Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Assessment of the Potential of Cardiac Glycosides as New Stars in Cancer Treatment

Yixuan Li *

School of Pharmacy, Shenyang Pharmaceutical University, Benxi, China

* Corresponding Author Email: LYX605066536@outlook.com

Abstract. Cancer is a critical burden to global health. Cardiac glycosides (CGs), a kind of cardiac drug, have been proven to have therapeutic effects for a variety of tumors. However, directly using conventional CGs to treat cancer will lead to dispensable cardiotoxicity. CGs work by inhibiting the Na^+/K^+-ATPase, STAT 1 and STAT 3. It can also block the tumor cell cycle. By doing comparison, it can be known that the anticancer potential of UNBS1450 01 is comparable to that of paclitaxel while the combination therapy of the former does less harm to blood cells. The structural modification of Bufalin, a CG, significantly improved the activity, and a further optimization strategy is provided in this article. The substituent ring at position 3 should have not only para-substituted secondary nitrogen but also oxygen and substituted hydroxyl group on the ring. The targeted delivery system can be considered as well. CGs can also be combined with radiotherapy to increase the sensitivity of tumors to radiotherapy. However, the pH decrease caused by CGs may lead to insulin resistance in skeletal muscle cells, increasing the risk of developing diabetes. Future studies can refer to the aforementioned aspects and can pay attention to reducing the gastrointestinal and metabolism side effects of CGs.

Keywords: Cardiac glycosides; Na^+/K^+-ATPase; STAT 1; STAT 3; UNBS1450.

1. Introduction

It is acknowledged that cancers are severe diseases that are characterized by uncontrolled growth and metastasis of abnormal cells within the body. It does critical harm to global health by causing numerous deaths. Global cancer statistics, which is calculated by the International Agency for Research on Cancer (IARC). There were nearly 20 million new cases of cancer and 9.7 million deaths in 2022 [1].

Because of its great lethality, cancers continuously attract global attention. Cancer therapy nowadays includes surgical intervention, chemotherapy, radiotherapy, precision-targeted therapy, and immunotherapy [2]. Recently researchers have begun to use machine learning-based automatic segmentation techniques [3]. More and more methods can be taken into consideration, encompassing using cardiac glycosides (CGs).

CGs are drugs conventionally acknowledged for their function in treating arrhythmias and heart failure. They are natural secondary metabolites and can be categorized according to the structure of their lactone ring. The CGs with a five-membered lactone ring are called cardenolides, and the bufadienolides are those with a six-membered lactone ring [4]. They can increase the contractility of the heart [5] by specifically binding to the Na^+/K^+-ATPase and increase intracellular calcium levels [6].

Over the years, the anti-tumor effect of CGs has been discovered and focused on. Studies have found that they can selectively kill malignant tumor cells without affecting normal cells [7]. Therefore, treatment with CGs is considered a promising anti-tumor drug therapy.

However, they are classical cardiovascular drugs instead of typical cancer drugs. The direct use of traditional CGs in cancer treatment will lead to unwanted cardiac toxicity and gastrointestinal disorders [4]. To prevent such side effects, the anticancer activities of several known CGs are profoundly studied and the structure of these compounds is modified based on chemical mechanisms

aiming at developing new analogs with higher selectivity. Proven by abundant discoveries and studies, lung, breast, and prostate cancer, etc., have all shown bright results following treatment with new CGs and their analogs [4,6].

Although the current use of CGs for tumor treatment is still in the optimized phase, based on the action mechanism, some apparent advantages can be revealed, and possible problems will be exposed. The following potential drugs and shorts of CG treatment will be discussed. An assessment can be done by comparing their effects in treating cancer with those of traditional chemotherapy and radiotherapy. Assessment not only foresees the possible direction of optimization in the future but also helps manufacture safer, more effective, more affordable drugs and relieve the physical and mental stress of patients so that cancer treatment is hopeful to make further advancements.

2. Pharmacological Mechanisms

2.1. Inhibition of the Na+ /K+ -ATPase

Compared with healthy tissues, cancer cells have a higher concentration of Na^+ and K^+ in micro-environment. The over-expression of ion channels is related to metastasis.

After CGs bind to their receptors, the Ras and MAPK routes can be activated so that the expression of mitochondrial reactive oxygen species (ROS) increases, which leads to the induction of cell apoptosis. What's more, the pH value of cancer cells is higher than that of normal cells, by inhibiting Na^+/K^+-ATPase, CGs, like Strophanthin, can increase the concentration of H^+ in cancer cells, and the basic environment inside them will be altered directly leading to their apoptosis [8].

2.2. Inhibition of Signal Transduction and Transcription Activators STAT 1 and STAT 3

Immune checkpoints (ICs) have an inhibitory effect on immune function, which aims at protecting the body from being damaged by immune reactions. But sometimes, tumors can escape due to this function. ID01 is a kind of IC protein whose expression cannot accomplished without the stimulation of IFN-γ(Interferon-gamma). By inhibiting the downstream IFN-γsignaling mediator, STAT 1, CGs can downregulate the effect of IFN-γon the induction of ID01 [9].

Ouabain is a kind of CG. In various kinds of tumor cells, STAT 3 is continuously activated and expressed at high levels. It can promote the proliferation, and metastasis of cancer cells and the growth of blood vessels. By blocking the protein translation of STAT 3, ouabain can effectively reduce its expression, thus inhibiting the activation of tumor growth signals [5].

2.3. Blockage of the Cell Cycle

Various CGs have been verified to be able to block the cell cycle. If the expression of oncogenes is downregulated and that of antioncogene and proapoptotic genes is upregulated, with activated Caspase-9 and the initiation of the apoptotic cascade, the cell cycle of cancer cells will stop in the G0 / G1 phase, then undergo apoptosis. In addition, some CGs can activate ERK 1/2(Extracellular Signal-Regulated Kinase 1/2), while some others can inhibit the expression of Fas (a cell surface death receptor) specifically, which means the normal cells are less affected [8].

3. Potential

3.1. Drug Therapies

3.1.1. UNBS1450 01

2-oxovoruschari is a kind of compound that has both anticancer potential and high toxicity. By doing the structural modification, the semi-synthetic CG analog UNBS1450 01 came into birth. It can inhibit Na^+/K^+-ATPase and the activation of the NF-κB pathway, thus leading to tumor autophagy.

Compared with traditional CGs, its anticancer activity exceeds natural derivatives such as digitoxin, oleandrin, or buffering, and has fewer cardiac side effects [8]. It has been proven that its maximum tolerated dose is equal to 24 times that of ouabain and 12 times of digoxin [10], and its suppressive effect on tumors can reach 20-100 times that of digoxin. It has a longer effect and lower toxicity than its toxicity is just 1/10 of digoxin [11].

By experimenting, it can be seen that the inhibition effect on cancer growth of UNBS1450 01 is similar to that of paclitaxel. To treat specific tumor cells, such as vincristine and doxorubicin-resistant ones, paclitaxel concentration is required to reach 10000 nM, such a high concentration will lead to adverse cytotoxic effects, while UNBS1450 01 is only required for 45 nM, which is expected to reduce patient suffering by reducing drug administration. And it has a promising future in dealing with treatment-resistant tumors [10].

To figure out the toxicity and side effects of paclitaxel as chemotherapy, 96 patients with pathologically confirmed malignant tumors were treated with paclitaxel for 304 treatment cycles. The results showed significant hematological toxicity, with the decrease of leukocyte, erythrocyte, hemocyte, and thrombocytes, the incidence rate can reach 61.8%, 50%, and 21.7% respectively. In addition, there were a series of other problems such as alopecia and myalgia [12], which made the patients miserable. So although paclitaxel is widely used as an anticancer drug, its toxicity is a big problem. It is time to speculate whether UNBS1450 also harms blood cells, if not, it can compensate for the deficiencies of paclitaxel therapy. Now UNBS1450 01 has been applied to treat leukemia [10]. In section 3.1.3, combination chemotherapy with UNBS1450 will be discussed. This innovative therapy is friendly to blood cells.

3.1.2. Bufalin-3 Compounds

The 3 positions of natural CGs connect to different kinds of sugars, which interact with the Na^+ / K^+ -ATPase receptor, and if more than one sugar is presented, only one of them can bind to the enzyme. Sugars are essential for the antitumor activity and pharmacokinetic properties of CGs.

By simulating the structure of sugars on CGs and using bioisosterism, the 3-position ester derivative bufalin-3-piperidine was synthesized, and its anticancer activity was higher than that of its parent compound Bufalin. Further, when the piperidine ring was replaced with other groups such as straight chain or cycloalkane, benzene ring, pyridine ring, and so on, the anticancer activity disappeared. Just the initial compound with piperidine shows the highest activity which equals 30 times Bufalin, and the imidazole substituted one showed little activity. The researchers focused on the NH on the piperidine ring and exchanged H with alkyl, acetyl, and benzyl. Unfortunately, although still active, cytotoxicity is still an unavoidable problem [11].

The researchers made a lot of modifications with N-containing groups, but oxygen or sulfur-containing branched, heterocyclic compounds have not been considered. Substituents containing only C have been proved inactivated. The bioisosteres of -NH- also include -O- and -S-, and they can be tried similarly.

As shown in Figure 1, the sugars on the 3 position of natural CGs always have O heterocycle which means O heterocycle-cotained group can be considered. In addition, the hydroxyl group on the ring may also play a significant role in increasing activity. In the structural modification process of Bufalin, compound 14, which has a hydroxyl group on its ring has certain activity, revealing that N-contained

heterocycle and hydroxyl group can be included at the same substituent. Firstly, replace H on the C of the pyridine ring with the hydroxyl group. Secondly, change the position and number of hydroxyl groups. There will be numerous new compounds with possible anticancer activity.

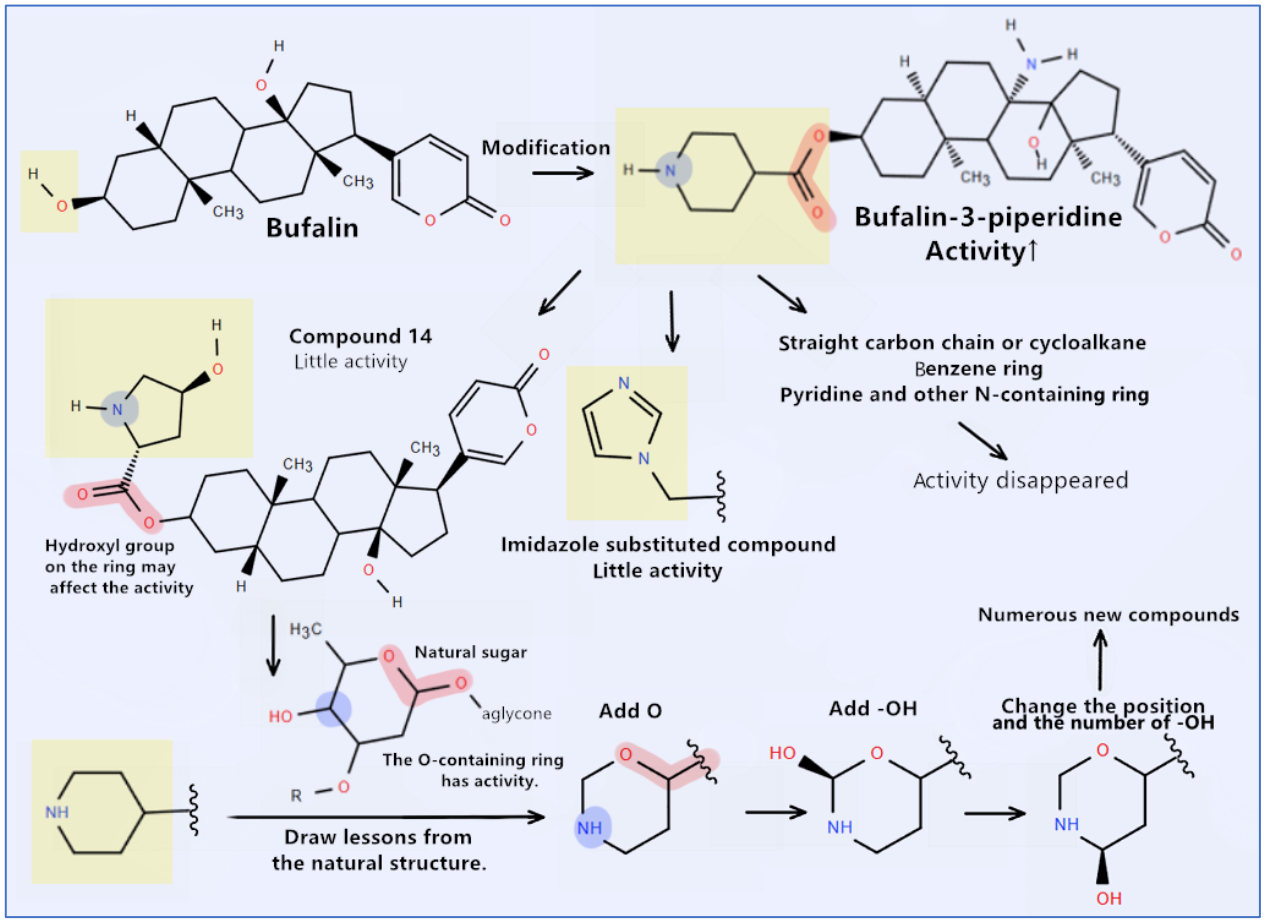

Fig. 1 The modification strategies of Bufalin 3 compounds [11].

It is known that basic N on piperidine is essential for increasing activity. If the N heterocycle is unsaturated, or if there are other N in the ring, the electrons on the unsaturated bond or other N will affect the important N so that the anticancer activity disappears.

After the H on N was replaced by other groups, the steric resistance increased. In addition, this H is necessary to form a hydrogen bond with the receptor. Above all, it is not suitable for modification. What's more, to overcome the toxicity, targeted delivery can be considered to specifically carry CGs toward tumor cells. There are also studies related to new CG delivery methods. In the experiment, acetyl thevetin B, which has severe vitro cytotoxicity, was encapsulated in chitosan-pluronic P123. The capsuled complex showed higher cytotoxic to A549 lung cancer cells than bare drugs. Loaded micelles are more likely to accumulate in the tumor rather than normal cells, thus it did not cause pathological damage to normal tissues. If CGs can be carried by chitosan-pluronic P123, they can be encapsulated and targeted to tumors, and the problem of cytotoxicity to normal tissues can be solved. This method also contributes to the improvement of the anticancer effects of CGs [13].

3.1.3. Combination with chemotherapy

Combining CGs with other chemotherapy drugs is a completely new strategy. The dose of CGs can be decreased to prevent cardiotoxicity, and they were administered with broad-spectrum and targeted classical anticancer drugs. After combining UNBS1450 with ABT-199, a synergistic effect was observed in dealing with acute myeloid leukemia (AML). This combination therapy is safe for platelets, lymphocytes, and healthy CD34+ stem cells. Studies have shown that patients who didn't respond to a single ABT-199(Venclexta, anticancer drug) treatment had good outcomes when ABT-199 was combined with UNBS1450 [13].

3.2. Radiotherapy

Radiation therapy may cause various injuries to patients, including skin peeling, darkening, and even breaking. The patients will feel weakness with deficient immunity, and suffer from gastrointestinal illness [14]. If the tumor responds more sensitively to radiotherapy, it will be possible to reduce the duration of radiation. With shorter exposure time, there will be less damage to healthy tissues and less harm to the body.

Experiments have demonstrated that oleandrin, a CG, can enhance the sensitivity of prostate tumor to radiation. The cells exhibited considerable sensitization to radiation within just one hour, and the effect intensified as time passed [15].

4. Possible Problem

CGs promote Na^+- H^+ exchange by inhibiting Na^+ /K^+ -ATPase, decreasing the pH inside the tumor cells and creating a more acidic environment to kill the tumor [8]. For most chemical reactions catalyzed by enzymes, the activity of the reaction depends on the pH of the body fluids. To maintain the homeostasis of the humoral environment, H^+ is excreted from the cell to the extracellular space and is eventually excreted out of the body [16]. So a decrease in intracellular pH will lead to a decrease in extracellular pH.

For skeletal muscle cells in a culture medium with low pH, the phosphorylation level of the insulin receptor and its affinity for insulin decreased. In addition, the phosphorylation of Akt (Protein Kinase B), downstream of the insulin receptor, also decreased, which led to reduced glucose uptake. This experiment mentioned that low extracellular pH may make skeletal muscle resistant to insulin. Too acidic environment may be a risk for the development of type 2 diabetes [16]. That should be paid attention to during CG use.

5. Conclusion

CGs have anticancer activity, their function is to inhibit Na^+ / K^+-ATPase, STATs, and the cell cycle, leading to effective suppression of tumor growth. CGs have many advantages as anticancer therapy. By doing a comparison, it can be seen that the traditional anticancer drug paclitaxel extremely harms blood cells while UNBS1450 combination therapy does not. Safer, more effective, and more specific are 3 characteristics of this combination therapy. Compared with traditional CGs, the activity of Bufalin-3 compounds is significantly improved, and the existing problems can be overcome by further structural modification or designing targeted delivery systems. Traditional radiotherapy can damage the skin and gastrointestinal tracts of patients. Combined with CGs can make tumors more sensitive, shorten the time of radiation, and reduce the damage. However, there are also some problems. CGs reduce intracellular pH, which induces insulin desensitization and increases the risk of diabetes.

By doing the assessment, the situation of the current development of CGs and the possible future optimization direction can be revealed. This information contributes to further enhancing CGs' original advantages, solving the existing problems, and promoting the improvement in antitumor treatment.

There are still side effects of CGs, like gastrointestinal reactions, that haven't been considered. The initial chemotherapy or radiotherapy can cause gastrointestinal unpleasantness, when they are combined with CGs, this harmful response may be aggravated. Future studies are expected to concentrate on many aspects. Firstly, the shortcomings of conventional drug therapies can be remedied by CGs. Secondly, the structure of CG derivatives and targeted delivery methods can be further optimized, aiming at achieving the highest efficiency and the lowest toxicity. The combination of radiotherapy with CGs will be more widely used. Finally is to solve the gastrointestinal stimulation problems and reduce the damage to the metabolism of CGs triggered by pH decrease.

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2024, 74 (3): 229-263.

[2] Rehman A, Ahmed S H, Ghias R, Ahmad I. Reinforcement learning based sliding mode control for optimal chemotherapy drug delivery in cancerous tumors [J]. Biomedical Signal Processing and Control, 2025, 103: 107485.

[3] Mazonakis M, Tzanis E, Kachris S, Lyraraki E, Damilakis J. A qualitative, quantitative, and dosimetric evaluation of a machine learning-based automatic segmentation method in treatment planning for gastric cancer [J]. Physica Medica, 2025, 130: 104896.

[4] Nik Nabil W N, Dai R, Liu M, Xi Z, Xu H. Repurposing cardiac glycosides for anticancer treatment: a review of clinical studies [J]. Drug Discovery Today, 2024, 29 (10): 104129.

[5] Jiang L J. Study on the Inhibitory Function and Mechanism of Cardiac Glycosides in Downregulating STAT3 Expression in Cancer Cells [D]. Southern Medical University, 2021.

[6] Tian D, Dmitrieva R I, Doris P A, Crary J F, Sondhi R, Sacktor T C, Bergold P J. Protein kinase M zeta regulation of Na/K ATPase: a persistent neuroprotective mechanism of ischemic preconditioning in hippocampal slice cultures [J]. Brain Res, 2008, 1213: 127-139.

[7] Newman R A, Yang P, Pawlus A D, Block K I. Cardiac glycosides as novel cancer therapeutic agents [J]. Mol Interv, 2008, 8 (1): 36-49.

[8] Wang F L, Hou J C. Research progress on the antitumor effects of cardiac glycosides [J]. Cancer Progress, 2017, 15 (03): 217-220.

[9] Shandell M A, Capatina A L, Lawrence S M, Brackenbury W J, Lagos D. Inhibition of the Na+/K+-ATPase by cardiac glycosides suppresses expression of the IDO1 immune checkpoint in cancer cells by reducing STAT1 activation [J]. Journal of Biological Chemistry, 2022, 298 (3): 101707.

[10] Juncker T, Schumacher M, Dicato M, Diederich M. UNBS1450 is a regulator of signaling pathways involved in proliferation and cell death [J]. Biochemical Pharmacology, 2009, 78 (1): 1-10.

[11] Chen Y J. Studies on the Structural Modification and Antitumor Activity of Cardiotonic Glycosides Natural Product Bufalin [D]. Zhejiang University of Technology, 2013.

[12] Lai Z N, Yu Z H, Chen Z H, et al. Observation of the toxic and side effects of paclitaxel-containing chemotherapy regimens [J]. Cancer Research and Clinic, 2007, 19 (09): 619-621.

[13] Schneider N F Z, Cerella C, Simões C M O, Diederich M. Anticancer and immunogenic properties of cardiac glycosides [J]. Molecules, 2017, 22 (11): 1932.

[14] Zhang X W. Common side effects of cancer radiotherapy and coping strategies [J]. People's Health, 2024(28): 70-71.

[15] Nasu S, Milas L, Kawabe S, Raju U, Newman R A. Enhancement of radiotherapy by oleandrin is a caspase-3 dependent process [J]. Cancer Letters, 2002, 185 (2): 145-151.

[16] Aoi W, Marunaka Y. Importance of pH homeostasis in metabolic health and diseases: crucial role of membrane proton transport [J]. Biomed Res Int, 2014, 2014: 598986.