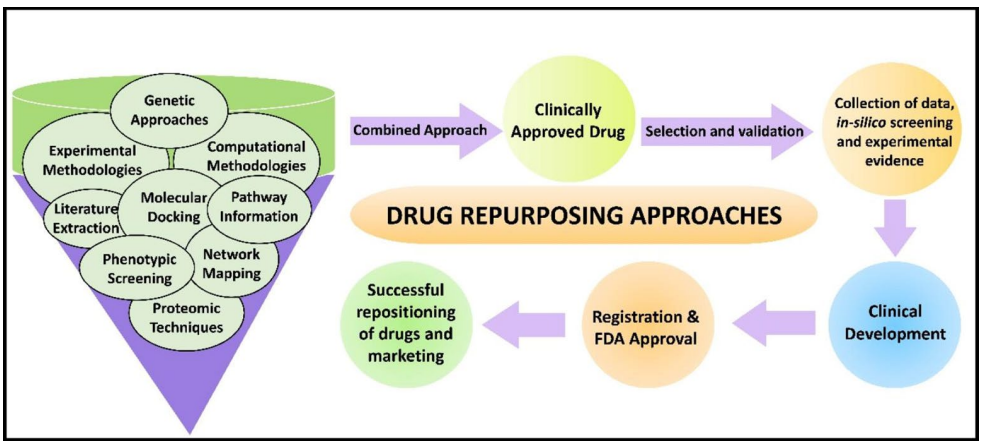


Fig. 1 Demonstrates the required approaches toward drug repurposing: An overview of various approaches required for drug repurposing to target cancer. The combined approaches with proper selection and validation studies like data collection, in-silico, and experimental shreds of evidence help in clinical development following registration and FDA approval for the successful repositioning of drugs and marketing

Furthermore, formerly employed for other conditions, these medications have robust drug safety data and are frequently affordable (particularly if accessible in their generic form) [21]. In some circumstances, a drug's pharmacological activity results from blocking specified targets, off-targets, or a hybrid of both. This tendency is known as "polypharmacology," originally characterized as a compound's bonding capacity to many targets [22], which encourages exploring the further indications of already approved drugs. The main research question was to discover the anticancer properties of these drugs and the interlink pathways of cancer and epilepsy. This review has highlighted various findings that can help repurpose the treatment of multiple types of cancer. We have focused on various drugs that have entered clinical trials with positive results and others that have depicted good results in preclinical studies.

Challenges with the existing therapies

Drug resistance is the primary obstruction to treating cancer patients. The primary approach to overcome the resistance is using a combination therapy of drugs with non-overlapping modes of action or polychemotherapy [2–4, 23, 24]. This pragmatic strategy was quite effective in some types of lymphoma, breast, and testicular cancer [25, 26]. As a result, combined chemotherapeutic approaches emerged as a new perspective for cancer therapy, resulting in a complicated regimen. Furthermore, various dose intensity techniques, such as shorter-interval infusions of chemotherapy or high doses of chemotherapeutic interventions with growth factor stimulation to prevent prolonged bone marrow depression, contributed to the better efficacy of these therapies by inhibiting early tumor re-growth [27, 28]. Polychemotherapy's accomplishments had plateaued by the turn of the century, some 50 years after its commencement. Surgery, radiation, and polychemotherapy were insufficient to cure many cancers [26]. These cause cancer cell inhibition and offer targeted and intelligent treatment options.

Consequently, novel treatment techniques to tackle the key enabling features and acquired capacities that turn healthy cells and tissues into cancers have begun to emerge. Introducing medicines that disturbed these distinguishing traits, such as targeted therapy, was a significant step forward. Indeed, greater comprehension of cancer biology drivers has evolved into highly effective medicines targeting nuclear receptors, tyrosine kinases, and other molecular targets. Following the early success of androgen receptor (AR) antagonists and epidermal receptor and BCR-ABL, HER2, and EGFR inhibitors, a great effort was launched to create medicines that target oncogenes and other critical cellular liabilities.

Oncological therapy has progressed by employing immunological techniques to recognize and attack cancer. Anti-PD-1/PD-L1 and anti-CTLA4 monoclonal antibodies that inhibit negative regulators of the adaptive immune system, or checkpoints, have generated significant antitumor activity and even cures in various ways tumor types [29–33]. Nonetheless, as it was formerly found with standard chemotherapy, subsequent resistance to targeted and immunological treatments is the expected norm [26]. According to statistics, drug resistance is responsible for more than 90% of deaths in cancer patients. Multidrug resistance (MDR) in cancerous cells undergoing chemotherapeutic treatment can be attributed to several processes, notably increased drug efflux, genetic variables (Mutations, gene rearrangements, epigenetic modifications), enhanced DNA repair capability and growth factors, and heightened xenobiotic metabolism. These mechanisms reduce the treatment effectiveness of given medications, making tumor treatment more challenging. Since cancer is a heterogeneous and multi-targeted disease, this approach is crucial for success in combating it.

The presently available anticancer drugs have many challenges, including drug resistance, side effects, cost, less efficacy, less potency, or non-responsiveness [3, 4, 25]. Cancer poses so many different challenges than any existing disease. The most potent anticancer drugs available today are their non-specificity towards cancer cells, like cisplatin, doxorubicin, etc., which make cytotoxic to normal cells leading to tissue damage [25]. The most important challenge is that these anticancer drugs are administered intravenously, making them more cytotoxic [34]. The anticancer drugs aimed to target the tumor sites affect the whole body leading to ineffectiveness against targeted cancer cells. The issue is that anticancer drugs like vincristine and vinblastine from the natural source have challenges of drug solubility, dosage, yield, sufficient delivery, and bioavailability [35]. The chemical stability of anticancer drugs is another challenge that affects the drug's potency and the drug uptake and activity in the tumor sites, leading to obstruction of the dose-effect [25]. The other challenges are discussed below.

Mechanisms of drug resistance

Drug efflux enhancement

P-Glycoproteins

Increased chemotherapeutic drug efflux from cancer cells results in lesser drug accumulation. MDR is the most common cause of chemotherapeutic drug resistance. Drug efflux transporters, or efflux pumps, are primarily accountable for MDR [36]. ATP binding cassette subfamily B member

1/P-glycoprotein (ABCB1/P-gp), or breast cancer resistance protein (BCRP), is an ABC protein found on the cell membrane that regulates the absorption, metabolism, distribution and excretion of various chemical substances. Since these proteins guard cells against apoptosis caused by elevated intracellular drug concentrations, they can also impede the administration of drugs by reducing bioavailability, intracellular concentration, and BBB transition. P-gp, extensively expressed on the endothelial cell membrane, leads to limited chemotherapeutic drug administration in specific areas, particularly in treating brain tumors, where anticancer medicines are often inefficient in passing through the BBB [37]. The size of the tumor is also important for drug penetration. Chemotherapeutic drugs are typically less effective in large tumors because of the low blood supply than in tiny tumors with practically free oxygen and nutrition supply exposure. The P-gp safeguards the brain from potentially harmful substances while limiting access to therapeutic medicines that are accountable for the greater intricacy of the therapy. Most of the time, the only option to get around the barrier is to elevate the quantity of the medicine, which typically results in general toxicity. That is why increased drug efflux has been identified as one of the primary mechanisms of tumor cell resistance to chemotherapeutics [38, 39]. MDR occurs when P-gp is overexpressed on cancer cells. P-gp's transporter structure contains several drug bindings sites that engage with various chemotherapeutic medicines, including etoposide, paclitaxel, doxorubicin, and many others.

Cancers of the liver, colon, adrenal gland, pancreas, and kidney have the top levels of P-gp expression, whereas soft tissue cancers, neuroblastoma, and hematological malignancies have moderate amounts. P-gp levels are initially low in breast, ovarian, oesophageal, and lung malignancies. However, the levels of P-gp efflux transporters rise when the tumor develops resistance to chemotherapeutic treatments [36, 40]. First-generation P-gp inhibitors include trifluoperazine, quinidine, cyclosporine-A, reserpine, verapamil, tamoxifen, yohimbine, and vincristine [41, 42]. ABCB1 overexpression has been linked to chemotherapeutic failure (Fig. 2). Furthermore, MDR murine melanoma cells have significant ABCB1 gene amplification. The biological basis for "MDR" p-glycoprotein's characteristic feature is its broad substrate selectivity, including vinca alkaloids, anthracyclines, and epipodophyllotoxins [43].

Cancer resistance protein (CRP)

ABCG2, one constituent of the extensive ABC superfamily, was overexpressed in adriamycin-resistant human-derived breast cancer cells. Additionally, the hypoxic state has been shown to influence ABCG2 expression. Because of increased ABCG2 expression, cancer cells or stem cells in hypoxic conditions resist medicines [44]. The ABCG2 gene codes for BCRP. It was discovered in a drug-resistant human breast cancer cell line exposed to mitoxantrone and tariquidar, both P-gp inhibitors [45].

Multidrug resistance-associated proteins (MRP) is a component of the mammalian ABC family of biological membrane transporters known to produce MDR. This transporter was identified while working on the H69AR cell line, a drug-resistant small-cell lung cancer [46]. MRP1 overexpression has been linked to anticancer drug resistance. The quantity of decreased GSH is required for unmodified chemotherapeutic drugs to be transported by MRP1 [47].

Cellular and non-cellular factors in the context of the tumor microenvironment

The interconnections involving cancer cells and nearby tumor microenvironment (TME) components cause TME-mediated innate resistance at the time involving chemotherapy. The interactions between cancer cells and nearby TME components cause TME-mediated innate resistance during cancer treatment. This established resistance given by the TME appears to be a host compensatory reaction to pharmacologic exposures. TME's cellular (fibroblasts, endothelial cells, immune cells) and non-cellular components (oxygenation, soluble substances such as cytokines, extracellular matrix, pH, vascular endothelial growth factor (VEGF)) contribute to drug resistance (Fig. 2) [48, 49]. In the particular instance of lung, breast, and prostate cancer, for example, IL-6 can significantly raise drug resistance by blocking apoptosis via stimulation of Janus kinases (JAK)/signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt), and Ras-MAPK pathways. Due to the hypoxic situation, the relatively low pH, changing oxygen levels, and increased reactive oxygen species (ROS) levels encourage angiogenesis, metastasis, tumor severity, and an elevation in MDR proteins, reducing the treatment effectiveness of chemotherapy drugs [50]. It was reported that efflux of anticancer medicines after encapsulating them in exosomes. They discovered a link between drug efflux and drug sensitivity in many tumor models and suggested that exosomes shed with drug resistance [48].

Tumour heterogeneity

A research group observed that the Kirsten rat sarcoma (KRAS) mutation was found to be the main reason for the resistance in esophagogastric cancer, so this synchronously augments epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER2), and it was demonstrated in roughly 50% of the mesenchymal-epithelial

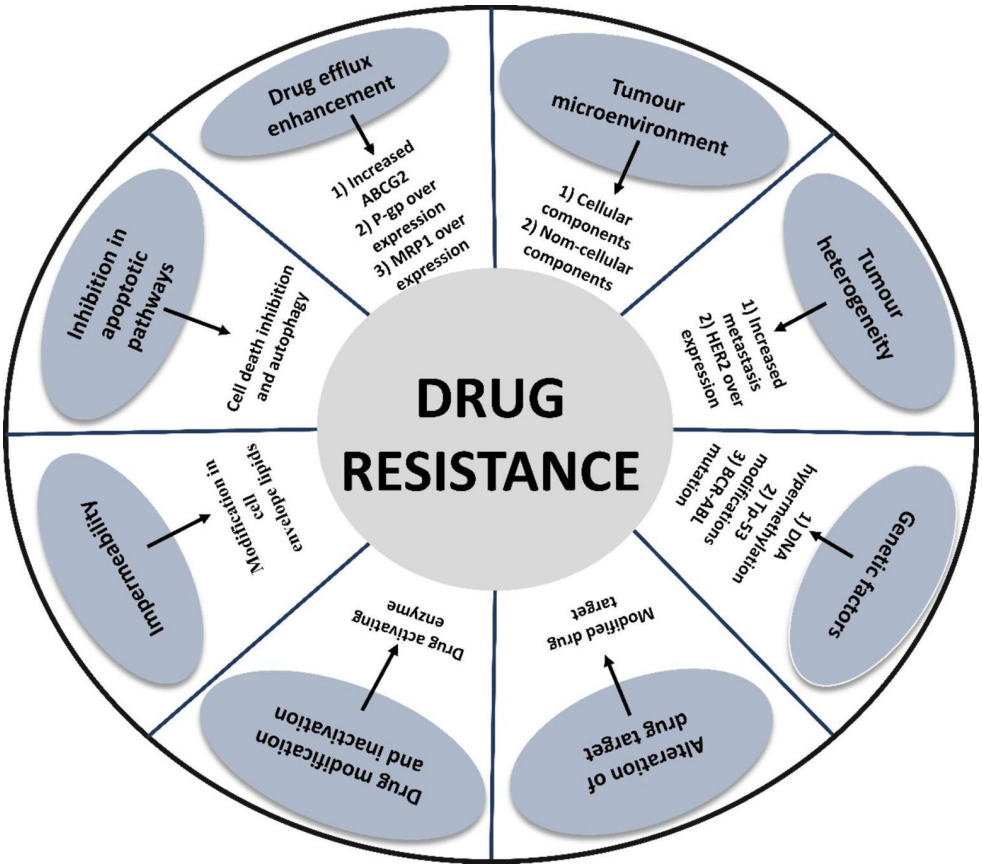


Fig. 2 An overview of several contributing factors responsible for drug resistance in cancer. Most importantly, these factors act via different mechanistic pathways like drug modification and inactivation, alteration of drug targets, genetic factors, tumor heterogeneity, tumor microenvironment, drug efflux pumps, and inhibition of apoptotic pathways. All these factors are responsible for cancer drug resistance

transition (MET)- exacerbated esophagogastric cancer in patients. The T790M EGFR mutation is a genetic foundation of acquired tyrosine kinase inhibitor (TKI) resistance. A change in KRAS/MAPK signaling or a BRAF or KRAS gene mutation causes drug resistance in MEK1/2 inhibitors in cancer cells like colorectal cancer, ovarian cancer, and others [51, 52]. Heterogeneity is a distinguishing trait of tumor cells in comparison to healthy ones. Cells are characterized by many phenotypic and morphological aspects that comprise gene expression, cellular morphology, epigenetics, metabolism, motility, proliferation, transcriptome, and metastatic potential. Intertumoral heterogeneity relates to the diversity among patients with identical histology but differing genetic differences, somatic mutation, and environmental variables, while intra-tumoral heterogeneity relates to variability inside the tumor. Intra-tumoral heterogeneity is a significant contributor to the deadly implications of cancer due to drug resistance. As a result, it is accountable for therapeutic failures and may be a non-heritable and heritable driver of variation. Cancer stem cells (CSCs) are thought to persist even after being formed predominantly from an organ's normal stem cells. A research group has published a detailed study of CSCs in drug resistance, including their therapeutic options for overcoming resistance as a subset of cells in a tumor microenvironment [48, 53].

Genetic alteration

Genetic alterations, widely detected in tumor cells, are considered one of the primary culprits of chemotherapeutic drug failure. Modifications in the TP53 gene, typically found in tumor cells, are one of the most well-known indicators of tumorigenesis. BCR-ABL tyrosine-kinase antagonists, like imatinib, popularly used as the drug of choice in patients with chronic myeloid leukemia (CML), inhibits ATP binding to the BCR-ABL kinase receptor, hence leading to apoptosis in tumor cells. According to the data, alterations in the BCR-ABL gene, which is connected with the drug-binding area, frequently result in imatinib resistance during CML chemotherapy [54, 55]. Topoisomerase-II targeted medicines, such as etoposide, are commonly used to suppress replication by inhibiting the expression of this enzyme. However, topoisomerase gene alterations modify its nuclear localization, resulting in resistance to tumor cells.

Furthermore, these medications are not exclusive to cancerous cells; instead, they interfere with the whole genome, severely limiting their safe use in managing cancer [56]. The most recent research underlines the critical significance of epigenetic changes in tumor cells in chemotherapeutic treatment resistance. Cancer development could be influenced by tumor suppressor gene silencing via DNA hypermethylation

or oncogene expression enhancement via DNA hypomethylation. The epigenome undergoes numerous modifications throughout carcinogenesis, including genome-wide loss of DNA methylation, localized hypermethylation (particularly in CpG promoter islands of tumor suppressor genes), and worldwide alteration in histone modifications, and modifications in miRNA expression [57, 58]. Healthy cells restore damage caused to DNA or undergo apoptosis; however, cancerous cells overcome the strict control mechanism and modify DNA repair. Some chemotherapeutic medications, such as platinum, actively cause DNA damage, while others, such as Irinotecan, doxorubicin, and others, degrade the DNA implicitly through topoisomerase enzyme inhibition. The ability of some tumor cells to restore DNA damage affects the efficacy of chemotherapeutic drugs [59, 60].

Cross-talk between oncogenic and epileptogenic pathways

Although the functions of the process involved in inflammation in epilepsy have recently been discovered, it has been historically recognized that cancer and inflammation progress simultaneously. A tumor induces an inflammatory reaction and vice versa. Tumor cells modulate the expression of chemokines and cytokines, assisting in the recruitment of inflammatory cells and supporting tumor expansion. In contrast, glutamate is released in inflamed regions surrounding the expanding mass that stimulates multiple number of cells, promoting an inflammatory micro-environment and thereby increasing DNA oxidative damage and the stimulation of both epigenetic and genetic alterations. These modifications affect cellular signaling pathways that control proliferation, survival, and invasions [61, 62]. Hyperactivation of specialized receptor subclass of glutamates (GluRs) like ionotropic NMDA, AMPA receptor, and metabotropic mGluR1-8 combined with impeded GABAergic inhibition due to a reduction in numerous GABA-A (Gamma-aminobutyric acid) subtypes and the decreased expression of its receptor like GABA-AR (GABA-Androgen receptor) suggests notable hyperexcitability of neurons that leads to spontaneous seizures [63].

Moreover, the same disbalance among excitatory and inhibitory receptors appears to have a part in the formation of tumor lesions. Multiple investigations have established that glutamate and the previously stated GluRs may play a role in tumorigenesis and invasion in non-neural and neural tumors [64, 65]. Dysfunction in the metabolism of GABA could be a symptom of a cell's defensive response during tumorigenesis, given the complex disparity between activating and inhibiting AA in brain tumor tissues. GABA has been identified as a significant down regulator of proliferation in stem cells. Analysis of GABA binding sites in glioblastomas revealed that those greater malignancies were linked to lesser GABA binding [66].

On the contrary, the significance of androgen receptor GABA-AR overexpression in breast cancer cerebral metastasis is unknown. However, it might be a malignant modification essential for brain colonization [67]. Interestingly, in contrast to GABA-AR amplification, breast cancer-lead cerebral metastasis stimulates GABA transporter and GABA transaminase, allowing the cell to utilize GABA as a source of energy via the GABA shunt pathway [68, 69]. Furthermore, even operationally changed voltage-dependent ion channels in tumor cells could promote hyperactivity, tumor development, and metastasis [70, 71]. The importance of these membrane pathways in cellular proliferation has been thoroughly described in various cellular forms in the context of various cancerous cells. This engagement was first established for potassium channels and additional voltage-gated ion channels like calcium and chloride [72, 73]. For instance, potassium and calcium ion channel activity and expression modifications have been linked to decreased patient survival and more severe brain tumor behavior [63, 74].

Valproic acid has received more attention regarding the antiepileptics that seem to provide anticancer impact. In vivo/in vitro investigations revealed that valproic acid inhibits histone deacetylases (HDAC) in patients with glioblastoma. Furthermore, epigenetic alterations, including abnormal histone acetylation and DNA methylation, are widespread in malignancies, providing a compelling argument for using these antiepileptic drugs as an epigenetic combination treatment [75, 76]. Other potential treatment signs for antiepileptics as antitumor agents include levetiracetam as an O(6)-Methylguanine-DNA-methyltransferase (MGMT) transcription antagonist and brivaracetam and lacosamide for their anticarcinogenic and anti-migration ramifications due to the attenuation of specific microRNAs, including miR-107 and miR-195-5p [77, 78].

Valproic acid

Valproic acid promotes GABAergic functioning and decreases excitatory signals by post-down-regulation of voltage-gated Na^{2+} channels and NMDA glutamatergic receptors. Furthermore, valproic acid has also evolved as an antineoplastic medication. Valproic acid suppresses tumor gene overexpression via controlling gene expression using epigenetic mechanisms (specifically, by substantially blocking histone deacetylase activity), which promotes cancer cell growth arrest, differentiation, and apoptosis (Fig. 3) [63]. Valproic acid has been studied in vivo and in vitro for its possible use in various malignancies [78, 79]. Acting

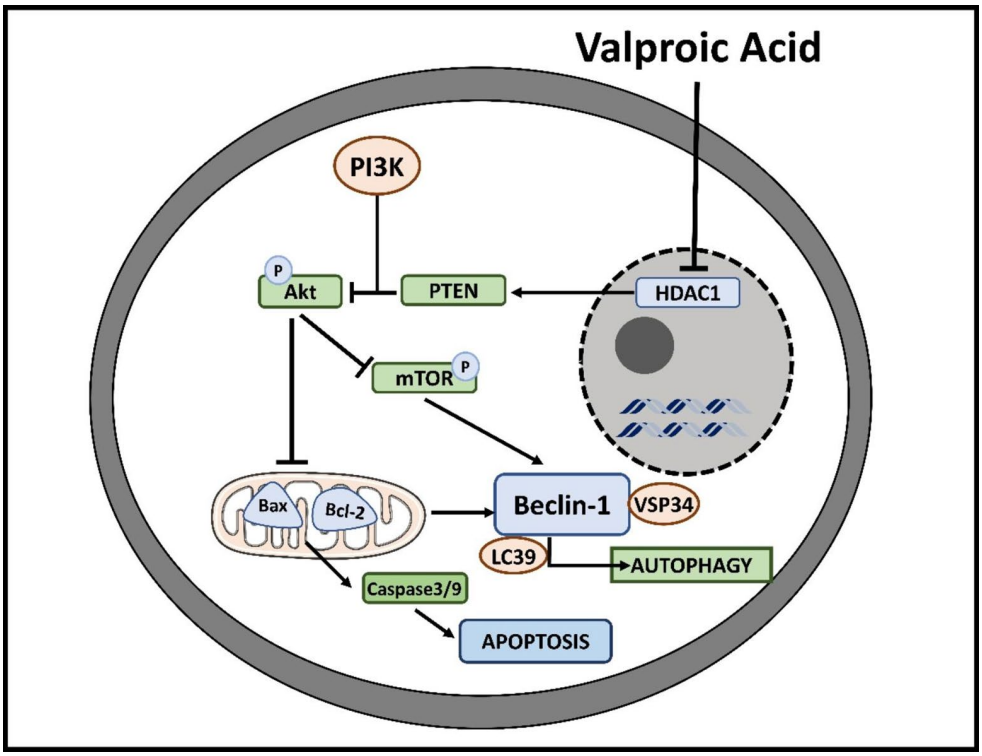


Fig. 3 Mechanism of action of valproic acid. An overview of valproic acid's mechanism blocks HDAC, which blocks the downstream PTEN/PI3K-Akt axis. This inhibition ultimately blocks mTOR and proteins Bax and Bcl-2, promoting caspase-3 and caspase9 expression and causing apoptosis and autophagy

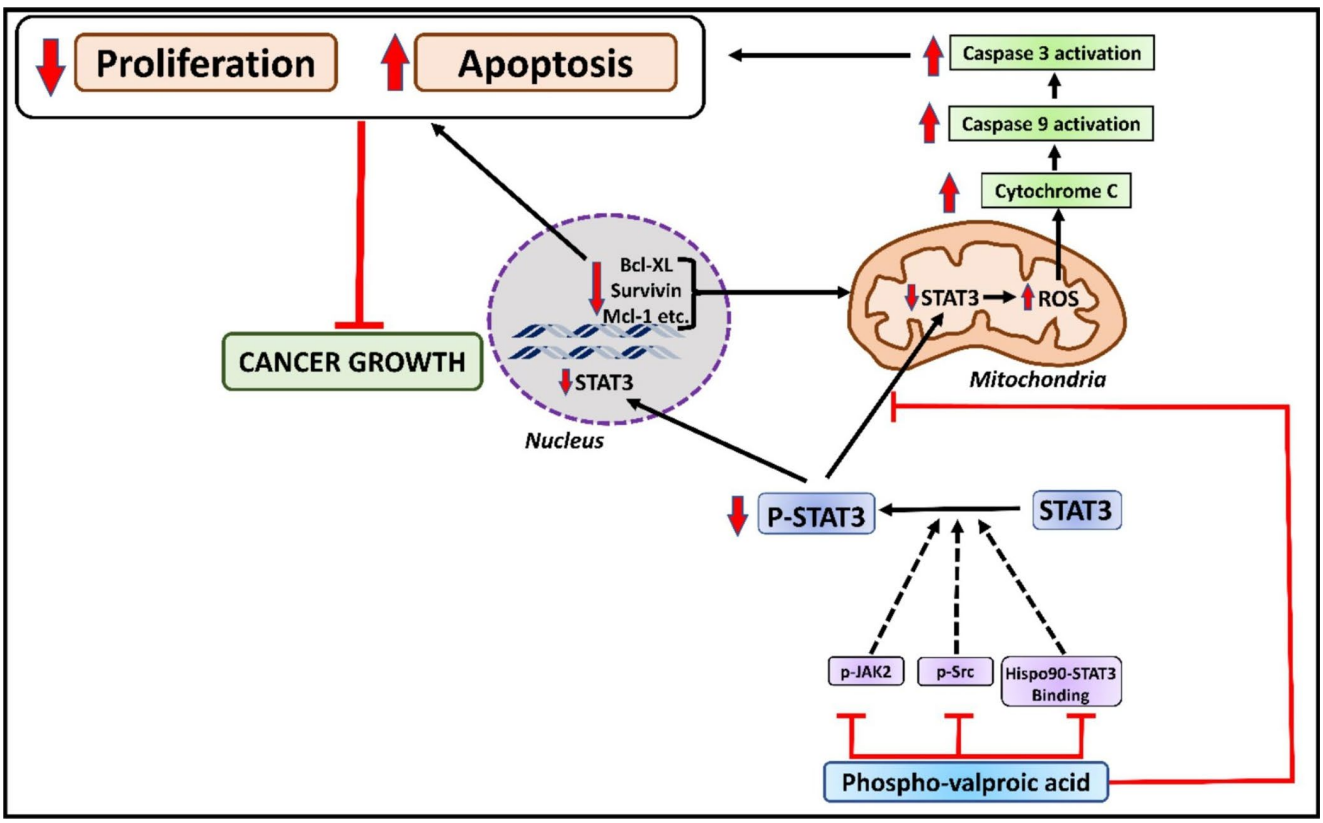


Fig. 4 Mechanism of action of Phospho-valproic acid: An overview of the mechanism of phospho-valproic acid that blocks JAK/p-SRC/Hispo-STAT3 binding, leading to inhibition of the proliferation of STAT3 and leading downregulation of STAT3 in mitochondria. The downregulation of STAT3 leads to an increase in ROS. The generation of ROS leads to the upregulation of cytochrome c and activation of caspase 9 and caspase 3, leading to apoptosis and a decrease in proliferation, causing a decrease in cancer growth

as an HDAC inhibitor at significantly high amounts (millimolar), valproic acid acts as a down regulator of peroxisome proliferator-activated receptors (PPAR), endorsing growth arrest, differentiation, and cell death in many types of genetic alterations of hemopoietic and non-hematopoietic origin, along with glioblastoma, melanoma, breast cancer, and lung cell lines, either alone or in combination with other chemotherapeutic agents (Fig. 3) [80, 81].

In recent years, randomized phase-2 studies have revealed that valproic acid and cytotoxic drugs show anticancer effects in hematological and solid malignancies. A post-hoc assessment of the pivotal EORT/NCI of Canada study on temozolomide. Chemoradiotherapy of patients with glioblastoma in 2011 revealed that including valproic acid contributed to a positive outcome when contrasted to the patient population with an enzyme-inducing antiepileptic drugs and those without antiepileptics drugs (Table 1) [82]. Reddy and colleagues released an article in 2014 describing the anticancer impact of valproic acid, whose concurrent administration appeared to increase the overall survival in patients with breast cancer who had brain metastasis treated with radiotherapy [83].

Phospho valproic acid (demonstrated in Fig. 4), a new valproic acid derivative, was identified as a powerful and effective STAT3 inhibitor (MDC-112). This agent was created using a basic methodology in which a particular chemical alteration of known drugs improves their preferred antitumor characteristics, most notably their efficacy. Phospho-valproic acid, a branched single chain fatty acid widely used as an antiepileptic drug, is being studied for its cytotoxic activity, particularly since it has been recognized as a histone HDAC inhibitor (Fig. 4). Currently, phospho-valproic acid trials yield promising outcomes for various human cancers [84]. Clinical trial findings are encouraging, particularly those that used valproic acid with cytotoxic agents. The combination of valproic acid and epirubicin was ascertained, as was FEC100 (5-fluorouracil, epirubicin, and cyclophosphamide), an accepted regimen for breast cancer patients. In 3-week rounds, participants were given increasing amounts of valproic acid (days 1–3) and epirubicin (day 3). With tolerable toxicity, sustained plasma levels of valproic acid exceeded those needed for in vitro synergy. Furthermore, valproic acid and epirubicin were found to have anticancer activity in patients with anthracycline-resistant tumors [85].

Oxcarbazepine

Oxcarbazepine is one of the commonly used antiepileptic drugs. Many preclinical studies have shown anticancer effects [86]. One of the studies has revealed that oxcarbazepine induces cell cycle arrest at the mitotic phase of the cell cycle. Some studies have shown that it inhibits the phosphorylation of PLK1, the main protein associated with the kinesin activation for the separation of the centrosome, cleavage of centrosomal protein, and separation of bipolar spindle assembly [86]. Other studies reveal that it inhibits HDAC, inhibiting the downstream PI3K-Akt-mTOR axis. This inhibition ultimately blocks cell proliferation and migration. This inhibition ultimately blocks mTOR and proteins Bax and Bcl-2, promoting caspase-3 and caspase9 expression and causing apoptosis and autophagy [87, 88]. Clinical investigations on the anticancer activity of oxcarbazepine are scarce and not intended to study this antiepileptic drug for antitumor action.

Furthermore, few investigations paired this drug with other enzyme-inducer antiepileptic drugs such as phenytoin, ethosuximide, primidone, phenobarbital, and carbamazepine. However, these findings are not promising. The previously stated national-wide putative Norwegian study, which recruited 1263 people with histopathological recommended glioblastoma between 2004 and 2010-half, of whom (526) were on antiepileptic drugs, found no promising effect on overall survival for the 6 examined antiepileptic drugs (valproic acid, n = 186 participants; carbamazepine, n = 163; levetiracetam, n = 195; oxcarbazepine, n = 82 and lamotrigine, n = 57).

Figure 5 depicts the mode of action of frequently used antiepileptic drugs like oxcarbazepine, levetiracetam, and valproic acid in patients with brain tumor cells and convulsions. As demonstrated, levetiracetam, valproic acid, and oxcarbazepine-controlled seizures and inhibited the fundamental mechanisms of cell proliferation and survival. In addition to oxcarbazepine, valproic acid, and levetiracetam, other medications of choice include lamotrigine, lacosamide, zonisamide, and perampanel. In case the monotherapy is ineffective or causes adverse drug reactions, adding lacosamide due to its interaction and safety profile in brain tumor-related epilepsies (BTREs), lamotrigine due to its good safety profile and synergism with valproic acid, or zonisamide, given its latest classification as a class A medication for focal epilepsies, could be a potential therapeutic substitute (Table 1) [79, 89].

Antitumor effects on cell lines of different tissue origin

Amid the limited preclinical studies on oxcarbazepine's potential anticancer activity, Cansu and colleagues' groundbreaking study established the apoptotic and degenerative effects of rodent ovarian and uterine cells of antiepileptic drugs [87, 88]. This intriguing finding piqued the curiosity of El Sharkawi and colleagues. They investigated the antitumor effect of oxcarbazepine on three distinct solid tumor cell lines: MCF-7 (breast cancer), HepG2 (hepatocellular

carcinoma), and HeLa (cervical cancer). In 2016, a parallel preliminary investigation aimed to identify the influence of antiepileptic drugs on the proliferation of glioblastoma cell lines (T98 G and U-87 MG) discovered that oxcarbazepine was considerably helpful in eliminating cell growth at therapeutic dosages, perhaps producing G2/M arrest and death (Fig. 5) [90].

.

Lacosamide

Lacosamide belongs to 3rd-generation antiepileptic drugs that increase the delayed inactivation of voltage-gated Na^+ channels [91]. It is regarded as an additional therapy in individuals with BTREs, capable of reducing seizure rate while causing no substantial alterations in mood or quality of life evaluations [92, 93]. The suppression of histone deacetylase is another action of lacosamide. This action may indicate that antitumor effects should be investigated. Furthermore, this mechanism has been hypothesized to explain the blockage of cell cycle migration in glioma cells, which the upregulation of miR-195-5p could cause. The same group hypothesized that by altering the transcription of other miRNAs (such as miR-107), lacosamide could decrease cellular proliferation, promote apoptotic events, and impede cell movement and invasions [94, 95]. It was demonstrated by a research group that collapsin-response-mediator-protein (CRMP2) phosphorylation (S522) was a substantial predictor of glioblastoma cellular proliferation. They used the CRMP2 phosphorylation inhibitor (S)-lacosamide to scrutinize the impact of CRMP2 phosphorylation at S522 on tumor growth and discovered that inhibiting CRMP2 phosphorylation with (S)-lacosamide reduced glioblastoma cell growth in all glioblastoma cell lines and also used showed that (S)-lacosamide inhibits glioblastoma growth in vivo models [96].

Lamotrigine

Lamotrigine is yet another sodium-blocking antiepileptic drug. It primarily blocks voltage-gated Na^+ channels, although it also blocks N-, L-, and P-type Calcium channels and, to a lesser extent, 5-HT3 receptors. Such effects decrease glutamate production and contribute to the stability of neuronal membranes. Lamotrigine, like lacosamide, is a suitable potential add-on medication for brain tumor individuals. According to the published research, it should be used with valproic acid, wherein the synergism can enhance the treatment of refractory epilepsies [63].

Brivaracetam and levetiracetam

Levetiracetam was hypothesized to alter the DNA repair protein, namely MGMT, which plays a crucial function in cancer cell resistance to cytotoxic drugs like alkylating agents [97]. Levetiracetam is reported to be the potent inhibitor of MGMT among antiepileptic drugs. A multicentre, single-arm, open-label, phase-2 study was performed in Korea, where a research group showed that the principal outcome was six-month progression-free survival (PFS), and the secondary outcome was 24-month overall survival (OS) (24mo- OS). Overall survival was characterized as the time between the date of the procedure and the date of mortality from any reason. The concluding analysis included 73 patients and found that using levetiracetam during concurrent chemoradiotherapy in patients with freshly confirmed glioblastoma may contribute to enhanced effects, but more research is needed (Table 1) [98]. In vitro, studies have also shown that levetiracetam improves the efficacy of temozolomide or other anticancer drugs [99, 100].

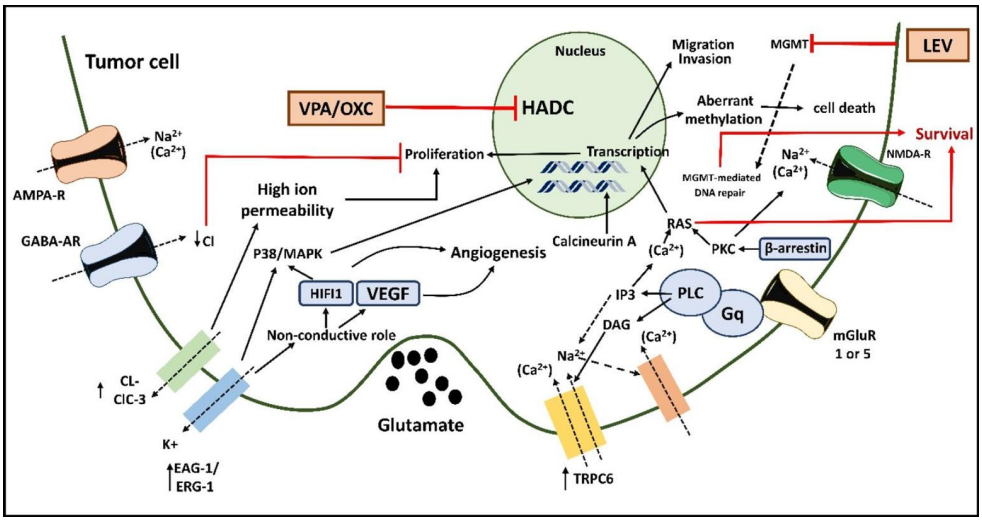


Fig. 5 Mechanism of action of antiepileptic drugs: valproic acid (VPA) and oxcarbazepine (OXC) block the HDAC proteins leading to inhibition which blocks the downstream PTEN/PI3K-Akt axis. This inhibition ultimately blocks cell proliferation and migration. The inhibition of HDAC blocks the downstream PTEN/PI3K-Akt axis. This inhibition ultimately blocks mTOR and proteins Bax and Bcl-2, promoting caspase-3 and caspase-9 expression and causing apoptosis and autophagy. Levetiracetam acts on MGMT, preventing DNA repair mechanisms and inhibiting cancer cell survival

Table 1 Summary of all repurposed drugs for cancer discussed in the review

Drug	Mechanism of action	Observation	Original indication	References
Valproic acid	1) Promotes GABAergic functioning 2) Decreases excitatory signals 3) Blocks histone deacetylase activity 4) Down-regulation of PPAR.	Growth arrest Cell differentiation Cell death	Anti-epileptic drug	[78, 79, 82, 86–88, 92, 93, 96, 97, 99, 100]
Phospho valproic acid	1) STAT inhibition 2) HDAC inhibition	↓ Proliferation ↑ Apoptosis ↑ Caspase 3	Anti-epileptic drug	
Oxcarbazepine	HDAC inhibition	↓ Cell growth Anti-proliferative Apoptosis	Anti-epileptic drug	
Lacosamide	1) ↑delayed inactivation of Na^+ channel 2) HDAC inhibition	↓ Cell growth Apoptosis	Anti-epileptic drug	
Lamotrigine	Inhibition of Na^+channel	Apoptosis Anti-proliferative	Anti-epileptic drug	
Brivaracetam and levetiracetam	MGMT inhibition	↑ OS. ↑ Cell death	Anti-epileptic drug	

Conclusions

To our understanding, this evaluation uncovers that certain anticonvulsants are beneficial in blocking tumor cell proliferation and expansion. Clinical evidence on potential antiepileptic drug influence is still limited, and numerous contributing factors have been linked to the research findings. Clinical data show unsatisfactory results in classifying anticonvulsants as antineoplastic drugs. Nevertheless, even though the necessity to construct and conduct potential clinical tests concentrated on the cytotoxic activity of antiepileptic drugs, and that can obtain a significant amount of people pre-emptively selected as per stringent and appropriate criteria for inclusion, persists to be an expansive concern, the current review provided evidence and statistics which may encourage the experimentation of novel pharmacological techniques for the cancer treatment, such as PK/PD designs and computational decision-making methods.

Author contribution Mir Aroosa: Writing – original draft; Jonaid Ahmad Malik: Conceptualization, Methodology, Software, Data curation, Writing – original draft; Sakeel Ahmed: Writing – review & editing; Onur Bender: Writing – review & editing; Nafees Ahemad: Writing – review & editing; Sirajudheen Anwar: Writing – Conceptualization, review & editing, Supervision.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Declarations

Competing interests The authors declare no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Zhang Z, Zhou L, Xie N, Nice EC, Zhang T, Cui Y, Huang C (2020) Overcoming cancer therapeutic bottleneck by drug repurposing. Signal Transduct Target Ther 2020 51:1–25. https://doi.org/10.1038/s41392-020-00213-8
2. Alamri A, Rauf A, Khalil AA, Alghamdi A, Alafnan A, Alshammari A, Alshammari F, Malik JA, Anwar S (2021) In Silico Screening of Marine Compounds as an Emerging and Promising Approach against Estrogen receptor alpha-positive breast Cancer. Biomed Res Int 2021:1–7. https://doi.org/10.1155/2021/9734279
3. Malik JA, Ahmed S, Momin SS, Shaikh S, Alafnan A, Alanazi J, Hajaj M, Almermesh S, Anwar S (2022) Drug Repurposing: a New Hope in Drug Discovery for prostate Cancer. ACS Omega. https://doi.org/10.1021/acsomega.2c05821
4. Anwar S, Malik JA, Ahmed S, Kameshwar VA, Alanazi J, Alamri A, Ahemad N (2022) Can Natural Products Targeting EMT serve as the future Anticancer therapeutics? Mol 2022 27:7668. https://doi.org/10.3390/MOLECULES27227668
5. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R et al (2022) PD-1 blockade in Mismatch Repair-Deficient, locally advanced rectal Cancer. N Engl J Med 1–14. https://doi.org/10.1056/NEJMoa2201445
6. Juárez-López D, Schcolnik-Cabrera A (2021) Drug Repurposing: considerations to surpass while re-directing Old Compounds for New Treatments. Arch Med Res 52:243–251. https://doi.org/10.1016/j.arcmed.2020.10.021

7. Kurzrock R, Kantarjian HM, Kesselheim AS, Sigal EV (2020) New drug approvals in oncology. Nat Rev Clin Oncol 17:140–146. https://doi.org/10.1038/s41571-019-0313-2
8. Pantziarka P (2017) Scientific advice-is drug repurposing missing a trick? Nat Rev Clin Oncol 14:455–456. https://doi.org/10.1038/nrclinonc.2017.69
9. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C et al (2018) Drug repurposing: Progress, challenges and recommendations. Nat Rev Drug Discov 18:41–58. https://doi.org/10.1038/nrd.2018.168
10. Bertolini F, Sukhatme VP, Bouche G (2015) Drug repurposing in oncology-patient and health systems opportunities. Nat Rev Clin Oncol 12:732–742. https://doi.org/10.1038/nrclinonc.2015.169
11. Nosengo N (2016) Can you teach old drugs new tricks? Nature 534:314–316. https://doi.org/10.1038/534314a
12. De Lellis L, Veschi S, Tinari N, Mokini Z, Carradori S, Brocco D, Florio R, Grassadonia A, Cama A (2021) Drug repurposing, an attractive strategy in pancreatic cancer treatment: preclinical and clinical updates. Cancers (Basel) 13:1–39. https://doi.org/10.3390/cancers13163946
13. Aggarwal S, Verma SS, Aggarwal S, Gupta SC (2021) Drug repurposing for breast cancer therapy: old weapon for new battle. Semin Cancer Biol 68:8–20. https://doi.org/10.1016/J.SEMCANCER.2019.09.012
14. Thilakasiri PS, Dmello RS, Nero TL, Parker MW, Ernst M, Chand AL (2021) *Repurposing of drugs as STAT3 inhibitors for cancer therapy*; Elsevier Ltd, ; Vol. 68; ISBN 0000016861
15. Lu C, Li X, Ren Y, Zhang X (2021) Disulfiram: a novel repurposed drug for cancer therapy. Cancer Chemother Pharmacol 87:159–172. https://doi.org/10.1007/s00280-020-04216-8
16. Huang A, Garraway LA, Ashworth A, Weber B (2020) Synthetic lethality as an engine for cancer drug target discovery. Nat Rev Drug Discov 19:23–38. https://doi.org/10.1038/s41573-019-0046-z
17. Swinney DC (2013) Phenotypic vs. target-based drug discovery for first-in-class medicines. Clin Pharmacol Ther 93:299–301
18. Dallavalle S, Dobričić V, Lazzarato L, Gazzano E, Machuqueiro M, Pajeva I, Tsakovska I, Zidar N, Fruttero R (2020) Improvement of conventional anti-cancer drugs as new tools against multidrug resistant tumors. Drug Resist Updat 50. https://doi.org/10.1016/j.drup.2020.100682
19. Patel MN, Halling-Brown MD, Tym JE, Workman P, Al-Lazikani B (2013) Objective assessment of cancer genes for drug discovery. Nat Rev Drug Discov 12:35–50. https://doi.org/10.1038/nrd3913
20. Nowak-Sliwinska P, Scapozza L, Altaba AR (2019) Drug repurposing in oncology: compounds, pathways, phenotypes and computational approaches for colorectal cancer. Biochim Biophys Acta - Rev Cancer 1871:434–454. https://doi.org/10.1016/j.bbcan.2019.04.005
21. Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, Molinski SV (2017) Giving drugs a second chance: overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. Front Oncol 7:1–8. https://doi.org/10.3389/fonc.2017.00273
22. Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 4:682–690. https://doi.org/10.1038/nchembio.118
23. Shinde SS, Ahmed S, Malik JA, Hani U, Khanam A, Ashraf Bhat F, Ahmad Mir S, Ghazwani M, Wahab S, Haider N et al (2023) Therapeutic Delivery of Tumor Suppressor miRNAs for Breast Cancer Treatment. *Biol* Vol. 12, Page 467 2023, *12*, 467, https://doi.org/10.3390/BIOLOGY12030467
24. Bender O, Shoman ME, Ali TFS, Dogan R, Celik I, Mollica A, Hamed MIA, Aly OM, Alamri A, Alanazi J et al (2023) Discovery of oxindole-based FLT3 inhibitors as a promising therapeutic lead for acute myeloid leukemia carrying the oncogenic ITD mutation. Arch Pharm (Weinheim) 356:2200407. https://doi.org/10.1002/ARDP.202200407
25. Malik JA, Ahmed S, Jan B, Bender O, Al Hagbani T, Alqarni A, Anwar S Drugs repurposed: an advanced step towards the treatment of breast cancer and associated challenges. Biomed Pharmacother *145*, 112375, https://doi.org/10.1016/J.BIOPHA.2021.112375
26. Vasan N, Baselga J, Hyman DM (2019) A view on drug resistance in cancer. Nature 575:299–309. https://doi.org/10.1038/s41586-019-1730-1
27. Sternberg CN, De Mulder PHM, Schornagel JH, Théodore C, Fossa SD, Van Oosterom AT, Witjes F, Spina M, Van Groeningen CJ, De Balincourt C et al (2001) Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: european organ. J Clin Oncol 19:2638–2646. https://doi.org/10.1200/JCO.2001.19.10.2638
28. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, Davidson NE, Martino S, Livingston R, Ingle JN et al (2003) Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and leukemia. J Clin Oncol 21:1431–1439. https://doi.org/10.1200/JCO.2003.09.081
29. Hanahan D, Weinberg RA (2011) Hallmarks of Cancer: the Next Generation. Cell 144:646–674. https://doi.org/10.1016/J.CELL.2011.02.013
30. Ribas A, Wolchok JD (2018) Cancer immunotherapy using checkpoint blockade. Sci (80-) 359:1350–1355. https://doi.org/10.1126/science.aar4060
31. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc. Natl. Acad. Sci. U. S. A. 99*, 12293–12297, https://doi.org/10.1073/pnas.192461099
32. Gollnick SO, Brackett CM (2010) Enhancement of antitumor immunity by photodynamic therapy. Immunol Res 46:216–226. https://doi.org/10.1007/s12026-009-8119-4
33. Stucchi G, Battevi N, Cairoli S, Consonni D (2016) The prevalence of musculoskeletal disorders in the retail sector: an italian cross sectional study on 3380 workers. Med Lav 107:251–262
34. Chidambaram M, Manavalan R, Kathiresan K (2011) Nanotherapeutics to overcome conventional cancer chemotherapy limitations. J Pharm Pharm Sci a Publ Can Soc Pharm Sci Soc Can des Sci Pharm 14:67–77. https://doi.org/10.18433/j30c7d
35. Bikiaris D, Papageorgiou G, Stergiou A, acta EP-T (2005) ; undefined Physicochemical studies on solid dispersions of poorly water-soluble drugs: evaluation of capabilities and limitations of thermal analysis techniques. *Elsevier*
36. Gote V, Nookala AR, Bolla PK, Pal D (2021) Drug resistance in metastatic breast cancer: Tumor targeted nanomedicine to the rescue. Int J Mol Sci 22. https://doi.org/10.3390/ijms22094673
37. Seelig AP-Glycoprotein (2020) One mechanism, many tasks and the Consequences for Pharmacotherapy of Cancers. Front Oncol 10:1–16
38. Wang J, Seebacher N, Shi H, Kan Q, Duan Z (2017) Novel strategies to prevent the development of multidrug resistance (MDR) in cancer. Oncotarget 8:84559–84571. https://doi.org/10.18632/oncotarget.19187
39. Bukowski K, Kciuk M, Kontek R (2020) Mechanisms of multidrug resistance in cancer chemotherapy. Int J Mol Sci 21. https://doi.org/10.3390/ijms21093233

40. Chen Z, Shi T, Zhang L, Zhu P, Deng M, Huang C, Hu T, Jiang L, Li J (2016) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: a review of the past decade. Cancer Lett 370:153–164. https://doi.org/10.1016/j.canlet.2015.10.010
41. Dantzig AH, De Alwis DP, Burgess M (2003) Considerations in the design and development of transport inhibitors as adjuncts to drug therapy. Adv Drug Deliv Rev 55:133–150. https://doi.org/10.1016/S0169-409X(02)00175-8
42. Palmeira A, Sousa E, Vasconcelos H, Pinto MM (2012) Three decades of P-gp inhibitors: skimming through several generations and scaffolds. Curr Med Chem 19:1946–2025. https://doi.org/10.2174/092986712800167392
43. Nikolaou M, Pavlopoulou A, Georgakilas AG, Kyrodimos E (2018) The challenge of drug resistance in cancer treatment: a current overview. Clin Exp Metastasis 35:309–318. https://doi.org/10.1007/s10585-018-9903-0
44. Robey RW, Polgar O, Deeken J, To KW, Bates SE (2007) ABCG2: determining its relevance in clinical drug resistance. Cancer Metastasis Rev 26:39–57. https://doi.org/10.1007/s10555-007-9042-6
45. Gottesman MM, Fojo T, Bates SE (2002) Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2:48–58. https://doi.org/10.1038/nrc706
46. Cole SPC, Bhardwaj G, Gerlach JH, Mackie JE, Grant CE, Almquist KC, Stewart AJ, Kurz EU, Duncan AMV, Deeley RG (1992) Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. Sci (80-) 258:1650–1654. https://doi.org/10.1126/science.1360704
47. Sodani K, Patel A, Kathawala RJ, Chen ZS (2012) Multidrug resistance associated proteins in multindrung resistance. Chin J Cancer 31:58–72. https://doi.org/10.5732/cjc.011.10329
48. Haider T, Pandey V, Banjare N, Gupta PN, Soni V (2020) Drug resistance in cancer: mechanisms and tackling strategies. Pharmacol Rep 72:1125–1151. https://doi.org/10.1007/s43440-020-00138-7
49. Sun Y (2016) Tumor microenvironment and cancer therapy resistance. Cancer Lett 380:205–215. https://doi.org/10.1016/j.canlet.2015.07.044
50. Sharma A, Arambula JF, Koo S, Kumar R, Singh H, Sessler JL, Kim JS (2019) Hypoxia-targeted drug delivery. Chem Soc Rev 48:771–813. https://doi.org/10.1039/c8cs00304a
51. Kwak EL, Ahronian LG, Siravegna G, Mussolin B, Godfrey JT, Clark JW, Blaszkowsky LS, Ryan DP, Lennerz JK, John Iafrate A et al (2015) Molecular heterogeneity and receptor coamplification drive resistance to targeted therapy in MET-Amplified esophagogastric cancer. Cancer Discov 5:1271–1281. https://doi.org/10.1158/2159-8290.CD-15-0748
52. Zhao BX, Wang J, Song B, Wei H, Lv WP, Tian LM, Li M, Lv S (2015) Establishment and biological characteristics of acquired gefitinib resistance in cell line NCI-H1975/gefinitib-resistant with epidermal growth factor receptor T790M mutation. Mol Med Rep 11:2767–2774. https://doi.org/10.3892/mmr.2014.3058
53. Makena MR, Ranjan A, Thirumala V, Reddy AP (2020) Cancer stem cells: Road to therapeutic resistance and strategies to overcome resistance. Biochim Biophys Acta - Mol Basis Dis 1866:pagerange. https://doi.org/10.1016/j.bbadis.2018.11.015
54. Chandrasekhar C, Kumar PS, Sarma PVGK (2019) Novel mutations in the kinase domain of BCR-ABL gene causing imatinib resistance in chronic myeloid leukemia patients. Sci Rep 9:1–17. https://doi.org/10.1038/s41598-019-38672-x
55. Greenfield G, McMullan R, Robson N, McGimpsey J, Catherwood M, McMullin MF (2019) Response to Imatinib therapy is inferior for e13a2 BCR-ABL1 transcript type in comparison to e14a2 transcript type in chronic myeloid leukaemia. BMC Hematol 19:1–9. https://doi.org/10.1186/s12878-019-0139-2
56. Lara LI, Fenner S, Ratcliffe S, Isidro-Llobet A, Hann M, Bax B, Osheroff N (2018) Coupling the core of the anticancer drug etoposide to an oligonucleotide induces topoisomerase II-mediated cleavage at specific DNA sequences. Nucleic Acids Res 46:2218–2233. https://doi.org/10.1093/nar/gky072
57. Kanwal R, Gupta S (2012) Epigenetic modifications in cancer. Clin Genet 81:303–311. https://doi.org/10.1111/j.1399-0004.2011.01809.x
58. Mohammad HP, Barbash O, Creasy CL (2019) Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Nat Med 25:403–418. https://doi.org/10.1038/s41591-019-0376-8
59. Bouwman P, Jonkers J (2012) The effects of deregulated DNA damage signalling on cancer chemotherapy response and resistance. Nat Rev Cancer 12:587–598. https://doi.org/10.1038/nrc3342
60. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. Nat Rev Cancer 13:714–726. https://doi.org/10.1038/nrc3599
61. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867. https://doi.org/10.1038/nature01322
62. Biber K, Neumann H, Inoue K, Boddeke HWGM (2007) Neuronal "On" and "Off" signals control microglia. Trends Neurosci 30:596–602. https://doi.org/10.1016/j.tins.2007.08.007
63. Cucchiara F, Pasqualetti F, Giorgi FS, Danesi R, Bocci G (2020) Epileptogenesis and oncogenesis: an antineoplastic role for antiepileptic drugs in brain tumours? Pharmacol Res 156:104786. https://doi.org/10.1016/j.phrs.2020.104786
64. Stepulak A, Rola R, Polberg K, Ikonomidou C (2014) Glutamate and its receptors in cancer. J Neural Transm 121:933–944. https://doi.org/10.1007/s00702-014-1182-6
65. Teh J, Chen S (2012) Metabotropic glutamate receptors and cancerous growth. Wiley Interdiscip Rev Membr Transp Signal 1:211–220. https://doi.org/10.1002/wmts.21
66. Young SZ, Bordey A (2009) GABA's control of stem and cancer cell proliferation in adult neural and peripheral niches. Physiology 24:171–185. https://doi.org/10.1152/physiol.00002.2009
67. Jussofie A, Reinhardt V, Kalff R (1994) GABA binding sites: their density, their affinity to muscimol and their behaviour against neuroactive steroids in human gliomas of different degrees of malignancy. J Neural Transm 96:233–241. https://doi.org/10.1007/BF01294790
68. Neman J, Termini J, Wilczynski S, Vaidehi N, Choy C, Kowolik CM, Li H, Hambrecht AC, Roberts E, Jandial R (2014) Human breast cancer metastases to the brain display GABAergic properties in the neural niche. *Proc. Natl. Acad. Sci. U. S. A. 111*, 984–989, https://doi.org/10.1073/pnas.1322098111
69. Ludewig F, Hüser A, Fromm H, Beauclair L, Bouché N (2008) Mutants of GABA transaminase (POP2) suppress the severe phenotype of succinic semialdehyde dehydrogenase (ssadh) mutants in arabidopsis. PLoS ONE 3. https://doi.org/10.1371/journal.pone.0003383
70. Klumpp L, Sezgin EC, Eckert F, Huber SM (2016) Ion channels in brain metastasis. Int J Mol Sci 17:1–14. https://doi.org/10.3390/ijms17091513
71. Molenaar RJ (2011) Ion Channels in Glioblastoma. *ISRN Neurol. 2011*, 1–7, https://doi.org/10.5402/2011/590249
72. Becchetti A (2011) Ion channels and transporters in cancer. 1. Ion channels and cell proliferationin cancer. Am J Physiol - Cell Physiol 301. https://doi.org/10.1152/ajpcell.00047.2011
73. Kunzelmann K (2005) Ion channels and cancer. J Membr Biol 205:159–173. https://doi.org/10.1007/s00232-005-0781-4
74. Watkins S, Sontheimer H (2012) Unique biology of gliomas: Challenges and opportunities. Trends Neurosci 35:546–556. https://doi.org/10.1016/j.tins.2012.05.001

75. Li X, 乳鼠心肌提取 HHS, Access P (2016) Physiol Behav 176:139–148. https://doi.org/10.1038/s41577-018-0051-1. Interplay
76. Vecht CJ, Kerkhof M, Duran-Pena A (2014) Seizure Prognosis in Brain Tumors: New Insights and Evidence-Based Management. *Oncologist 19*, 751–759, https://doi.org/10.1634/theoncologist.2014-0060
77. Gefroh-Grimes HA, Gidal BE (2016) Antiepileptic drugs in patients with malignant brain tumor: beyond seizures and pharmacokinetics. Acta Neurol Scand 133:4–16. https://doi.org/10.1111/ane.12437
78. Duenas-Gonzalez A, Candelaria M, Perez-Plascencia C, Perez-Cardenas E, de la Cruz-Hernandez E, Herrera LA (2008) Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors. Cancer Treat Rev 34:206–222. https://doi.org/10.1016/j.ctrv.2007.11.003
79. Englot DJ, Chang EF, Vecht CJ (2016) *Epilepsy and brain tumors*; 1st ed.; Elsevier B.V., ; Vol. 134; ISBN 9780128029978
80. Göttlicher M, Minucci S, Zhu P, Krämer OH, Schimpf A, Giavara S, Sleeman JP, Lo Coco F, Nervi C, Pelicci PG et al (2001) Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J 20:6969–6978. https://doi.org/10.1093/emboj/20.24.6969
81. Kuendgen A, Gattermann N (2007) Valproic acid for the treatment of myeloid malignancies. Cancer 110:943–954. https://doi.org/10.1002/cncr.22891
82. Corsetti MT, Salvi F, Perticone S, Baraldi A, De Paoli L, Gatto S, Pietrasanta D, Pini M, Primon V, Zallio F et al (2011) Hematologic improvement and response in elderly AML/RAEB patients treated with valproic acid and low-dose Ara-C. Leuk Res 35:991–997. https://doi.org/10.1016/j.leukres.2011.02.021
83. Reddy JP, Dawood S, Mitchell M, Debeb BG, Bloom E, Gonzalez-Angulo AM, Sulman EP, Buchholz TA, Woodward WA (2015) Antiepileptic drug use improves overall survival in breast cancer patients with brain metastases in the setting of whole brain radiotherapy. Radiother Oncol 117:308–314. https://doi.org/10.1016/j.radonc.2015.10.009
84. Mackenzie GG, Huang L, Alston N, Ouyang N, Vrankova K, Mattheolabakis G, Constantinides PP, Rigas B (2013) Targeting mitochondrial STAT3 with the Novel Phospho-Valproic acid (MDC-1112) inhibits pancreatic Cancer growth in mice. PLoS ONE 8. https://doi.org/10.1371/journal.pone.0061532
85. Wawruszak A, Halasa M, Okon E, Kukula-Koch W, Stepulak A (2021) Valproic acid and breast cancer: state of the art in 2021. Cancers (Basel) 13:1–23. https://doi.org/10.3390/cancers13143409
86. Ota M, Funakoshi T, Aki T, Unuma K, Uemura K (2021) Oxcarbazepine induces mitotic catastrophe and apoptosis in NRK-52E proximal tubular cells. Toxicol Lett 350:240–248. https://doi.org/10.1016/J.TOXLET.2021.07.018
87. El Sharkawi FZ, El Shemy HA, Khaled HM (2014) Possible anticancer activity of rosuvastatine, doxazosin, repaglinide and oxcarbazepin. Asian Pac J Cancer Prev 15:199–203. https://doi.org/10.7314/APJCP.2014.15.1.199
88. Cansu A, Ekinci Ö, Serdaroglu A, Gürgen SG, Ekinci Ö, Erdogan D, Coskun ZK, Tunc L (2011) Effects of chronic treatment with valproate and oxcarbazepine on testicular development in rats. Seizure 20:203–207. https://doi.org/10.1016/j.seizure.2010.11.019
89. Maschio M, Dinapoli L, Zarabla A, Maialetti A, Giannarelli D, Fabi A, Vidiri A, Cantelmi T (2017) Zonisamide in brain tumor-related epilepsy: an observational pilot study. Clin Neuropharmacol 40:113–119. https://doi.org/10.1097/WNF.0000000000000218
90. Lee CY, Lai HY, Chiu A, Chan SH, Hsiao LP, Lee ST (2016) The effects of antiepileptic drugs on the growth of glioblastoma cell lines. J Neurooncol 127:445–453. https://doi.org/10.1007/s11060-016-2056-6
91. Errington AC, Stöhr T, Heers C, Lees G (2008) The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. Mol Pharmacol 73:157–169. https://doi.org/10.1124/mol.107.039867
92. Saria MG, Corle C, Hu J, Rudnick JD, Phuphanich S, Mrugala MM, Crew LK, Bota DA, Fu BD, Kim RY et al (2013) Retrospective analysis of the tolerability and activity of lacosamide in patients with brain tumors. J Neurosurg 118:1183–1187. https://doi.org/10.3171/2013.1.JNS12397
93. Maschio M, Zarabla A, Maialetti A, Fabi A, Vidiri A, Villani V, Giannarelli D (2017) Quality of life, mood and seizure control in patients with brain tumor related epilepsy treated with lacosamide as add-on therapy: a prospective explorative study with a historical control group. Epilepsy Behav 73:83–89. https://doi.org/10.1016/j.yebeh.2017.05.031
94. Bang SR, Ambavade SD, Jagdale PG, Adkar PP, Waghmare AB, Ambavade PD (2015) Lacosamide reduces HDAC levels in the brain and improves memory: potential for treatment of Alzheimer's disease. Pharmacol Biochem Behav 134:65–69. https://doi.org/10.1016/j.pbb.2015.04.011
95. Li M, Li J, Liu L, Li W, Yang Y, Yuan J (2013) MicroRNA in human glioma. Cancers (Basel) 5:1306–1331. https://doi.org/10.3390/cancers5041306
96. Moutal A, Villa LS, Yeon SK, Householder KT, Park KD, Sirianni RW, Khanna R (2018) CRMP2 phosphorylation drives Glioblastoma Cell Proliferation. Mol Neurobiol 55:4403–4416. https://doi.org/10.1007/s12035-017-0653-9
97. Rizzo A, Donzelli S, Girgenti V, Sacconi A, Vasco C, Salmaggi A, Blandino G, Maschio M, Ciusani E (2017) In vitro antineoplastic effects of brivaracetam and lacosamide on human glioma cells. J Exp Clin Cancer Res 36:1–13. https://doi.org/10.1186/S13046-017-0546-9/FIGURES/6
98. Hwang K, Kim J, Kang SG, Jung TY, Kim JH, Kim SH, Kang SH, Hong YK, Kim TM, Kim YJ et al (2022) Levetiracetam as a sensitizer of concurrent chemoradiotherapy in newly diagnosed glioblastoma: an open-label phase 2 study. Cancer Med 11:371–379. https://doi.org/10.1002/cam4.4454
99. Scicchitano BM, Sorrentino S, Proietti G, Lama G, Dobrowolny G, Catizone A, Binda E, Larocca LM, Sica G (2018) Levetiracetam enhances the temozolomide effect on glioblastoma stem cell proliferation and apoptosis. Cancer Cell Int 18:1–18. https://doi.org/10.1186/s12935-018-0626-8
100. Manchon JFM, Dabaghian Y, Uzor NE, Kesler SR, Wefel JS, Tsvetkov AS (2016) Levetiracetam mitigates doxorubicin-induced DNA and synaptic damage in neurons. Sci Rep 6:1–12. https://doi.org/10.1038/srep25705

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Authors and Affiliations

Mir Aroosa[1] · Jonaid Ahmad Malik[2,3] · Sakeel Ahmed[4] · Onur Bender[5] · Nafees Ahemad[6] · Sirajudheen Anwar[7]

✉ Nafees Ahemad
nafees.Ahemad@monash.edu

✉ Sirajudheen Anwar
si.anwar@uoh.edu.sa

[1] Department of Pharmacology, Jamia Hamdard, New Delhi, India

[2] Department of Biomedical Engineering, Indian Institute of Technology Ropar, Rupnagar, Punjab, India

[3] Department of Biomedical Engineering, Indian Institute of Technology (IIT), Ropar, Ropar, India

[4] Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India

[5] Biotechnology Institute, Ankara University, Ankara, Turkey

[6] School of Pharmacy, Monash University Malaysia, Jalan lagoon selatan, Petaling Jaya, Selangor, DE, Malaysia

[7] Department of Pharmacology and Toxicology, College of Pharmacy, University of Hail, Hail, Saudi Arabia