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Non-Patentable Chemicals for Cancer Therapy

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Abstract

A large number of chemicals are unpatentable within the current patent framework and existing structure for protection of intellectual property in drug development. Funding to study safety and efficacy of non-patentable molecules is very limited. Researchers commonly make modifications to the structure of unpatentable molecules in an attempt to make derivatives that can be patented, instead of testing for effective and safe molecules that are not patentable. This article discusses the potential of non-patentable chemicals and impact of relevant policies. A case study of dichloroacetate (DCA) role in cancer treatment demonstrates existing potential for developing novel anti-cancer compounds, despite the current structure of the patenting system that creates financial unviability of pursuing the research of non-patentable molecules. Testing efficacy and safety of unpatentable chemicals and their derivatives would expand access to more cancer therapeutic molecules and advance oncological research.

Keywords: Non-Patentable Chemicals; Cancer Therapy; Orphan Drugs; DCA; DCMAH

Introduction

Development of novel cancer therapies involves drug discovery and testing of test article efficacy and safety in a preclinical setting to seek regulatory approval. Following these steps, there are three main phases of clinical trials and final compliance review. The median cost of developing a single cancer drug was estimated to be $757 million [1] in 2017. Patent protection is a key element in securing the costs, but not all patents are equally strong and often failure to follow subtle rules can significantly impact a patent's value. Moreover, a large number of chemicals are part of the public domain and are non-patentable. The existing system of intellectual property protection implies that without patents, patients will not be able to benefit from life sciences and medical research results because they are publically available [2]. Manufacturers of non-patentable chemicals do not need to demonstrate safety or efficacy but no claims of improving health or treating illness can be made for these products by their manufacturers. Unfortunately, violations of this policy are not uncommon [3]. This creates a situation where there is no economic incentive for testing safety and efficacy, even in pre-clinical setting.

The concept of the existing patenting system relies on the economic incentive for pharmaceutical and medical device companies that would lead to further investment into research and development, as well as innovative products to enhance healthcare. This perspective have been increasingly criticized within the last few decades [4]. Patents are criticized for obstructing healthcare by elevating the cost of vital medications and hindering biomedical research by restricting access to essential patented materials. Public discussion and active participation of regulatory institutions led to new programs for expedited drug development [5], including the U.S. Orphan Drug Act that successfully delivered a number of novel treatments for rare cancers, of which some were subsequently used in other, nonorphan indications. Oncological drug development proves to be a major player in overall orphan drug research, displayed by more than one-third of all US FDA-approved orphan drugs with oncological indications [5,6].

Cancer therapy encompasses a diverse array of treatments aimed at combating malignant cell growth. Traditional modalities such as chemotherapy, radiation therapy, and surgery have long been cornerstones in cancer management. However, recent decades have witnessed a burgeoning interest in novel therapeutic approaches that target specific molecular pathways driving tumorigenesis. Non-patentable chemicals and off-patent drugs represent an important avenue in cancer therapy research and development. These compounds, which are not protected by patents and are often available as lower-cost alternatives to branded medications, have garnered significant interest for their potential in cancer treatment. These compounds may exhibit diverse mechanisms of action, making them valuable candidates for combination therapies, personalized and targeted cancer therapy, and overcoming drug resistance in cancer. By harnessing the collective knowledge of these compounds, the new treatment strategies can be used to improve patient outcomes in oncology.

Platinum-based drugs (cisplatin, carboplatin, and oxaliplatin) have been pivotal in treating various cancers for over 30 years. These agents are widely used for chemotherapeutic treatment of cancer and are often selected as first-line treatment despite their side effects, elevated systemic toxicity, and the development of resistance to the drugs. Platinates work primarily by forming platinum DNA crosslinks, disrupting cancer cell DNA and activating signal transduction pathways. However, their effectiveness is limited by resistance mechanisms, including reduced drug uptake, neutralization by antioxidants, and enhanced DNA repair. Recent research focuses on understanding these resistance pathways, identifying genes that may contribute to resistance, and exploring the clinical side effects of treatment. Development of targeted cancer treatments often utilize platinates as cargo molecules. Advances in nanotechnology have led to the development of Pt-based nanodrugs, offering targeted cancer therapy with potentially lower side effects and improved efficacy [7].

Camptothecin was first identified in the mid-60s by Wall and Wani showed promising anticancer effects, but the poor solubility and unpredictable side effects prevented the drug from being approved. Camptothecin is a naturally occurring, pentacyclic quinoline alkaloid that possesses high cytotoxic activity in a variety of cell lines. Camptothecin remains at equilibrium in an active lactone form and inactive hydrolyzed carboxylate form. The active lactone binds to DNA topoisomerase I cleavage complex, believed to be the single site of activity. Binding inhibits DNA religation, resulting in apoptosis. A series of small molecule camptothecin derivatives have been developed that increase solubility, lactone stability and bioavailability to varying levels of success. A number of macromolecular agents have also been described wherein camptothecin(s) are covalently appended or noncovalently associated with the goal of improving solubility and lactone stability, while taking advantage of the tumor physiology to deliver larger doses of drug to the tumor with lower systemic toxicity [8].

Adriamycin (ADM) has been effective against many types of solid tumors in clinical applications. However, its use is limited because of systemic toxicities, primarily cardiotoxicity, and multidrug resistance. A new active receptor-mediated complex, ADM conjugated with 2-amino-2-deoxy-d-glucose and succinic acid (2DG–SUC–ADM), was designed to target tumor cells through glucose transporter 1 (GLUT1). Cell proliferation MTT assays and confocal images showed that the complex had better inhibition rate to tumor cells and low toxicity level to normal cells. Most importantly, the complex displayed a potential to reverse overcome multidrug resistance in cancer cells, with more complex transported into the nucleus of tumor cells. In vivo experiments demonstrated that ADM complexes could significantly decrease organ toxicity and enhance the antitumor efficacy compared with free ADM, indicating a promising drug of 2DG–SUC–ADM for targeted cancer therapy [9].

Curcumin has been shown to suppress the expression of cyclin D1 in many types of cancer including colon, breast, bladder, head and neck, cervical, and pancreatic carcinomas. The anticancer effect is attributed to curcumin's inhibition of NF-κB activation and subsequent suppression of downstream gene products [10].

Salicylic acid and acetylsalicylic acid have well-known applications in medicine with demonstrated anticancer activity against melanoma via Akt/mTOR/AMPK-dependent activation of nitric oxide synthase 3 (eNOS). In both *in vitro* and *in vivo* models, salicylic acid triggered endoplasmic reticulum (ER) stress, which culminates with the upregulation of the pro-apoptotic transcription factor C/EBP homologous protein [11].

Dichloroacetate Case Study

Dichloroacetate is an example of a non-patentable chemical that was studied by Otto Warburg back in the 1920s relating to cancer physiology (in particular the associated buildup of lactate). The chemical compound has a relatively complicated function in living cells. One of its first early uses several decades ago was to treat the buildup of lactate in human tissues [12]. In recent years, DCA has been studied in connection to cancer research and a number of reports demonstrated promising anti-cancer activity, suggesting its use in clinical trials as an anti-cancer treatment [13, 14]. A number of in vitro studies linked the compound to the inhibition of breast cancer [15], colon cancer [16], prostate cancer [17], glioblastoma [18], lung cancer [19] , leukemia [20], and other types of cancer (Table 2).

Table 1: Cancer suppression mechanism of action for selected non-patentable chemicals.

Medication class	Platinating agents, statins, camptothecins, benzoic acids
Drugs and chemicals	Doxorubicin, ivermectin, salinomycin, metformin, thalidomide, disulfiram, sildenafil, propranolol, digoxin, bupropion, verapamil, tamoxifen
Herbal and natural	Curcumin, cannabidiol (CBD), medicinal plants, phytochemicals

Table 2: Selected reports of DCA anticancer effects against different types of cancer.

Title	Cancer	Year
Sensitization of breast cancer cells to paclitaxel by dichloroacetate through inhibiting autophagy	Breast cancer [15]	2017
Long-term stabilization of stage 4 colon cancer using sodium dichloroacetate therapy	Colon cancer [16]	2016
The effect of dichloroacetate in canine prostate adenocarcinomas and transitional cell carcinomas in vitro	Prostate cancer [17,24]	2016
Metabolic modulation of glioblastoma with dichloroacetate	Glioblastoma [18,24]	2010
Impact of sodium dichloroacetate alone and in combination therapies on lung tumor growth and metastasis	Lung cancer [19,26]	2021
Sodium dichloroacetate exhibits anti-leukemic activity in B-chronic lymphocytic leukemia (B-CLL) and synergizes with the p53 activator Nutlin-3	Leukemia [20,27]	2014
The influence of sodium dichloroacetate on the oxidative processes in sarcoma	Sarcoma [28]	2011
Metformin and sodium dichloroacetate effects on proliferation, apoptosis, and metabolic activity tested alone and in combination in a canine prostate and a bladder cancer cell line	Bladder cancer [29]	2021
Dichloroacetate attenuates the stemness of colorectal cancer cells via trigerring ferroptosis through sequestering iron in lysosomes.	Colorectal cancer [30]	2021
Non-Hodgkin's lymphoma reversal with dichloroacetate	Lymphoma [31]	2010
Dichloroacetate affects mitochondrial function and stemness-associated properties in pancreatic cancer cell lines	Pancreatic cancer [32]	2019
Dichloroacetate enhances the anti-tumor effect of sorafenib via modulating the ROS-JNK-Mcl-1 pathway in liver cancer cells	Liver cancer [33]	2021
Dichloroacetate as a novel pharmaceutical treatment for cancer-related fatigue in melanoma	Melanoma [34]	2023

Studying DCA's mechanism of action revealed it functions as an inhibitor of pyruvate dehydrogenase kinase (PDK), effectively reversing the Warburg effect and inducing tumor cell death. Despite its potential, studies on DCA's anti-cancer properties have highlighted the necessity for high dosages and documented instances of toxicity [21]. Showing promise, DCA was tested in an initial clinical trial, but the compound's toxic effects prevented it from becoming a common and affordable cancer therapeutic [22]. Despite DCA's promising preclinical anticancer efficacy, its transition to clinical application has been restrained by concerns over its neurotoxicity, however there is a clinical potential for DCA analogs or when used in synergy with chemotherapy, radiotherapy, and other anticancer agents, to amplify therapeutic efficacy while mitigating toxicity. Synergistic effects observed when DCA is combined with various chemotherapeutic agents across different cancer models were demonstrated with improved treatment outcomes and the ability to circumvent chemoresistance [22]. It elaborates on the integration of DCA with other potential anticancer drugs and natural compounds, highlighting instances of enhanced anticancer activity and reduced adverse effects, thereby presenting a compelling case for the combinatory use of DCA in oncology.

The effect of DCA on cancer stem cells (CSCs) demonstrated potential to target this notoriously resilient cancer cell population. By modulating the metabolic profile of CSCs, DCA presents a promising strategy to prevent tumor relapse, addressing one of the paramount challenges in cancer treatment [22]. Further development suggested DCA combinatorial use with traditional cancer treatments, testing new delivery methods for DCA therapy, and development and subsequent testing of DCA analog compounds [23].

The study of DCA alternatives evaluated eight small compounds with a conserved dichloric terminal for their in vitro and in vivo potential for anticancer activity [23]. Two compounds out of the initial eight ended up substantially reducing tumor growth. Data demonstrated that cationic dichloric compounds DCAH and DCMAH inhibit tumor growth in the U87 xenograft model of glioblastoma, suggesting their clinical potential as accessible anti-cancer drugs. Studies of cationic DCAH and DCMAH molecular mechanism of action demonstrated that analog compounds are likely to be different from that of the terminally carboxylic DCA, highlighting the need for further investigation to fully understand their therapeutic potential.

DCA and its analogs sparked an interest and received certain attention from the scientific community. However, most other classes of non-patentable chemical molecules are unlikely to be developed or even tested as potential cancer drugs due to the existing patenting structure and associated lack of funding. Under the existing structure for protection of intellectual property in drug development, the financially justified research choice is limited to modification of the structure of non-patentable molecules in an attempt to make derivatives that can be patented, instead of testing for effective and safe molecules that are not patentable. This structure limits the expansion of safe chemical molecules available to advance scientific research, as it is financially nonviable to pursue. If adequate grant funding was made available, it would create opportunity to investigate the potential of molecules such as DCA and DCA analogs within the structure of the current patenting system. Consequently, this would expand understanding of safety and anticancer efficacy of many non-patentable compounds, providing more therapeutic options to advance oncological research and cancer treatment.

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Conflict of Interest

No Conflict of Interest.

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