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Review

Cytotoxic agents for electrochemotherapy: Efficacy, mechanisms of action, potential candidates

Arnoldas Morozas [a,1], Veronika Malyško-Ptašinskė [b,c,*,1], Aušra Nemeikaitė-Čėnienė [b], Julita Kulbacka [b,e], Nina Rembiałkowska [e], Justinas Ivaška [a,d], Vitalij Novickij [b,c,*]

[a] Departament of Personalized Medicine, State Research Institute Centre of Innovative Medicine, Vilnius, Lithuania
[b] Department of Immunology and Bioelectrochemistry, State Research Institute Centre of Innovative Medicine, Vilnius, Lithuania
[c] Faculty of Electronics, Vilnius Gediminas Technical University, Vilnius, Lithuania
[d] Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[e] Department of Molecular and Cellular Biology, Faculty of Pharmacy, Wroclaw Medical University, Wroclaw, Poland

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ABSTRACT

Electrochemotherapy (ECT) is a popular clinical anticancer treatment modality that combines chemotherapy with electroporation to enhance drug uptake by tumor cells. One of its key advantages is the ability to use significantly reduced drug concentrations, thereby, minimizing cytotoxic effects on healthy cells and thus, side-effects of the therapy when compared to conventional chemotherapy. The therapeutic efficacy of ECT depends upon two main components: pulsed electric field (PEF) parameters and physiochemical properties of anticancer agents, including their molecular structure, mechanism of action, and tumor specificity. This review provides the comprehensive survey of cytotoxic compounds that are either currently used or are under investigation for ECT-compatibility. Bleomycin and cisplatin are most established drugs in this context, however, other compound such as mitomycin C, doxorubicin, or calcium have showed encouraging outcomes in preclinical and clinical studies. We have further analyzed the cytotoxic profiles, mechanisms of action, and therapeutic outcomes of various agents, compatibility with pulsed electric field protocols based on data of clinical trials, *in vivo* and *in vitro* models. Furthermore, we discuss and summarize other potential cytotoxic agent candidates, which have not been yet tested in ECT context, which include chemotherapeutics and natural compounds categorized by their cytotoxic potential and synergy with electroporation.

1. Introduction

Cancer remains one of the leading causes of morbidity worldwide, posing significant challenges to effective treatment [1]. Despite extensive efforts to treat advanced cancers using diverse cytotoxic agents and dosage regimens, significant improvements in treatment outcomes for most cancer types have been limited over the past decade [2]. Notable exceptions include chemotherapeutic successes such as vinca alkaloids in acute juvenile leukemia, platinum-based therapies in testicular cancer, and cytotoxic drugs in gestational choriocarcinoma and Hodgkin disease [3–6]. Unfortunately, this has not been the case for the majority of other advanced solid cancers, which affect a significant amount of the population. Each year, there are 19.3 million new cases of cancer worldwide and almost 10.0 million deaths [7]. By 2050, annual cancer cases are expected to nearly double, increasing from 20 million to over 35 million [8].

Another critical obstacle in cancer treatment is the development of multidrug resistance (MDR), a phenomenon wherein cancer cells adapt to evade the cytotoxic effects of multiple chemotherapeutic agents through mechanisms such as increased drug efflux, enhanced DNA repair or altered drug targets. Addressing MDR has become a key priority in cancer research, with efforts focused on devising innovative therapeutic strategies to overcome the complex and dynamic mechanisms driving resistance, both from the onset of treatment and as the disease evolves [9]. One possible solution for MDR is electrochemotherapy (ECT), which combines electroporation (EP) with chemotherapeutic agents. ECT enhances effects of various drugs while enabling the use of lower dosages, thereby minimizing the adverse

* Correspondence to: Vilnius Gediminas Technical University, Plytinės str. 25, Vilnius LT-10105, Lithuania.
E-mail addresses: veronika.malysko-ptasinske@vilniustech.lt (V. Malyško-Ptašinskė), vitalij.novickij@vilniustech.lt (V. Novickij).
[1] authors contributed equally to this work

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effects [10]. It can also be used for patients who previously received chemotherapy in drug-resistant cases [11].

Anticancer agents play an important role in the success of ECT, however, the flexibility in terms of drugs that are used for ECT is quite low. According to Clarivate Analytics Web of Science, the most commonly used cytotoxic agents in papers focusing on ECT include bleomycin, cisplatin and more recently calcium (Fig. 1).

The limited array of used anticancer compounds for ECT could be influenced by several factors related to the specifics of the procedure. Firstly, ECT is based on electroporation, therefore, due to application of pulsed electric fields transient pores are formed in the cell plasma membrane[13], which allow targeted intracellular delivery of drugs [14]. The electroporation-induced pores are hydrophilic and their size varies based on the used pulse amplitude/duration, which implies that the molecular delivery is highly dependent on the passive diffusion following pulse application[15]. As a result, in order to induce the synergistic effect (i.e., successful ECT) the drug molecular size should be big enough to prevent effective passive diffusion [16,17], however, when pores are formed it should be capable of entering the cell – basically the cell plasma membrane should be the major barrier preventing drug lethality[18]. Bleomycin (BLM) is one of such drugs, i.e., at low concentrations the drug is nontoxic (limited diffusion), however, when membrane is permeabilized bleomycin cytotoxicity increases by more than 3 orders of magnitude, which made the drug the golden standard for ECT [19]. Cisplatin (CP) is another popular drug for ECT [20], however, it's smaller in size and its' effectiveness potentiation by ECT is significantly lower when compared to bleomycin. Nevertheless, both drugs are successfully used in clinics and the European Standard Operating Procedures for Electrochemotherapy (ESOPE) are based on these two compounds.

Recently, another modality of ECT has appeared – known as calcium electroporation [21,22]. Opposite to bleomycin and cisplatin, the method relies on natural cellular mechanisms involving calcium as a universal messenger and destabilization of the cellular homeostasis by delivering high concentrations of calcium inside the cells. As a result, the cells experience extensive ATP depletion and are unable to return to the homeostatic state – die [23]. Careful selection of the most suitable chemotherapeutic agent is essential, as different cancers exhibit distinct

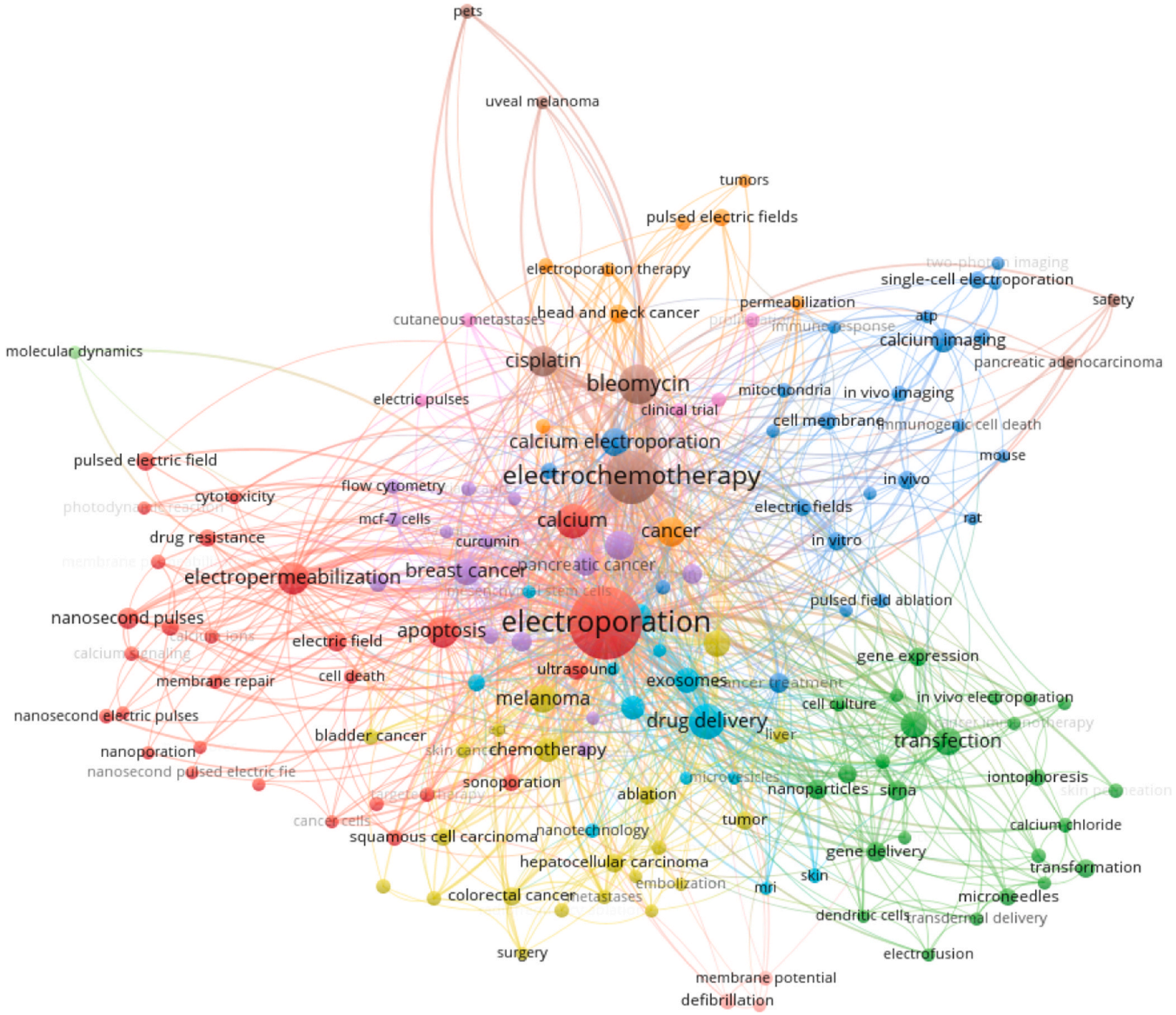

Fig. 1. Most common keywords used in electrochemotherapy studies according to Clarivate Analytics Web of Science. Visualized using VOS viewer software [12], version 1.6.18 (Leiden University). A filter of at least 5 minimum occurrences of the keywords has been used. Larger circle size indicates higher rate of occurrence of a specific keyword.

sensitivities to drugs. Simultaneously, the electric field parameters, such as intensity and duration, must be contemplated and optimized to achieve maximal therapeutic outcomes while minimizing damage to surrounding tissues [24].

This work aims to review electroporation and electrochemotherapy and to evaluate existing and potential chemotherapeutic agents and compounds for use with electroporation across different cancer types. The goal is to highlight the newest therapeutic strategies that may enhance the efficacy of ECT and identify potential candidates to be used as cytotoxic agents.

2. Electroporation, its application, and mechanism of action

The effect of electric fields on cell permeability was first observed in 1957, and the idea of employing electric fields to modify cell membranes has existed since then [25]. Electroporation occurs due to cell membrane polarization and when the threshold cell's membrane potential is exceeded lipid reorientation results in the formation of hydrophilic pores. The efficacy of electroporation is highly dependent on the parameters of the pulsed electric field, particularly the electric field strength and duration, as illustrated in Fig. 2. The ESOPE pulses rely on a sequence of 100 μs x 8 pulses, therefore, the amplitude of the pulse determines the nature of induced electroporation (reversible or irreversible).

Lower-dose PEF (below 600–700 V/cm) does not trigger significant effect on biological tissues with ESOPE pulses, due to insufficient polarization of cell membrane (the critical transmembrane potential is not reached). Increasing the amplitude to 800–1500 V/cm results in reversible electroporation (RE), which is applicable for ECT or gene transfer. As mentioned above, the phenomenon of RE enables intracellular delivery of various hydrophilic compounds that are usually too large to pass the cell membrane passively [26]. Further, an increase of PEF amplitude triggers irreversible electroporation (IRE), which damages the cell membrane severely and the cells are not able to recover. The technology is highly utilized as an ablation technique, and thus does not depend on drugs.

This review focuses the ECT methodology (i.e., reversible electroporation) based on ESOPE protocols, which were initially published in 2006 [27] and updated in 2018 [28]. According to ESOPE, the pulses are administered immediately or within a few minutes following the drug injection, enhancing uptake into the targeted cells [29]. ECT enables the possibility of employing medications with reduced concentrations, which minimizes negative effects like systemic toxicity and damage to healthy tissues [30],[31]. Initially, ECT was used mostly for cutaneous and subcutaneous metastasis and primary skin tumors [32–34]. Over time, its use expanded to include tumors in the oral cavity, oropharynx, and other mucosal regions [35–39]. Subsequently, the application was extended to include deep-seated tumors [40–42]. Moreover, ECT has been proven to be effective when standard treatment options are exhausted or cannot be applied [43–52]. In addition, beyond its direct cytotoxic effects on tumor cells, electrochemotherapy has been shown to engage indirect mechanisms, including immunological activation [53, 54] and vascular disruption [55,56]. Nowadays, ECT is established as one of the tools for the management of late-stage tumors or inoperable cases. Fig. 3 summarizes the effects of electrochemotherapy.

As it was mentioned above, unlike RE, which temporarily opens cell membranes to facilitate drug delivery, IRE targets cells directly, providing a non-thermal ablation method without the introduction of chemotherapeutic drugs. Due to its advantages — non-thermal and highly precise ablation that spares surrounding critical structures, the feasibility of targeting tumors located in anatomically challenging regions - IRE is being used in treating colorectal cancer, pancreatic cancer,

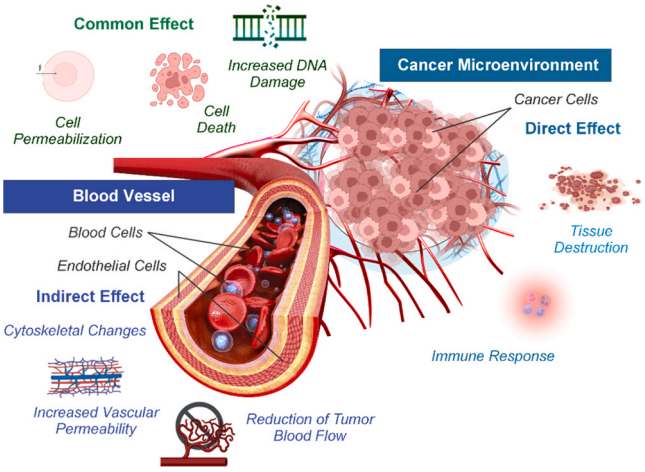

Fig. 3. Effects of electrochemotherapy on tumor and endothelial cells. The direct effects on tumor cells include increased cell permeabilization, DNA damage, cell death, and tissue destruction. Indirect effects on endothelial cells involve similar mechanisms like increased cell permeability and DNA damage, leading to cytoskeletal changes, increased vascular permeability, and reduced tumor blood flow, ultimately contributing to cell death and immune response activation.

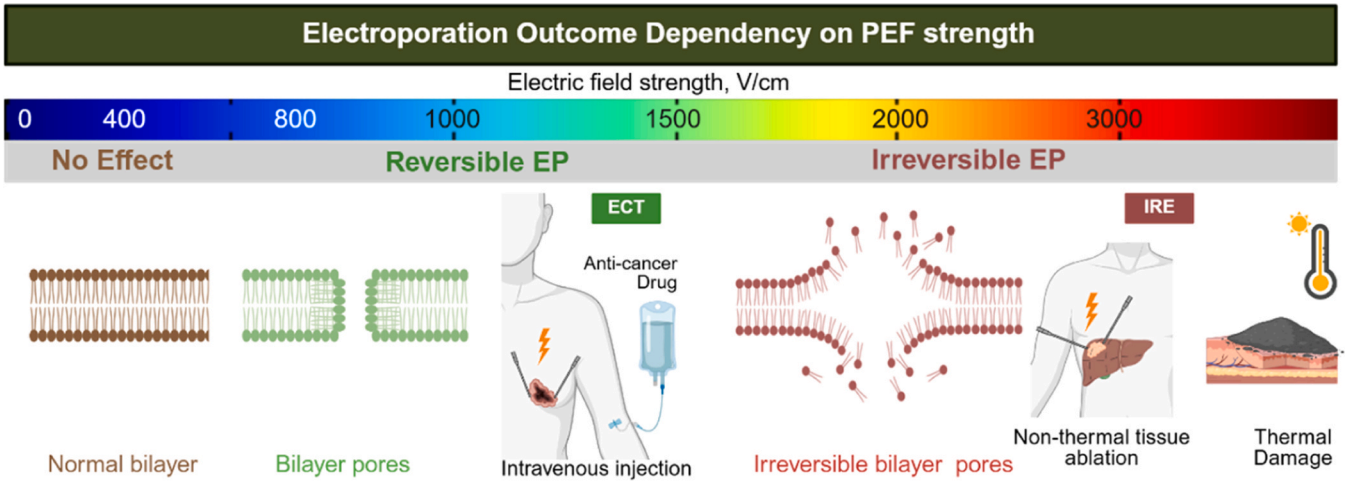

Fig. 2. Overview of microsecond range (100 μs x 8) electroporation effects based on electric field strength. Reversible electroporation (around ≤1500 V/cm) creates temporary membrane pores, enabling applications like gene transfer and electrochemotherapy. Irreversible electroporation (>1500 V/cm) causes permanent membrane disruption, used in tumor and cardiac ablation.

metastatic sarcomas, and other areas of deeply seated tumors [57–60]. Moreover, IRE can potentially be considered as an immunomodulator, when treating solid tumors too due to facilitation of the release of intracellular tumor antigens, which act as an "in-situ tumor vaccine," inducing an antitumor immune response to destroy leftover tumor cells after ablation while limiting local recurrence and distant metastasis [61, 62].

3. Mechanisms of action of standard ECT agents

Currently, the most widely used agents in ECT include bleomycin, cisplatin and calcium. Other substances, such as mitomycin C, doxorubicin, etc., have also been used in the context of ECT, however, the incidence rate currently is dramatically lower. The summary of used agents in the context of ECT and their mechanism of action are presented in Fig. 4.

Since the most commonly used anticancer drugs in ECT are bleomycin and cisplatin – their mechanisms of action are presented in more detail in Fig. 5 A and B, respectively.

In case of bleomycin, electroporation transiently increases plasma membrane permeability, thereby facilitating the intracellular delivery of bleomycin. Inside the cell, bleomycin binds to DNA and chelates metal ions, typically iron (Fe^{2+}), to form a bleomycin-Fe^{2+} complex. This complex reacts with oxygen, generating reactive oxygen species (ROS) such as superoxide and hydroxyl radicals [63,64]. ROS mediate oxidative damage to DNA, inducing both single-strand and double-strand breaks. This genotoxic stress interferes with critical cellular processes such as DNA replication and transcription, ultimately leading to cell cycle arrest and the initiation of apoptosis.

Cisplatin (cis-diamminedichloroplatinum(II) (CDDP)), effectiveness in context of ECT was firstly demonstrated by Serša et al. on SA-1, EAT, and melanoma B16 tumors in mice [65]. Cisplatin-based electroporation transiently increases plasma membrane permeability, thereby facilitating the intracellular delivery of cisplatin. Upon entry into the cell, cisplatin undergoes hydrolysis, which leads to the formation of highly reactive platinum complexes [66,67]. These complexes bind to DNA, forming intrastrand and interstrand crosslinks between adjacent guanine bases. The DNA crosslinks disrupt the structure of the DNA helix, inhibiting DNA replication and transcription. This interference stalls the cell cycle at the G2/M phase, prevents DNA repair, and ultimately leads to apoptosis.

Bleomycin induces double-strand breaks in DNA, while cisplatin forms DNA crosslinks, both of which disrupt DNA replication and transcription processes [68,69]. EP is used as a physical method to enhance the delivery of these drugs into cancer cells, improving their cytotoxic effects and overall efficacy in tumor treatment.

The last established (already used in clinics) modality of electrochemotherapy is calcium electrochemotherapy, utilizing calcium ions, which are not toxic by themselves, but play a critical role in the physiology and biochemistry of cellular processes [70]. Under normal conditions, calcium is tightly regulated within cells, however, electroporation disrupts these regulatory mechanisms, allowing excessive calcium to be internalized into tumor cells. This calcium overload leads to a severe energy crisis, as the excessive ion influx depletes cellular ATP levels [71,72]. The inability to replenish ATP results in cellular necrosis, effectively killing tumor cells and offering a non-chemotoxic therapeutic approach to cancer treatment. Calcium electroporation mechanism of action is summarized in Fig. 6.

In case of calcium electroporation, EP enhances membrane permeability allowing a substantial influx of calcium ions. The elevated intracellular calcium concentration disrupts osmotic homeostasis, contributing to cellular destabilization. Excess Ca^{2+} activates various calcium-dependent enzymes, such as proteases, phospholipases, and endonucleases, which can damage cellular structures and biomolecules [73]. Moreover, high intracellular calcium impairs mitochondrial function, leading to ATP depletion and the release of pro-apoptotic factors. This sequence of events triggers cell death pathways, culminating in apoptosis or, in cases of severe cellular damage, necrosis.

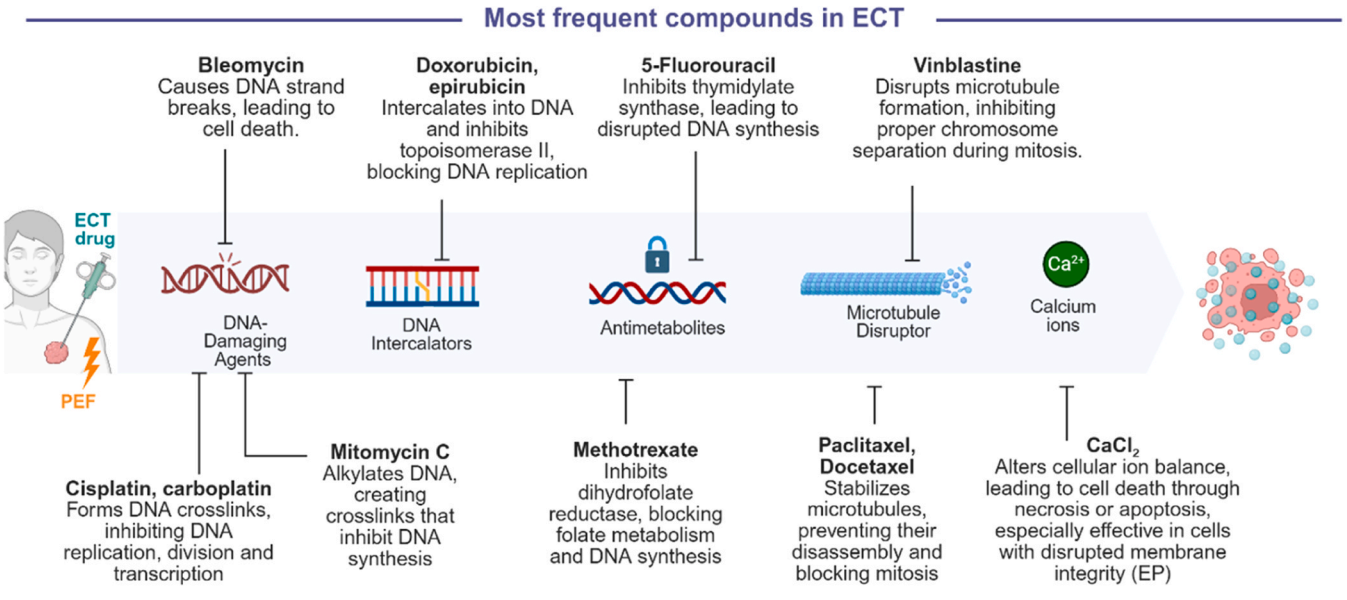

Fig. 4. Overview of the most frequently used agents in electrochemotherapy and their mechanisms of action. The agents are categorized by their mode of action: DNA-damaging agents (e.g., bleomycin, cisplatin) cause DNA strand breaks or form DNA crosslinks, leading to inhibition of replication and transcription. DNA intercalators (e.g., doxorubicin, epirubicin) insert themselves between DNA strands, blocking topoisomerase II and halting DNA replication. Antimetabolites (e.g., 5-fluorouracil, methotrexate) inhibit enzymes involved in nucleotide synthesis, leading to disrupted DNA and RNA synthesis. Microtubule disruptors (e.g., vinblastine, paclitaxel) interfere with mitotic spindle formation, blocking cell division. Calcium ions, when delivered via electroporation, disrupt cellular ion balance, leading to apoptosis or necrosis.

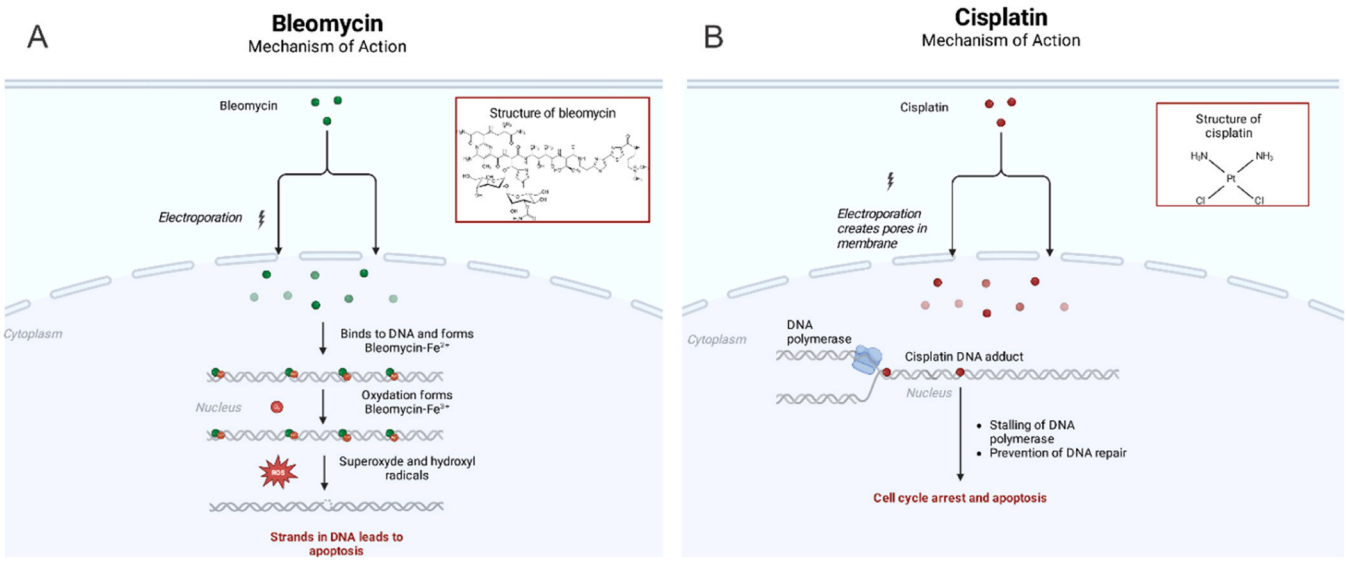

Fig. 5. Mechanism of action of the two most common cytotoxic agent in ECT, where A) bleomycin; B) cisplatin.

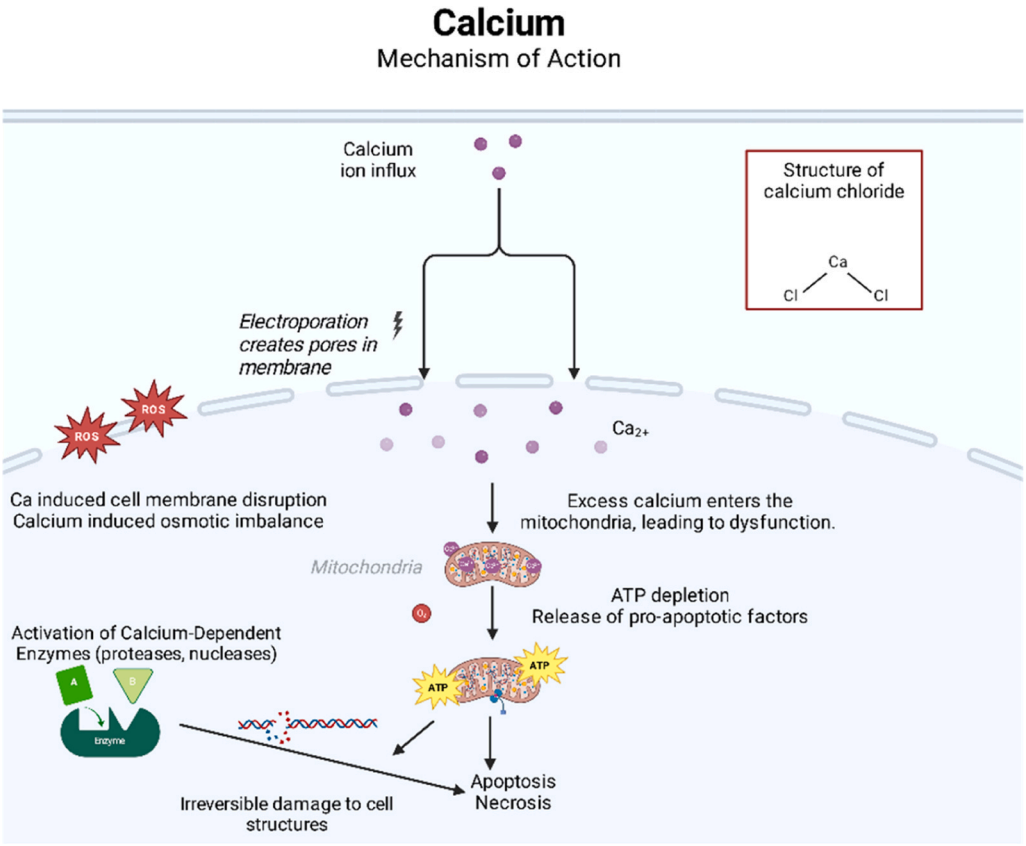

Fig. 6. Mechanism of action of calcium electroporation.

4. Applications of other cytotoxic compounds in ECT

Most studies focus on bleomycin- or cisplatin-based ECT treatments. However, recent research has broadened the scope to include other promising agents, which can be used as an alternative or as an adjuvant therapy. It also should be noted that these studies are focusing on the *in vitro* effects unless specified otherwise. For instance, in 2014, Saczko et al. explored the application of 5-fluorouracil (5-FU) alongside cisplatin in ovarian carcinoma, chemo-resistant ovarian carcinoma, noting enhanced cytotoxic effects on cancer cells with minimal damage to healthy fibroblasts [74]. In the same year, Frandsen et al. highlighted the success of calcium compounds (calcium chloride and calcium gluconate) and bleomycin on Chinese hamster lung fibroblast, Lewis lung carcinoma, and human leukemia cancer cells while applying the same parameters of PEF [75].

Camarillo *et al.* simultaneously investigated the effects of doxorubicin, paclitaxel, tamoxifen, bleomycin, and curcumin on human breast cancer cell lines in 2014 [76]. Electroporation increased drug delivery,

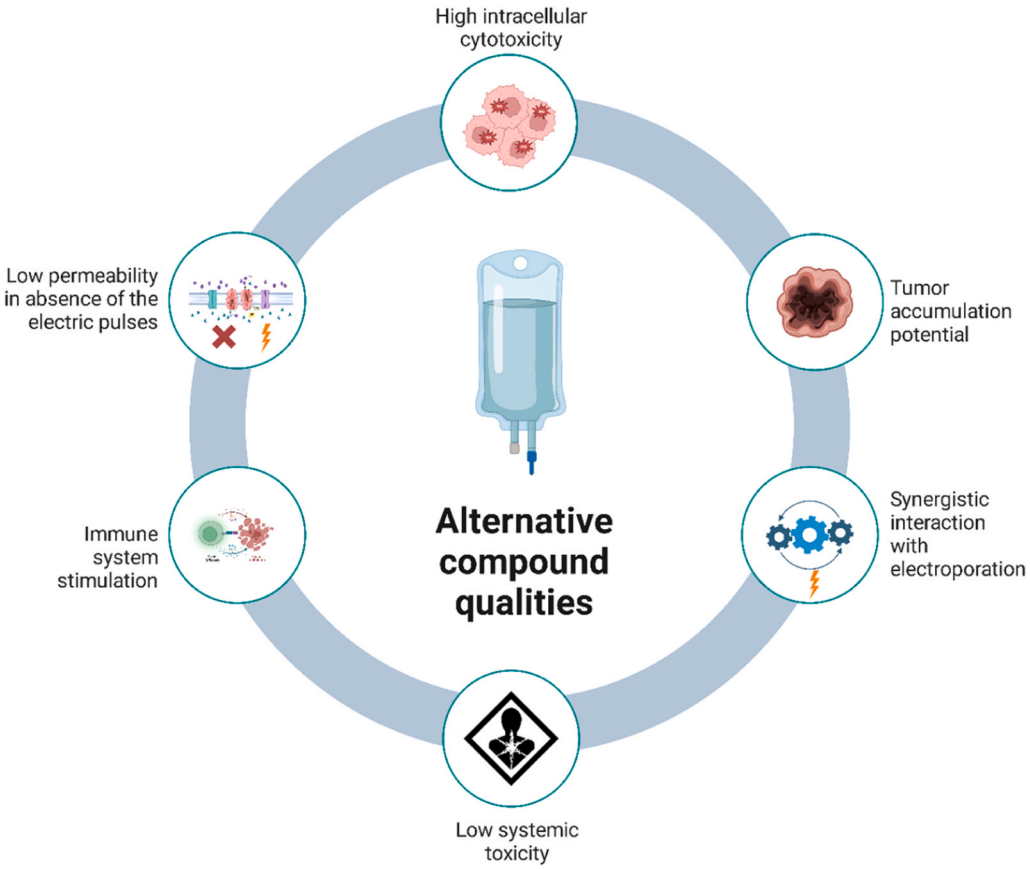

Fig. 7. Summarized qualities required for alternative compounds that can be used in ECT.

effectively creating pores that allowed these chemotherapeutic agents to penetrate the cell membrane. This supports the idea that combining electroporation with low-dose chemotherapy enhances cancer cell sensitivity. Most electroporated samples showed a reduced number of viable cells.

Vasquez *et al.* [77] evaluated cisplatin and mitomycin C drugs on a human bladder cancer cell line. The study concluded that ECT, either with cisplatin or mitomycin C, was more effective than chemotherapy alone in a bladder cancer model. It significantly enhanced cisplatin and mitomycin C cytotoxicity, 6.6 and 30 %, respectively, leading to tumor size reduction and improved treatment outcomes *in vivo*.

Alternative compounds like curcumin have also gained attention for their anti-cancer properties. Ramachachandar *et al.* [78] demonstrated curcumin's enhanced efficacy against human promyelocytic leukemia, acute myeloid leukemia, and cervical cancer cells when combined with EP and with bleomycin-based ECT. The study has highlighted ECT applicability for non-solid tumors.

Souza *et al.* [79] in 2017, have used equine sarcoid cells for research of bleomycin, cisplatin and carboplatin applicability. The electroporation increased the cytotoxic effects of bleomycin, cisplatin, and carboplatin on the equine sarcoid cell line by 5-fold, 4-fold, and 3-fold, respectively. On the other hand, the proportion of surviving cells in the group treated with the drug alone and the group treated with ECT differed significantly. Carboplatin showed inferior efficacy and applicability for ECT when compared to bleomycin or cisplatin-based therapies.

Kranjc *et al.* [80] investigated a novel cisplatin-based treatment and synthesized platinum compound trans [PtCl2 (3-Hmpy)2] (3-Hmpy = 3-hydroxymethylpyridine) (compound 2 or CP2) platinum compounds, and found it effective against sarcoma cells [81]. Cell survival following the ECT treatment was reduced *in vitro* in all examined sarcoma cells, regardless of their intrinsic cisplatin sensitivity, however, this effect was lesser than that of cisplatin. Nevertheless, the CP2 cytotoxicity enhancement factor (5-fold) was the same in cisplatin-sensitive and cisplatin-resistant cells.

In 2018, the applicability of ECT for rare tumors was also explored. Michel *et al.* [82] analyzed the cytotoxic effect of cisplatin and leucovorin calcium (LeuCa) on chondrosarcoma cells from lung metastasis using primary cell culture cultivated from the patient. Both cisplatin and LeuCa increased their cytotoxic effect when EP was applied. Although combining cisplatin and LeuCa together increased their toxicity and supported apoptosis, application of EP brought no advantage in terms of efficacy.

In 2019, Fiorentzis *et al.* extended research on human normal conjunctival and conjunctival melanoma cell lines, finding BLM-based ECT effective without harming healthy conjunctival cells [83]. The *in vitro* part of this study showed that neither MMC and 5-FU together with EP did not significantly enhance the cytotoxic effect on CM cell lines, which was not the case for BLM. MMC and 5-FU with or without EP demonstrated higher cytotoxicity for the normal conjunctival cells, while CM cells were resistant using a 3D spheroid model.

In 2019, Maczysnka *et al.* [84] researched another compound that could potentially be used with ECT. *In vitro* research was conducted on two metastatic cancer lines- an ovarian adenocarcinoma and melanoma. Novel compounds- betulinic acid (BTA) and cisplatin were used. BTA combined with EP exhibited similar efficacy to cisplatin with EP after 24 and 48 h in both cancer lines, and research findings indicate possible use of the BTA in this context.

Drag-Zalesinska *et al.* [85] determined the effect of cisplatin and vinorelbine with EP on MDR of human small cell lung cancer cell lines. Cisplatin and vinorelbine alone showed a dose-dependent effect on cell viability. Combined with EP, both materials required reduced doses for the same cytotoxic effect. Higher immunoreactivity was achieved when EP was used as well.

Oxaliplatin (OXA), another platinum-based chemotherapeutic agent compatible with electrochemotherapy, has also demonstrated comparable efficacy to conventional drugs such as cisplatin and bleomycin [86]. This was shown in studies by Uršič Valentinuzzi et al. (2018 and 2025) [87,88], which evaluated OXA's effects on 4T1 and B16F10 cell lines. Moreover, both studies confirmed that oxaliplatin induces immunogenic cell death at rates comparable to those observed with other tested chemotherapeutic agents.

The integration of electrochemotherapy (ECT) with immunotherapy is gaining traction, with proven efficacy in various tumor models [89]. In 2021, Trotovšek et al. demonstrated that combining ECT with IL-12 immunogene therapy is effective against hepatocellular carcinoma (HCC) [90], while Barca et al. reported similar benefits in cutaneous squamous cell carcinoma (SCC) [91].

Alkis *et al.* [92] conducted *in vitro* research on two human brain tumor cell lines. Human dermal fibroblast (HDF) cell lines were used to control the effect. The 5FU compound and Zn(II) complex were used and their cytotoxic activity was measured when applied together with EP. The Zn(II) complex showed good cytotoxicity against brain tumor cell lines, while it was safe on HDF healthy cells. The 5-FU exhibited less cytotoxicity than the Zn(II) complex in brain tumor cell lines.

In 2022, Kreamer *et al.* [93] published a study on calcium electroporation with bleomycin to treat human uveal melanoma (UM) cell lines. The study was performed *in vitro,* and in the 3D tumor spheroid model and there were a total of four different cell lines used. In all four *in vitro* and 3D spheroid cell cultures, there was a noticeable decrease in the intracellular adenosine triphosphate (ATP) level after both calcium and bleomycin ECT. In both 2D monolayer cell cultures and 3D tumor spheroid models, the results point to a dose-dependent ATP depletion with a broad range of sensitivity across the tested UM cell lines, control groups, and the applied conditions. This study shows that both compounds can be used for treating uveal melanoma and have possible clinical application due to the minimal effect on surrounding tissues, which is important when treating such a sensitive organ like an eye.

In 2022, Wolff *et al.* [94] conducted a study in which a new possible compound- glutathione, was researched. The *in vitro* study was conducted on Human melanoma, cutaneous cell carcinoma, squamous cell carcinoma, Jurkat lymphoma, and acute myeloid leukemia cell lines. In monotherapy, neither EP nor glutathione gave results. However, combined glutathione with EP exerted strong cytotoxic effects and declined metabolic activity in four skin cancer cell lines *in vitro*.

A study conducted by Rembiałkowska *et al.* [95] focused on combining different anticancer drugs (bleomycin, cisplatin, metformin, vinorelbine, and Dp44mT) with different PEF. The study revealed that bleomycin-based ECT was more effective than cisplatin-based treatments. Drug combinations, mainly bleomycin + cisplatin, led to synergistic effects, while others (vinorelbine or Dp444mT) exhibited some antagonism, especially in the most resistant cell lines.

The summary of the selected studies is presented in Table S1 (supplementary material). Studies involving mono-therapy with cisplatin, bleomycin or calcium were not highlighted in the text due to high availability of reviews on the topic, however, they are included in the table for comparison purposes.

Most of the covered research focused on human cell lines, primarily solid tumor cells, with fewer investigations on cancers like leukemia. Solid tumors research included 16 cell lines derived from ovarian, breast, bladder, pancreatic, and small cell lung cancers, as well as more specific lines like radioresistant squamous cell carcinoma and metastatic chondrosarcoma. Leukemia studies targeted malignant pathologies like acute myeloid leukemia, promyelocytic leukemia, and T-cell leukemia. Normal cell lines, including mal human fibroblasts, endothelial cells, gingival fibroblasts, and others, were often employed as control groups to better understand ECT mechanisms. Animal cells and *in vitro* models were also involved, primarily murine cells- Chinese hamster lung fibroblasts and murine sarcoma cells, with *in vivo* experiments conducted on murine models for uveal melanoma xenografts and colon cancer. A summary of the used compounds is described in Table 1.

5. Potential candidates for cytotoxic agents to be used in ECT

As mentioned above, various compounds have been researched alongside electroporation: antitumor antibiotics (bleomycin, mitomycin C), platinum-based chemotherapeutic agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), topoisomerase inhibitors (doxorubicin, irinotecan), antimetabolites (5-fluorouracil, gemcitabine), calcium compounds ($CaCl_2$) [98–109]. Considering the listed drugs' characteristics and mechanisms of action, key qualities can be identified for substances suitable for electrochemotherapy. The most important criteria for a drug to be effective in ECT are:

1. High intracellular cytotoxicity: selected drugs should be highly toxic inside the cell, inducing apoptosis or other cell killing mechanism [110].
2. Low permeability in the absence of electric pulses: drugs in physiological conditions should have limited ability to pass through cell membrane passively to ensure selectivity of the treatment [111].
3. Tumor accumulation potential: the drug should preferentially accumulate in tumor cells, minimizing systemic effects while maximizing cytotoxicity within the tumor [112].
4. Low systemic toxicity: at the low doses typically used in ECT, the drug should exhibit minimal systemic toxicity, reducing adverse effects on healthy tissues [113].
5. Synergistic interaction with electroporation: the intracellular delivery of the compound and cytotoxic effects should be significantly enhanced when combined with electroporation [114].
6. Immune system stimulation: Certain compounds not only exert a direct cytotoxic effect but also activate an immune response against cancer, further enhancing therapeutic efficacy, which is beneficial for the prevention of metastases [115].

The qualities required for alternative compounds that can be used in ECT are summarized in Fig. 7. The listed characteristics of potential ECT drugs are critical in determining their suitability. While primary features such as tumor selectivity, low systemic toxicity, and compatibility with electroporation are predominant, secondary characteristics also should be considered. These may also include a short half-life to minimize systemic effects, effectiveness in a low oxygen environment (as drugs that rely on ROS against cancer cells could work worse in solid tumors, which usually have a hypoxic zone due to rapid growth) [116]. Other

Table 1
Frequency based overview of substances and drugs used in ECT based on this review. Values are based on Handbook of Electroporation by Miklavic *et al.* [96], unless specified differently.

Substance / Drug	Molecular Mass (g/mol)	Type	Cytotoxicity Increase with EP
Bleomycin	1415.56	Hydrophilic	30–5000-fold
Cisplatin	300.05	Hydrophilic	~80 fold
Calcium ions ($CaCl_2$)	110.98	Hydrophilic	< 100 fold
5-Fluorouracil	130.08	Hydrophilic	~1.25 fold
Doxorubicin	543.52	Less Hydrophilic	~0.67 fold
Mitomycin C	334.32	Hydrophilic	~1.3–1.4 fold
Vinblastine	811.03	Hydrophobic	1–1.3-fold
Paclitaxel	853.91	Hydrophobic	No increase
Docetaxel	807.88	Hydrophobic	Limited studies
Betulinic Acid	456.70	Hydrophobic	Limited studies
Leucovorin Calcium	511.51	Hydrophilic	Limited studies
Zn(II) Complexes	136–800	Varies	Limited studies
Curcumin	368.39	Hydrophobic	Limited studies
Oxaliplatin	391.10 [97]	Hydrophobic	2–10-fold [87]

desirable traits include compatibility across diverse cancer types, the production of non-toxic metabolites and etc. [117].

According to current knowledge and requirements, three main groups of potential ECT drugs can be derived: 1) chemotherapy drugs, and 2) natural compounds.

Chemotherapy Drugs. Emerging chemotherapy drugs with specific properties are promising candidates for ECT, e.g., Sotorasib could be considered. It was approved by the FDA in 2021 for non-small cell lung cancer (NSLC). Sotorasib is poorly permeable throughout the cell membrane without external stimuli, and simultaneously, it demonstrates potential due to its mechanism of inducing apoptosis in KRAS-mutated cancer cells, which are typically resistant to traditional chemotherapy. KRAS mutations are common in aggressive cancers such as NSCLC, colorectal, and pancreatic cancers. The poor membrane permeability of Sotorasib, with a molecular weight of 560 g/mol could be improved with electroporation, making it a strong ECT candidate [118–120]. Similarly, Belzutifan was approved in 2021. It is a hypoxia-induced factor 2-alpha (HIF-2ά) inhibitor and targets mostly hypoxic tumors, primarily renal cell carcinoma. HIF-2ά is a key regulator of tumor growth, angiogenesis, and immune evasion in hypoxic tumors. Belzutifan inhibits this gene and slows it down, which may potentially reduce the growth of the tumor. Its 460 g/mol molecular weight and limited permeability make it another promising candidate for ECT [121–123].

Vemurafenib, a selective BRAF V600E inhibitor, targets the MAPK/ERK signaling pathway and suppresses melanoma cell proliferation [124]. While not typically used in ECT due to its lipophilic nature and passive cellular uptake [125], its combination with ECT has showed synergistic cytotoxic effects. Though, the treatment normally involves bleomycin [125]. Concurrent vemurafenib treatment may sensitize tumor cells by downregulating repair mechanisms and promoting immunogenic cell death, thereby enhancing both direct cytotoxicity and antitumor immune responses [126]. Another compound under investigation is sunitinib – a multi-targeted tyrosine kinase inhibitor that blocks VEGFR, PDGFR, c-KIT, and other signaling pathways involved in tumor angiogenesis, proliferation, and survival [127]. Its broad mechanism of action makes it a promising candidate for ECT. Ongoing studies are exploring its synergistic potential in combination with other treatments, including electrochemotherapy. However, neither drug is approved for use with ECT yet.

Antibiotics have shown promise as chemotherapeutic agents in ECT, with bleomycin – the most successful ECT drug to date – serving as a key example. There are potentially a few more antibiotics that could be researched for ECT. For instance, mithramycin – an antibiotic whose antitumoral effects are achieved by binding to GC-rich (guanine (G) and cytosine (C)) DNA regions, owns the genes that regulate cell growth and survival. Mithramycin blocks transcription factors like Sp1, which activate oncogenes involved in cancer proliferation, like c-myc and surviving, and promotes apoptosis and cell cycle arrest. Mithramycin has been researched for pancreatic, breast cancer, osteosarcoma, glioblastoma, and others. However, its amphiphilic nature and high molecular weight (1085 g/mol) limit its permeability and increase systemic toxicity risk, making it a strong candidate for ECT applications [128–131]. Another antibiotic, daunorubicin, binds to DNA and inhibits topoisomerase II, causing DNA damage and apoptosis. While primarily studied for hematological malignancies, it has also shown potential in breast, ovarian, and small-cell lung cancer. It has poor membrane permeability and a molecular weight of 528 g/mol, daunorubicin could benefit from electroporation-enhanced delivery [132–135].

Natural Compounds. Natural compounds can also offer unique opportunities in ECT procedures. One possible material to use is Withaferin A. It is a natural material derived from the plant Withania somnifera (Ashwagandha). It is widely researched as an anticancer agent. Yet, it has shown anticancer activity against breast and pancreatic cancers by inducing reactive oxygen species (ROS), disrupting mitochondrial function, and activating p53 pathways to promote apoptosis. It is a compound with a molecular mass of 470 g/mol and has limited permeability, suggesting it could benefit from electroporation [136–138]. Another promising compound is Cannabidiol (CBD), known for its analgesic and immunomodulating properties. CBD has demonstrated anticancer effects inducing apoptosis in cancer cells, proliferation inhibition, enhancement of the immune system, and, in some cases, increased cytotoxicity and effectiveness of other anti-cancerous drugs. Its poor membrane permeability, and molecular weight of 315 g/mol make it an intriguing candidate for further ECT research [139–142].

The summary of potential cytotoxic agent candidates to be used in ECT is presented in Table 2.

6. Conclusions

Electrochemotherapy is a promising tool in oncology, allowing drugs to enter cells that would otherwise not cross the cell membrane effectively, making it especially useful for treating drug-resistant tumors. It requires lower doses of chemotherapy compared to traditional methods and is already used for cutaneous and subcutaneous cancers, and its applications are expanding. The most commonly used drugs are bleomycin and cisplatin. Bleomycin uptake during electroporation increases 300–5000-fold, while cisplatin achieves an ~80-fold increase. Calcium EP has also emerged as a promising option, effectively inducing tumor cell death in cancers such as melanoma, squamous cell carcinoma, and breast cancer. Additionally, calcium EP has shown the potential to overcome multidrug resistance and trigger immunogenic effects [143], enhancing its therapeutic impact. Other medications, such as doxorubicin, 5-fluorouracil, mitomycin C, and experimental substances, such as Zn (II) complexes or curcumin, have also been investigated. Certain chemicals have demonstrated promise, such as increasing the absorption of doxorubicin in myeloma mice and raising the efficacy of MMC in bladder cancer through improved drug delivery or curcumin in increasing cancer cell death in cervical cancer and leukemia. The Zn (II) complexes have shown selective cytotoxicity against brain tumor cells while protecting healthy tissues, highlighting the ECT suitability even in brain cancer treatment. Ongoing research into new drugs and improved protocols continues to expand the potential of ECT as a targeted, less toxic treatment for resistant cancers.

CRediT authorship contribution statement

Vitalij Novickij: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation. **Arnoldas Morozas:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Malyško-Ptašinskė Veronika:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Justinas Ivaška:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology. **Rembiałkowska Nina:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation. **Julita Kulbacka:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation. **Aušra Nemeikaitė-Čėnienė:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

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Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 2
Summary of potential cytotoxic agent candidates to be used in ECT, where SCLCS- small cell lung cancer; KRAS- Kirsten rat sarcoma viral oncogene homolog; AML- acute myeloid leukemia.

Drug/ compound	Type, Molecular weight	Cytoxicity	Systemic toxicity	Immune system stimulation	Notes
Sotorasib	Chemotherapy drug 560 g/mol	High toxicity in KRAS mutant cells	Well-tolerated at therapeutic doses	No known immune stimulation	Effective in SCLC with KRAS mutation, good for targeted ECT applications
Vemurafenib	BRAF V600E kinase inhibitor 489.9 g/mol	High toxicity in BARF mutant cells	Severe toxicity; requires dose management	May promote immunogenic cell death (ICD)	Synergistic in BRAF-mutant melanoma when combined with ECT; not effective alone due to lipophilicity
Sunitinib	Multi-targeted tyrosine kinase inhibitor (TKI) 398.5 g/mol	Effective in Renal cell carcinoma, GIST and pNETs	Severe toxicity; requires dose management	Enhances response to immunotherapy	Promising for ECT due to angiogenesis inhibition and immune modulation; under investigation
Belzutifan	Chemotherapy drug 460 g/mol	Effective in hypoxic tumors	Low toxicity in renal carcinoma	Minimal immune response	Effective in renal cell carcinoma, hemangioblastoma; targets hypoxic targets for potential synergy with ECT
Withaferin A	Natural Compound 470,6 g/mol	Cytotoxic, induces apoptosis, more toxic to tumor cells	Minimal toxicity outside tumor	Potential immune modulation	Effective in breast and pancreatic cancers; known for selective cytotoxicity in cancer cells, good for ECT
CBD (Cannabidiol)	Natural Compound 314,5 g/mol	Cytotoxic and anti-proliferative effects, some tumor specificity	Minimal toxicity outside cancer cells	Modulates immune response	Promising for glioblastoma and breast cancer; ECT may enhance accumulation and immune benefits
Mithramycin	Antitumor Antibiotic 1085 g/mol	High DNA-binding toxicity, could more specific to tumor cells	High systemic toxicity risk	Minimal immune activity	Used in testicular, breast cancers; suitable candidate for ECT to reduce required dose and limit toxicity
Daunorubicin	Antitumor Antibiotic 527,5 g/mol	DNA-intercalating, highly toxic, induces apoptosis	Known systemic toxicity; requires dose management	Limited immune-stimulating effects	Primarily used in AML; potential for solid tumors in ECT due to limited permeability

the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2025.118451.

Data availability

Data will be made available on request.

References

[1] J.M. Kocarnik, K. Compton, F.E. Dean, W. Fu, B.L. Gaw, J.D. Harvey, H. J. Henrikson, D. Lu, A. Pennini, R. Xu, et al., Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019, JAMA Oncol. 8 (2022) 420, https://doi.org/10.1001/jamaoncol.2021.6987.

[2] M.L. Ashdown, A.P. Robinson, S.L. Yatomi-Clarke, M.L. Ashdown, A. Allison, D. Abbott, S.N. Markovic, B.J. Coventry, Chemotherapy for late-stage cancer patients: meta-analysis of complete response rates, F1000Res 4 (2015) 232, https://doi.org/10.12688/f1000research.6760.1.

[3] A.D. Napper, V.G. Watson, Targeted drug discovery for pediatric leukemia, Front Oncol. 3 (2013), https://doi.org/10.3389/fonc.2013.00170.

[4] B.L. Asselin, P. Gaynon, J.A. Whitlock, Recent advances in acute lymphoblastic leukemia in children and adolescents, Curr. Opin. Oncol. 25 (2013) S1–S13, https://doi.org/10.1097/CCO.0000000000000017.

[5] I.A. Voutsadakis, The chemosensitivity of testicular germ cell tumors, Cell. Oncol. 37 (2014) 79–94, https://doi.org/10.1007/s13402-014-0168-6.

[6] P. Savage, J. Stebbing, M. Bower, T. Crook, Why does cytotoxic chemotherapy cure only some cancers? Nat. Clin. Pr. Oncol. 6 (2009) 43–52, https://doi.org/10.1038/ncponc1260.

[7] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[8] Ferlay J., E.M.L.F.L.M.C.M.M.L.P.M.Z.A.S.I.B.F Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.

[9] Z. Nozhat, S. Heydarzadeh, Z. Memariani, A. Ahmadi, Chemoprotective and chemosensitizing effects of apigenin on cancer therapy, Cancer Cell Int 21 (2021) 574, https://doi.org/10.1186/s12935-021-02282-3.

[10] U. Probst, I. Fuhrmann, L. Beyer, P. Wiggermann, Electrochemotherapy as a new modality in interventional oncology: a review, Technol. Cancer Res Treat. 17 (2018), https://doi.org/10.1177/1533033818785329.

[11] A. Morozas, V. Malyško-Ptašinskė, J. Kulbacka, J. Ivaška, T. Ivaškienė, V. Novickij, Electrochemotherapy for head and neck cancers: possibilities and limitations, Front Oncol. 14 (2024), https://doi.org/10.3389/fonc.2024.1353800.

[12] VOSviewer - Visualizing Scientific Landscapes Available online: ⟨https://www.vosviewer.com/⟩ (accessed on 21 October 2024).

[13] L. Delemotte, M. Tarek, Molecular dynamics simulations of lipid membrane electroporation, J. Membr. Biol. 245 (2012) 531–543, https://doi.org/10.1007/s00232-012-9434-6.

[14] J. Shi, Y. Ma, J. Zhu, Y. Chen, Y. Sun, Y. Yao, Z. Yang, J. Xie, A review on electroporation-based intracellular delivery, Molecules 23 (2018), https://doi.org/10.3390/molecules23113044.

[15] S. Becker, B. Zorec, D. Miklavčič, N. Pavšelj, Transdermal transport pathway creation: electroporation pulse order, Math. Biosci. 257 (2014) 60–68, https://doi.org/10.1016/J.MBS.2014.07.001.

[16] K. Ita, Perspectives on transdermal electroporation, Pharm. 2016 Vol. 8 Page 9 8 (2016) 9, https://doi.org/10.3390/PHARMACEUTICS8010009.

[17] G. Serša, M. Čemažar, D. Miklavčič, Z. Rudolf, Electrochemotherapy of tumours, Curr. Oncol. 16 (2009) 34, https://doi.org/10.3747/CO.V16I2.368.

[18] J.L. Vásquez, P. Ibsen, H. Lindberg, J. Gehl, In vitro and in vivo experiments on electrochemotherapy for bladder cancer, J. Urol. 193 (2015) 1009–1015, https://doi.org/10.1016/J.JURO.2014.09.039.

[19] A. Gothelf, L.M. Mir, J. Gehl, Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation, Cancer Treat. Rev. 29 (2003) 371–387, https://doi.org/10.1016/S0305-7372(03)00073-2.

[20] V. De Giorgi, F. Scarfì, E. Saqer, A. Gori, G.M. Tomassini, P. Covarelli, The use of cisplatin electrochemotherapy in nonmelanoma skin cancers: a Single-Center study, Dermatol. Ther. 33 (2020) 1–8, https://doi.org/10.1111/dth.13547.

[21] S.K. Frandsen, M. Vissing, J. Gehl, A comprehensive review of calcium Electroporation-A novel cancer treatment modality, Cancers 2020 Vol. 12 Page 290 12 (2020) 290, https://doi.org/10.3390/CANCERS12020290.

[22] A. Szewczyk, D. Baczyńska, A. Choromańska, Z. Łapińska, A. Chwiłkowska, J. Saczko, J. Kulbacka, Advancing cancer therapy: mechanisms, efficacy, and limitations of calcium electroporation, Biochimica et Biophysica Acta (BBA) Reviews Cancer 1880 (2025) 189319, https://doi.org/10.1016/J.BBCAN.2025.189319.

[23] Y. Tokudome, K. Sugibayashi, Mechanism of the synergic effects of calcium chloride and electroporation on the in vitro enhanced skin permeation of drugs,

J. Control. Release 95 (2004) 267–274, https://doi.org/10.1016/J.JCONREL.2003.12.014.
[24] D. Zhao, M. Wu, D. Huang, Z. Liang, Z. Wei, Z. Li, Parametric optimization of electric field strength for cancer electrochemotherapy on a Chip-Based model, Theranostics 8 (2018) 358–368, https://doi.org/10.7150/thno.21099.
[25] R. Stämpfli, M. Willi, Membrane potential of a ranvier node measured after electrical destruction of its membrane, Experientia 13 (1957) 297–298, https://doi.org/10.1007/BF02158430.
[26] S. Orlowski, J. Belehradek, C. Paoletti, L.M. Mir, Transient electropermeabilization of cells in culture, Biochem Pharm. 37 (1988) 4727–4733, https://doi.org/10.1016/0006-2952(88)90344-9.
[27] L.M. Mir, J. Gehl, G. Sersa, C.G. Collins, J.-R. Garbay, V. Billard, P.F. Geertsen, Z. Rudolf, G.C. O'Sullivan, M. Marty, Standard operating procedures of the electrochemotherapy: instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the CliniporatorTM by means of invasive or Non-Invasive electrodes, Eur. J. Cancer Suppl. 4 (2006) 14–25, https://doi.org/10.1016/j.ejcsup.2006.08.003.
[28] J. Gehl, G. Sersa, L.W. Matthiessen, T. Muir, D. Soden, A. Occhini, P. Quaglino, P. Curatolo, L.G. Campana, C. Kunte, et al., Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases, Acta Oncol. 57 (2018) 874–882, https://doi.org/10.1080/0284186X.2018.1454602.
[29] M. Marty, G. Sersa, J.R. Garbay, J. Gehl, C.G. Collins, M. Snoj, V. Billard, P. F. Geertsen, J.O. Larkin, D. Miklavcic, et al., Electrochemotherapy – an easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study, Eur. J. Cancer Suppl. 4 (2006) 3–13, https://doi.org/10.1016/j.ejcsup.2006.08.002.
[30] M. Condello, G. D'Avack, E.P. Spugnini, S. Meschini, Electrochemotherapy: an alternative strategy for improving therapy in Drug-Resistant SOLID tumors, Cancers (Basel) 14 (2022) 4341, https://doi.org/10.3390/cancers14174341.
[31] A. Morozas, V. Malyško-Ptašinskė, J. Kulbacka, J. Ivaška, T. Ivaškienė, V. Novickij, Electrochemotherapy for head and neck cancers: possibilities and limitations, Front Oncol. 14 (2024), https://doi.org/10.3389/fonc.2024.1353800.
[32] R. Heller, M.J. Jaroszeski, L.F. Glass, J.L. Messina, D.P. Rapaport, R.C. DeConti, N.A. Fenske, R.A. Gilbert, L.M. Mir, D.S. Reintgen, Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy, Cancer 77 (1996) 964–971, doi:10.1002/(SICI)1097-0142(19960301)77:5<964::AID-CNCR24>3.0.CO;2-0.
[33] K. Quan, Analysis of the clinical effectiveness of 144 cases of soft tissue and superficial malignant tumours treated with electrochemical therapy, Eur. J. Surg. Suppl. (1994) 37–40.
[34] L.M. Mir, M. Belehradek, C. Domenge, S. Orlowski, B. Poddevin, J. Belehradek, G. Schwaab, B. Luboinski, C. Paoletti, Electrochemotherapy, a new antitumor treatment: first clinical trial, C. R. Acad. Sci. III 313 (1991) 613–618.
[35] B. Pichi, G. Petruzzi, J. Zocchi, G. Pepe, S. Moretto, V. Manciocco, R. Pellini, Response to electrochemotherapy in a patient with advanced oropharyngeal squamous cell carcinoma, JAMA Otolaryngol. Head. Neck Surg. 146 (2020) 1178, https://doi.org/10.1001/jamaoto.2020.2093.
[36] C.C. Plaschke, H.H. Johannesen, R.H. Hansen, H.W. Hendel, K. Kiss, J. Gehl, I. Wessel, The DAHANCA 32 study: electrochemotherapy for recurrent mucosal head and neck cancer, Head. Neck 41 (2019) 329–339, https://doi.org/10.1002/hed.25454.
[37] C.C. Plaschke, G. Bertino, J.A. McCaul, J.J. Grau, R. de Bree, G. Sersa, A. Occhini, A. Groselj, C. Langdon, D.A. Heuveling, et al., European research on electrochemotherapy in head and neck cancer (EURECA) project: results from the treatment of mucosal cancers, Eur. J. Cancer 87 (2017) 172–181, https://doi.org/10.1016/j.ejca.2017.10.008.
[38] F.J. Landström, J. Reizenstein, G.-B. Adamsson, M. von Beckerath, C. Möller, Long-Term Follow-up in patients treated with curative electrochemotherapy for cancer in the oral cavity and oropharynx, Acta Otolaryngol. 135 (2015) 1070–1078, https://doi.org/10.3109/00016489.2015.1049663.
[39] F.J. Landström, C.O.S. Nilsson, J.A. Reizenstein, K. Nordqvist, G.-B. Adamsson, A. L. Löfgren, Electroporation therapy for T1 and T2 oral tongue cancer, Acta Otolaryngol. 131 (2011) 660–664, https://doi.org/10.3109/00016489.2010.541937.
[40] B. Mali, V. Gorjup, I. Edhemovic, E. Brecelj, M. Cemazar, G. Sersa, B. Strazisar, D. Miklavcic, T. Jarm, Electrochemotherapy of colorectal liver metastases - an observational study of its effects on the electrocardiogram, Biomed. Eng. Online 14 (2015) S5, https://doi.org/10.1186/1475-925X-14-S3-S5.
[41] I. Edhemovic, E. Brecelj, G. Gasljevic, M. Marolt Music, V. Gorjup, B. Mali, T. Jarm, B. Kos, D. Pavliha, B. Grcar Kuzmanov, et al., Intraoperative electrochemotherapy of colorectal liver metastases, J. Surg. Oncol. 110 (2014) 320–327, https://doi.org/10.1002/jso.23625.
[42] M. Djokic, M. Cemazar, P. Popovic, B. Kos, R. Dezman, M. Bosnjak, M.N. Zakelj, D. Miklavcic, S. Potrc, B. Stabuc, et al., Electrochemotherapy as treatment option for hepatocellular carcinoma, a prospective pilot study, Eur. J. Surg. Oncol. 44 (2018) 651–657, https://doi.org/10.1016/j.ejso.2018.01.090.
[43] L.G. Campana, B. Mali, G. Sersa, S. Valpione, C.A. Giorgi, P. Strojan, D. Miklavcic, C.R. Rossi, Electrochemotherapy in Non-Melanoma head and neck cancers: a retrospective analysis of the treated cases, Br. J. Oral. Maxillofac. Surg. 52 (2014) 957–964, https://doi.org/10.1016/j.bjoms.2014.08.004.
[44] C. Jamsek, G. Sersa, M. Bosnjak, A. Groselj, Long term response of electrochemotherapy with reduced dose of bleomycin in elderly patients with head and neck Non-Melanoma skin cancer, Radio. Oncol. 54 (2020) 79–85, https://doi.org/10.2478/raon-2020-0009.
[45] C.C. Plaschke, H.H. Johannesen, R.H. Hansen, H.W. Hendel, K. Kiss, J. Gehl, I. Wessel, The DAHANCA 32 study: electrochemotherapy for recurrent mucosal head and neck cancer, Head. Neck 41 (2019) 329–339, https://doi.org/10.1002/hed.25454.
[46] A. Groselj, M. Bosnjak, P. Strojan, M. Krzan, M. Cemazar, G. Sersa, Efficiency of electrochemotherapy with reduced bleomycin dose in the treatment of nonmelanoma head and neck skin cancer: preliminary results, Head. Neck 40 (2018) 120–125, https://doi.org/10.1002/hed.24991.
[47] M. Gargiulo, J.M. Serra Mestre, A. Cortese, D.C. Murphy, S. Parascandolo, S. Razzano, Long term effectiveness of electrochemotherapy for the treatment of lower lip squamous cell carcinoma, J. CranioMaxillofac. Surg. 46 (2018) 1968–1974, https://doi.org/10.1016/j.jcms.2018.08.013.
[48] B. Pichi, R. Pellini, G. Spriano, Electrochemotherapy – a locoregional therapy with Well-Established palliative effect in patient with large recurrent lesion of head and neck, J. CranioMaxillofac. Surg. 47 (2019) 41–46, https://doi.org/10.1016/j.jcms.2018.10.014.
[49] V. De Giorgi, F. Scarfì, E. Saqer, A. Gori, G.M. Tomassini, P. Covarelli, The use of cisplatin electrochemotherapy in nonmelanoma skin cancers: a Single-Center study, Dermatol. Ther. 33 (2020), https://doi.org/10.1111/dth.13547.
[50] F. Longo, F. Perri, E. Pavone, C. Aversa, M.G. Maglione, A. Guida, M. Montano, S. Villano, A. Daponte, F. Caponigro, et al., Electrochemotherapy as palliative treatment in patients with advanced head and neck tumours: outcome analysis in 93 patients treated in a single institution, Oral. Oncol. 92 (2019) 77–84, https://doi.org/10.1016/j.oraloncology.2019.03.016.
[51] L.W. Matthiessen, R.L. Chalmers, D.C.G. Sainsbury, S. Veeramani, G. Kessell, A. C. Humphreys, J.E. Bond, T. Muir, J. Gehl, Management of cutaneous metastases using electrochemotherapy, Acta Oncol. (Madr.) 50 (2011) 621–629, https://doi.org/10.3109/0284186X.2011.573626.
[52] Mevio, N.; Bertino, G.; Occhini, A.; Scelsi, D.; Tagliabue, M.; Mura, F.; Benazzo, M. *Electrochemotherapy for the Treatment of Recurrent Head and Neck Cancers: Preliminary Results*;
[53] G. Sersa, J. Teissie, M. Cemazar, E. Signori, U. Kamensek, G. Marshall, D. Miklavcic, Electrochemotherapy of tumors as in situ vaccination boosted by immunogene electrotransfer, Cancer Immunol. Immunother. 64 (2015) 1315, https://doi.org/10.1007/S00262-015-1724-2.
[54] K. Uršič Valentinuzzi, U. Kamenšek, S. Kranjc Brezar, C. Heranney, T. Komel, S. Buček, M. Čemažar, G. Serša, Electrochemotherapy with bleomycin, oxaliplatin, or cisplatin in mouse tumor models, from tumor ablation to in situ vaccination, Front Immunol. 16 (2025) 1470432, https://doi.org/10.3389/FIMMU.2025.1470432/BIBTEX.
[55] G. Serša, M. Cemažar, B. Markelc, Blood flow modifying and Vascular-Disrupting effects of electroporation and electrochemotherapy, Handb. Electro 1 (2017) 691–705, https://doi.org/10.1007/978-3-319-32886-7_165.
[56] B. Markelc, G. Sersa, M. Cemazar, Differential mechanisms associated with vascular disrupting action of electrochemotherapy: intravital microscopy on the level of single normal and tumor blood vessels, PLoS One 8 (2013), https://doi.org/10.1371/JOURNAL.PONE.0059557.
[57] Y. Koethe, N. Wilson, G. Narayanan, Irreversible electroporation for colorectal cancer liver metastasis: a review, Int. J. Hyperth. 39 (2022) 682–687, https://doi.org/10.1080/02656736.2021.2008025.
[58] M. Vailas, A. Syllaios, N. Hashemaki, M. Sotiropoulou, D. Schizas, A. Papalampros, E. Felekouras, E. Pikoulis, Irreversible electroporation and sarcomas: where do we stand? J. BUON 24 (2019) 1354–1359.
[59] A. Gajewska-Naryniecka, U. Szwedowicz, Z. Łapińska, J. Rudno-Rudzińska, W. Kielan, J. Kulbacka, Irreversible electroporation in pancreatic Cancer—An evolving experimental and clinical method, Int J. Mol. Sci. 24 (2023) 4381, https://doi.org/10.3390/ijms24054381.
[60] J.-P. Tasu, D. Tougeron, M.-P. Rols, Irreversible electroporation and electrochemotherapy in oncology: state of the art, Diagn. Inter. Imaging 103 (2022) 499–509, https://doi.org/10.1016/j.diii.2022.09.009.
[61] N. Zhang, Z. Li, X. Han, Z. Zhu, Z. Li, Y. Zhao, Z. Liu, Y. Lv, Irreversible electroporation: an emerging immunomodulatory therapy on solid tumors, Front Immunol. 12 (2022), https://doi.org/10.3389/fimmu.2021.811726.
[62] J.S. Shankara Narayanan, T. Hayashi, S. Erdem, S. McArdle, H. Tiriac, P. Ray, M. Pu, Z. Mikulski, A. Miller, K. Messer, et al., Treatment of pancreatic cancer with irreversible electroporation and intratumoral CD40 antibody stimulates systemic immune responses that inhibit liver metastasis in an orthotopic model, J. Immunother. Cancer 11 (2023) e006133, https://doi.org/10.1136/jitc-2022-006133.
[63] A.D. Bolzán, M.S. Bianchi, DNA and chromosome damage induced by bleomycin in mammalian cells: an update, Mutat. Res Rev. Mutat. Res 775 (2018) 51–62, https://doi.org/10.1016/j.mrrev.2018.02.003.
[64] V. Murray, J.K. Chen, L.H. Chung, The interaction of the Metallo-Glycopeptide Anti-Tumour drug bleomycin with DNA, Int J. Mol. Sci. 19 (2018), https://doi.org/10.3390/IJMS19051372.
[65] G. Serša, M. čemažar, D. Miklavčič, Antitumor effectiveness of electrochemotherapy with Cis-Diamminedichloroplatinum(II) in mice, Cancer Res 55 (1995) 3450–3455.
[66] R. Ali, M. Aouida, A.A. Sulaiman, S. Madhusudan, D. Ramotar, Can cisplatin therapy be improved? Pathways that can be targeted, Int J. Mol. Sci. 23 (2022), https://doi.org/10.3390/IJMS23137241.
[67] S. Ghosh, Cisplatin: the first metal based anticancer drug, Bioorg. Chem. 88 (2019), https://doi.org/10.1016/j.bioorg.2019.102925.

[68] S. Dasari, P.B. Tchounwou, Cisplatin in cancer therapy: molecular mechanisms of action, Eur. J. Pharm. 740 (2014) 364–378, https://doi.org/10.1016/j.ejphar.2014.07.025.

[69] Brandt, J.P.; Gerriets, V. *Bleomycin*; 2024;

[70] S.K. Frandsen, M. Vissing, J. Gehl, A comprehensive review of calcium electroporation -A novel cancer treatment modality, Cancers (Basel) 12 (2020), https://doi.org/10.3390/cancers12020290.

[71] S.K. Frandsen, J. Gehl, A review on differences in effects on normal and malignant cells and tissues to Electroporation-Based therapies: a focus on calcium electroporation, Technol. Cancer Res Treat. 17 (2018), https://doi.org/10.1177/1533033818788077.

[72] S.K. Frandsen, H. Gissel, P. Hojman, J. Eriksen, J. Gehl, Calcium electroporation in three cell lines: a comparison of bleomycin and calcium, calcium compounds, and pulsing conditions, Biochim Biophys. Acta Gen. Subj. 1840 (2014) 1204–1208, https://doi.org/10.1016/j.bbagen.2013.12.003.

[73] D. Zhang, F. Wang, P. Li, Y. Gao, Mitochondrial Ca2+ homeostasis: emerging roles and clinical significance in cardiac remodeling, Int J. Mol. Sci. 23 (2022), https://doi.org/10.3390/IJMS23063025.

[74] J. Saczko, I. Kamińska, M. Kotulska, J. Bar, A. Choromańska, N. Rembiałkowska, K. Biezuńska-Kusiak, J. Rossowska, D. Nowakowska, J. Kulbacka, Combination of therapy with 5-Fluorouracil and cisplatin with electroporation in human ovarian carcinoma model in vitro, Biomed. Pharmacother. 68 (2014) 573–580, https://doi.org/10.1016/j.biopha.2014.05.005.

[75] S.K. Frandsen, H. Gissel, P. Hojman, J. Eriksen, J. Gehl, Calcium electroporation in three cell lines: a comparison of bleomycin and calcium, calcium compounds, and pulsing conditions, Biochim Biophys. Acta Gen. Subj. 1840 (2014) 1204–1208, https://doi.org/10.1016/j.bbagen.2013.12.003.

[76] I.G. Camarillo, F. Xiao, S. Madhivanan, T. Salameh, M. Nichols, L.M. Reece, J. F. Leary, K. Otto, A. Natarajan, A. Ramesh, et al., Low and high voltage electrochemotherapy for breast cancer: an in vitro model study. In Electroporation-Based Therapies for Cancer: From Basics to Clinical Applications, Elsevier, 2014, pp. 55–102. ISBN 9781907568152.

[77] J.L. Vásquez, P. Ibsen, H. Lindberg, J. Gehl, In vitro and in vivo experiments on electrochemotherapy for bladder cancer, J. Urol. 193 (2015) 1009–1015, https://doi.org/10.1016/j.juro.2014.09.039.

[78] R.P. Ramachandran, S. Madhivanan, R. Sundararajan, C. Wan-Ying Lin, K. Sankaranarayanan, An in vitro study of electroporation of leukemia and cervical cancer cells. In Electroporation-Based Therapies for Cancer: From Basics to Clinical Applications, Elsevier, 2014, pp. 161–183. ISBN 9781907568152.

[79] C. Souza, N.F. Villarino, K. Farnsworth, M.E. Black, Enhanced cytotoxicity of bleomycin, cisplatin, and carboplatin on equine sarcoid cells following Electroporation-Mediated delivery in vitro, J. Vet. Pharm. Ther. 40 (2017) 97–100, https://doi.org/10.1111/jvp.12331.

[80] S. Kranjc, M. Cemazar, G. Sersa, J. Scancar, S. Grabner, In vitro and in vivo evaluation of electrochemotherapy with Trans-Platinum analogue Trans-[PtCl2 (3-Hmpy)2], Radio. Oncol. 51 (2017) 295–306, https://doi.org/10.1515/RAON-2017-0034.

[81] S. Kranjc, M. Cemazar, G. Sersa, J. Scancar, S. Grabner, In vitro and in vivo evaluation of electrochemotherapy with Trans-Platinum analogue Trans-[PtCl2 (3-Hmpy)2], Radio. Oncol. 51 (2017) 295–306, https://doi.org/10.1515/raon-2017-0034.

[82] O. Michel, P. Błasiak, J. Saczko, J. Kulbacka, M. Drąg-Zalesińska, A. Rzechonek, Electropermeabilization of metastatic chondrosarcoma cells from primary cell culture, Biotechnol. Appl. Biochem 66 (2019) 945–954, https://doi.org/10.1002/bab.1809.

[83] M. Fiorentzis, P. Katopodis, H. Kalirai, B. Seitz, A. Viestenz, S.E. Coupland, Conjunctival melanoma and electrochemotherapy: preliminary results using 2D and 3D cell culture models in vitro, Acta Ophthalmol. 97 (2019) e632–e640, https://doi.org/10.1111/aos.13993.

[84] J. Mączyńska, A. Choromańska, J. Kutkowska, M. Kotulska, M. Zalewski, J. Zalewski, J. Kulbacka, J. Saczko, Effect of electrochemotherapy with betulinic acid or cisplatin on regulation of heat shock proteins in metastatic human carcinoma cells in vitro, Oncol. Rep. 41 (2019) 3444–3454, https://doi.org/10.3892/or.2019.7103.

[85] M. Drąg-Zalesińska, J. Saczko, A. Choromańska, A. Szewczyk, N. Rembiałkowska, J. Kulbacka, A. Rzechonek, Cisplatin and vinorelbine -Mediated electrochemotherapeutic approach against multidrug resistant small cell lung cancer (H69Ar) in vitro, Anticancer Res 39 (2019) 3711–3718, https://doi.org/10.21873/anticanres.13519.

[86] U. Kesar, B. Markelc, T. Jesenko, K. Ursic Valentinuzzi, M. Cemazar, P. Strojan, G. Sersa, Effects of electrochemotherapy on immunologically important modifications in tumor cells, Vaccin. (Basel) 11 (2023) 925, https://doi.org/10.3390/VACCINES11050925/S1.

[87] K. Uršič Valentinuzzi, U. Kamenšek, S. Kranjc Brezar, C. Heranney, T. Komel, S. Buček, M. Čemažar, G. Serša, Electrochemotherapy with bleomycin, oxaliplatin, or cisplatin in mouse tumor models, from tumor ablation to in situ vaccination, Front Immunol. 16 (2025) 1470432, https://doi.org/10.3389/FIMMU.2025.1470432/BIBTEX.

[88] K. Ursic, S. Kos, U. Kamensek, M. Cemazar, J. Scancar, S. Bucek, S. Kranjc, B. Staresinic, G. Sersa, Comparable effectiveness and immunomodulatory actions of oxaliplatin and cisplatin in electrochemotherapy of murine melanoma, Bioelectrochemistry 119 (2018) 161–171, https://doi.org/10.1016/J.BIOELECHEM.2017.09.009.

[89] B. Hadzialjevic, M. Omerzel, B. Trotovsek, M. Cemazar, T. Jesenko, G. Sersa, M. Djokic, Electrochemotherapy combined with immunotherapy – a promising potential in the treatment of cancer, Front Immunol. 14 (2023) 1336866, https://doi.org/10.3389/FIMMU.2023.1336866/BIBTEX.

[90] B. Trotovšek, M. Djokić, M. Čemažar, G. Serša, New era of electrochemotherapy in treatment of liver tumors in conjunction with immunotherapies, World J. Gastroenterol. 27 (2021) 8216, https://doi.org/10.3748/WJG.V27.I48.8216.

[91] I. Barca, F. Ferragina, E. Kallaverja, M.G. Cristofaro, Synergy of electrochemotherapy and immunotherapy in the treatment of skin squamous cell carcinoma of the head and neck, Oral. Maxillofac. Surg. Cases 9 (2023) 100330, https://doi.org/10.1016/J.OMSC.2023.100330.

[92] M.E. Alkış, N. Turan, Y. Alan, S. Irtegun Kandemir, K. Buldurun, Effects of electroporation on anticancer activity of 5-FU and newly synthesized Zinc(II) complex in Chemotherapy-Resistance human brain tumor cells, Med. Oncol. 38 (2021) 129, https://doi.org/10.1007/s12032-021-01579-7.

[93] M.M. Kraemer, T. Tsimpaki, U. Berchner-Pfannschmidt, N.E. Bechrakis, B. Seitz, M. Fiorentzis, Calcium electroporation reduces viability and proliferation capacity of four uveal melanoma cell lines in 2D and 3D cultures, Cancers (Basel) 14 (2022), https://doi.org/10.3390/cancers14122889.

[94] C.M. Wolff, S. Bekeschus, Synergistic in vitro anticancer toxicity of pulsed electric fields and glutathione, Int J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms232314772.

[95] N. Rembiałkowska, V. Novickij, E. Radzevičiūtė-Valčiukė, E. Mickevičiūtė, A. Gajewska-Naryniecka, J. Kulbacka, Susceptibility of various human cancer cell lines to nanosecond and microsecond range electrochemotherapy: feasibility of Multi-Drug cocktails, Int J. Pharm. 646 (2023), https://doi.org/10.1016/j.ijpharm.2023.123485.

[96] D. Miklavčič, Handbook of electroporation, Springer International Publishing, 2017, pp. 1–4. ISBN 9783319328867.

[97] W. Zhang, L. Seymour, E.X. Chen, Determination of intact oxaliplatin in human plasma using high performance liquid Chromatography-Tandem mass spectrometry, J. Chromatogr. B 876 (2008) 277–282, https://doi.org/10.1016/J.JCHROMB.2008.10.055.

[98] S.R. Wiegell, K. Hendel, C.S.K. Fuchs, J. Gehl, M. Vissing, S.W. Bro, J.T. Troelsen, G.B.E. Jemec, M. Haedersdal, An explorative study on calcium electroporation for Low-Risk basal cell carcinoma, Acta Derm. Venereol. 104 (2024) adv19678, https://doi.org/10.2340/actadv.v104.19678.

[99] J.-Y. Fang, C.-F. Hung, Y.-P. Fang, T.-F. Chan, Transdermal iontophoresis of 5-Fluorouracil combined with electroporation and laser treatment, Int J. Pharm. 270 (2004) 241–249, https://doi.org/10.1016/j.ijpharm.2003.10.025.

[100] J.L. Vásquez, J. Gehl, G.G. Hermann, Electroporation enhances mitomycin c cytotoxicity on T24 bladder cancer cell line: a potential improvement of intravesical chemotherapy in bladder cancer, Bioelectrochemistry 88 (2012) 127–133, https://doi.org/10.1016/j.bioelechem.2012.08.001.

[101] H. Falk, L.W. Matthiessen, G. Wooler, J. Gehl, Calcium electroporation for treatment of cutaneous metastases; a randomized Double-Blinded phase II study, comparing the effect of calcium electroporation with electrochemotherapy, Acta Oncol. (Madr.) 57 (2018) 311–319, https://doi.org/10.1080/0284186X.2017.1355109.

[102] W.R. Panje, N. Sadeghi, Endoscopic and electroporation therapy of paranasal sinus tumors, Am. J. Rhinol. 14 (2000) 187–192, https://doi.org/10.2500/105065800782102744.

[103] M.A. Esmekaya, H. Kayhan, A. Coskun, A.G. Canseven, Effects of cisplatin electrochemotherapy on human neuroblastoma cells, J. Membr. Biol. 249 (2016) 601–610, https://doi.org/10.1007/s00232-016-9891-4.

[104] M. Cemazar, Z. Pipan, S. Grabner, N. Bukovec, G. Sersa, Cytotoxicity of different platinum (II) analogues to human tumour cell lines in vitro and murine tumour in vivo alone or combined with electroporation, Anticancer Res 26 (2006) 1997–2002.

[105] H. Sun, K. Bhandari, S. Burrola, J. Wu, W.-Q. Ding, Pancreatic ductal Cell-Derived extracellular vesicles are effective drug carriers to enhance Paclitaxel's efficacy in pancreatic cancer cells through Clathrin-Mediated endocytosis, Int J. Mol. Sci. 23 (2022) 4773, https://doi.org/10.3390/ijms23094773.

[106] Y. Wang, M. Guo, D. Lin, D. Liang, L. Zhao, R. Zhao, Y. Wang, Docetaxel-Loaded exosomes for targeting Non-Small cell lung cancer: preparation and evaluation *in vitro* and *in vivo*, Drug Deliv. 28 (2021) 1510–1523, https://doi.org/10.1080/10717544.2021.1951894.

[107] S. Meschini, M. Condello, P. Lista, B. Vincenzi, A. Baldi, G. Citro, G. Arancia, E. P. Spugnini, Electroporation adopting trains of biphasic pulses enhances in vitro and in vivo the cytotoxic effect of doxorubicin on multidrug resistant colon adenocarcinoma cells (LoVo), Eur. J. Cancer 48 (2012) 2236–2243, https://doi.org/10.1016/j.ejca.2011.11.031.

[108] N. Bhutiani, Y. Li, Q. Zheng, H. Pandit, X. Shi, Y. Chen, Y. Yu, Z.R. Pulliam, M. Tan, R.C.G. Martin, Electrochemotherapy with irreversible electroporation and FOLFIRINOX improves survival in murine models of pancreatic adenocarcinoma, Ann. Surg. Oncol. 27 (2020) 4348–4359, https://doi.org/10.1245/s10434-020-08782-2.

[109] N. Bhutiani, S. Agle, Y. Li, S. Li, R.C.G. Martin, Irreversible electroporation enhances delivery of gemcitabine to pancreatic adenocarcinoma, J. Surg. Oncol. 114 (2016) 181–186, https://doi.org/10.1002/jso.24288.

[110] M.J. Jaroszeski, V. Dang, C. Pottinger, J. Hickey, R. Gilbert, R. Heller, Toxicity of anticancer agents mediated by electroporation in vitro, Anticancer Drugs 11 (2000) 201–208, https://doi.org/10.1097/00001813-200003000-00008.

[111] N. Mondal, D.C. Dalal, Modelling of reversible tissue electroporation and its thermal effects in drug delivery, Eur. J. Pharm. Biopharm. 190 (2023) 47–57, https://doi.org/10.1016/j.ejpb.2023.07.005.

[112] X.-N. Tao, H.-T. Liu, X.-W. Xiang, C.-H. Zhu, J. Qiu, H. Zhao, K.-F. Liu, Regulating the distribution and accumulation of charged molecules by progressive

electroporation for improved intracellular delivery, ACS Appl. Mater. Interfaces 16 (2024) 36063–36076, https://doi.org/10.1021/acsami.4c05340.
[113] R. Cadossi, M. Ronchetti, M. Cadossi, Locally enhanced chemotherapy by electroporation: clinical experiences and perspective of use of electrochemotherapy, Future Oncol. 10 (2014) 877–890, https://doi.org/10.2217/fon.13.235.
[114] X. Gong, Z. Chen, J.J. Hu, C. Liu, Advances of Electroporation-Related therapies and the synergy with immunotherapy in cancer treatment, Vaccin. (Basel) 10 (2022) 1942, https://doi.org/10.3390/vaccines10111942.
[115] S.K. Frandsen, M. Vissing, J. Gehl, A comprehensive review of calcium Electroporation—A novel cancer treatment modality, Cancers (Basel) 12 (2020) 290, https://doi.org/10.3390/cancers12020290.
[116] A. Emami Nejad, S. Najafgholian, A. Rostami, A. Sistani, S. Shojaeifar, M. Esparvarinha, R. Nedaeinia, S. Haghjooy Javanmard, M. Taherian, M. Ahmadlou, et al., The role of hypoxia in the tumor microenvironment and development of cancer stem cell: a novel approach to developing treatment, Cancer Cell Int 21 (2021) 62, https://doi.org/10.1186/s12935-020-01719-5.
[117] R.J. DeBerardinis, N.S. Chandel, Fundamentals of cancer metabolism, Sci. Adv. 2 (2016) e1600200, https://doi.org/10.1126/sciadv.1600200.
[118] P. Cardona, M. Spring, J. Bao, Y. Xie, B. Houk, Relative bioavailability of sotorasib following administration as a water dispersion to healthy subjects and compatibility with enteral administration, Clin. Pharm. Drug Dev. (2024), https://doi.org/10.1002/cpdd.1468.
[119] I. Vuu, U.P. Dahal, Z. Wang, X. Shen, J. Rodgers, J. Wahlstrom, B. Houk, Absorption, metabolism and excretion of [14C]-Sotorasib in healthy Male subjects: characterization of metabolites and a minor Albumin-Sotorasib conjugate, Cancer Chemother. Pharm. 90 (2022) 357–367, https://doi.org/10.1007/s00280-022-04470-y.
[120] E.C. Nakajima, N. Drezner, X. Li, P.S. Mishra-Kalyani, Y. Liu, H. Zhao, Y. Bi, J. Liu, A. Rahman, E. Wearne, et al., FDA approval summary: sotorasib for *kras g12c* -Mutated metastatic NSCLC, Clin. Cancer Res. 28 (2022) 1482–1486, https://doi.org/10.1158/1078-0432.CCR-21-3074.
[121] A.D. Pumford, M. Bauman, S. Bouchal, C. Riviere-Cazaux, I. Jusue-Torres, S. Hong, B.J. Neth, U. Sener, I.F. Parney, Neurosurgical implications of targeting hypoxia-inducible factor 2α in hemangioblastomas with belzutifan, World Neurosurg. 190 (2024) 291–296, https://doi.org/10.1016/j.wneu.2024.07.175.
[122] W.W. Choi, J.L. Boland, A. Kalola, J. Lin, Belzutifan (MK-6482): biology and clinical development in solid tumors, Curr. Oncol. Rep. 25 (2023) 123–129, https://doi.org/10.1007/s11912-022-01354-5.
[123] T. Else, E. Jonasch, O. Iliopoulos, K.E. Beckermann, V. Narayan, B.L. Maughan, S. Oudard, J.K. Maranchie, A.B. Iversen, C.M. Goldberg, et al., Belzutifan for von Hippel–Lindau disease: pancreatic lesion population of the phase 2 LITESPARK-004 study, Clin. Cancer Res. 30 (2024) 1750–1757, https://doi.org/10.1158/1078-0432.CCR-23-2592.
[124] T. Dolinsek, L. Prosen, M. Cemazar, T. Potocnik, G. Sersa, Electrochemotherapy with bleomycin is effective in BRAF mutated melanoma cells and interacts with BRAF inhibitors, Radio. Oncol. 50 (2016) 274–279, https://doi.org/10.1515/raon-2016-0042.
[125] T. Żołek, A. Mazurek, I.P. Grudzinski, In silico studies of novel vemurafenib derivatives as BRAF kinase inhibitors, Molecules 28 (2023) 5273, https://doi.org/10.3390/MOLECULES28135273/S1.
[126] C. Tabolacci, M. Cordella, S. Mariotti, S. Rossi, C. Senatore, C. Lintas, L. Levati, D. D'arcangelo, A. Facchiano, S. D'atri, et al., Melanoma cell resistance to vemurafenib modifies Inter-Cellular communication signals, **2021**, *9*, 79, Biomedicines 9 (2021) *79*, https://doi.org/10.3390/BIOMEDICINES9010079.
[127] A. Carrato Mena, E. Grande Pulido, C. Guillén-Ponce, Understanding the Molecular-Based mechanism of action of the tyrosine kinase inhibitor: sunitinib, Anticancer Drugs 21 (2010), https://doi.org/10.1097/01.CAD.0000361534.44052.C5.
[128] S. Wang, C. Gilbreath, R.K. Kollipara, R. Sonavane, X. Huo, P. Yenerall, A. Das, S. Ma, G.V. Raj, R. Kittler, Mithramycin suppresses DNA damage repair via targeting androgen receptor in prostate cancer, Cancer Lett. 488 (2020) 40–49, https://doi.org/10.1016/j.canlet.2020.05.027.
[129] V. Duverger, A.-M. Murphy, D. Sheehan, K. England, T.G. Cotter, I. Hayes, F. J. Murphy, The anticancer drug mithramycin a sensitises tumour cells to apoptosis induced by tumour necrosis factor (TNF), Br. J. Cancer 90 (2004) 2025–2031, https://doi.org/10.1038/sj.bjc.6601824.
[130] Z. Jia, Y. Gao, L. Wang, Q. Li, J. Zhang, X. Le, D. Wei, J.C. Yao, D.Z. Chang, S. Huang, et al., Combined treatment of pancreatic cancer with mithramycin a and tolfenamic acid promotes Sp1 degradation and synergistic antitumor activity, Cancer Res 70 (2010) 1111–1119, https://doi.org/10.1158/0008-5472.CAN-09-3282.
[131] D. Schweer, J.R. McCorkle, J. Rohr, O.V. Tsodikov, F. Ueland, J. Kolesar, Mithramycin and analogs for overcoming cisplatin resistance in ovarian cancer, Biomedicines 9 (2021) 70, https://doi.org/10.3390/biomedicines9010070.
[132] P. Houba, E. Boven, C. Erkelens, R. Leenders, J. Scheeren, H. Pinedo, H. Haisma, The efficacy of the anthracycline prodrug Daunorubicin-GA3 in human ovarian cancer xenografts, Br. J. Cancer 78 (1998) 1600–1606, https://doi.org/10.1038/bjc.1998.729.
[133] H.M. Al-Aamri, H.R. Irving, C. Bradley, T. Meehan-Andrews, Intrinsic and extrinsic apoptosis responses in leukaemia cells following daunorubicin treatment, BMC Cancer 21 (2021) 438, https://doi.org/10.1186/s12885-021-08167-y.
[134] A. Seno, A. Mizutani, K. Aizawa, R. Onoue, J. Masuda, N. Ochi, S. Taniguchi, T. Sota, Y. Hiramoto, T. Michiue, et al., Daunorubicin can eliminate IPS-Derived cancer stem cells via ICAD/CAD-Independent DNA fragmentation, Cancer Drug Resist. (2019), https://doi.org/10.20517/cdr.2019.01.
[135] R.-J. Ju, L. Cheng, X.-M. Peng, T. Wang, C.-Q. Li, X.-L. Song, S. Liu, J.-P. Chao, X.-T. Li, Octreotide-Modified liposomes containing daunorubicin and dihydroartemisinin for treatment of invasive breast cancer, Artif. Cells Nanomed. Biotechnol. 46 (2018) 616–628, https://doi.org/10.1080/21691401.2018.1433187.
[136] I.-C. Lee, B. Choi, Withaferin-A-A natural anticancer agent with pleitropic mechanisms of action, Int J. Mol. Sci. 17 (2016) 290, https://doi.org/10.3390/ijms17030290.
[137] I.-C. Lee, B. Choi, Withaferin-A-A natural anticancer agent with pleitropic mechanisms of action, Int J. Mol. Sci. 17 (2016) 290, https://doi.org/10.3390/ijms17030290.
[138] M. Atteeq, Evaluating anticancer properties of withaferin A—a potent phytochemical, Front Pharm. 13 (2022), https://doi.org/10.3389/fphar.2022.975320.
[139] L. García-Morales, A.M. Castillo, J. Tapia Ramírez, H. Zamudio-Meza, M. del C. Domínguez-Robles, I. Meza, CBD reverts the mesenchymal invasive phenotype of breast cancer cells induced by the inflammatory cytokine IL-1β, Int J. Mol. Sci. 21 (2020) 2429, https://doi.org/10.3390/ijms21072429.
[140] R. Likar, M. Köstenberger, G. Nahler, Cannabidiol bei tumorerkrankungen, Der Schmerz 34 (2020) 117–122, https://doi.org/10.1007/s00482-019-00438-9.
[141] C.G. Heider, S.A. Itenberg, J. Rao, H. Ma, X. Wu, Mechanisms of cannabidiol (CBD) in cancer treatment: a review, Biol. (Basel) 11 (2022) 817, https://doi.org/10.3390/biology11060817.
[142] L. García-Morales, M.G. Mendoza-Rodríguez, J. Tapia Ramírez, I. Meza, CBD inhibits in vivo development of human breast cancer tumors, Int J. Mol. Sci. 24 (2023) 13235, https://doi.org/10.3390/ijms241713235.
[143] L.F. Tremble, C.C.B.B. Heffron, P.F. Forde, The effect of calcium electroporation on viability, phenotype and function of melanoma conditioned macrophages, Sci. Rep. 10 (2020) 20645, https://doi.org/10.1038/s41598-020-77743-2.