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A REVIEW ON: CARDIAC GLYCOSIDES AS ANTI-CANCER AGENT

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ABSTRACT

cardiac glycosides are naturally occurring compounds. They are mainly known for their activity in treating congestive heart failure and cardiac arrhythmias. Recently, they are recognized as potential anticancer compounds. The primary target of cardiac glycosides as anticancer is Na+/K+-ATPase pump. Cardiac glycosides also activates the intracellular signaling pathways by which they mediate the apoptosis, autophagy, immunogenic responses. Most recently, it has been suggested that cardiac glycosides cause tumor-specific immune responses. This is a brief review of the anticancer aspects of CGs as new strategies for immunotherapy.

KEYWORDS: Cardiac glycoside, Anti-cancer agents, Na+/K+-ATPase pump.

INTRODUCTION

According to the Global Cancer Observatory study (GLOBOCAN), in 2020 there was an enhancement of 19.3 million new cases of cancer across the world. So there is the need of novel anticancer drugs. For new drug synthesis there is huge time required to go through all the process of drug discovery as new compound synthesis, pre-clinical trial, clinical trial. In recent days scientists developed screening of drugs which are already used in treatment of other diseases, as they formerly proven safe.[1] cardiac glycosides that contains steroidal moiety are known in treating congestive heart failure and some cardiac arrhythmias. In past years, reports have suggested that cardiac glycoside also have effects on cancer cells. Some in-vitro and ex-vivo tests showed that cardiac glycosides have anticancer effect on patients who had previously consumed cardiac glycoside for other malady.[2] some epidemiological studies have showed the effect of cardiac glycosides on the risk of cancer but led to

incompatible results. many reports have suggested that using cardiac glycoside was related with a higher risk of estrogen-sensitive tumors such as breast and ovarian cancers.[3] To date, no systematic review and meta-analysis have been conducted regarding the effect of cardiac glycoside on cancer risk. Therefore, we provide a comprehensive review of the effect of cardiac glycoside on cancer risk and mortality of cancer patients.[4]

Cardiac glycosides

Cardiac glycosides have been used for the treatment of heart disease for over 200 years; in 1785, the physician William Withering published a book entitled "An account of the foxglove and its medical uses".[5] Cardiac glycosides are naturally occurring substances that acts on human heart. As the name suggests it has some cardiotonic activity. Cardiac glycosides(Fig:1) chemically contains a steroid ring, a unsaturated lactone moiety and sugar moiety in their structure. Depending on the lactone ring cardiac glycosides are of two types- Cardiac glycosides containing furanone at 2nd position of lactone ring called Cardenolide(Fig:2), Cardiac glycosides containing pyrone at 2nd postion of lactone ring called bufadienolides(fig:3). Plants are the most abundant source of cardiac glycosides like Digitalis purpurea, Digitalis lanata, Strophanthus gratus, and Nerium oleander are the souces of digitoxin, digoxin, ouabain, and oleandrin. Amphibians & mammals are also the sources of cardiac glycosides. Cardiac glycosides obtained from Amphibians & mammals are digoxin, ouabain, bufalin, marinobufagenin, and telecinobufagin.[6]

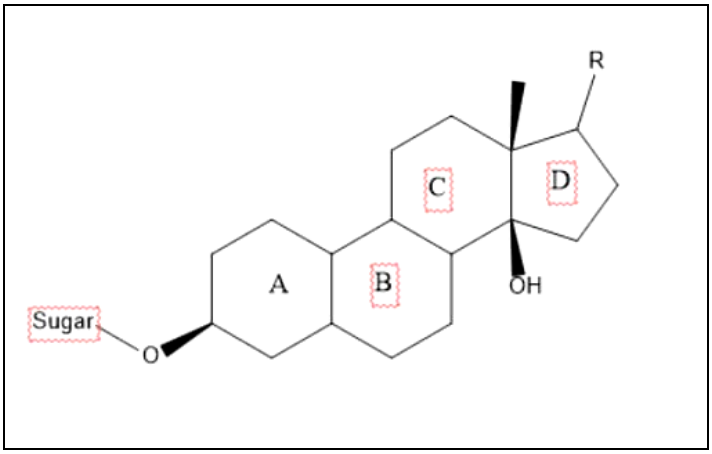

Fig 1: basic structure of cardiac glycosides.

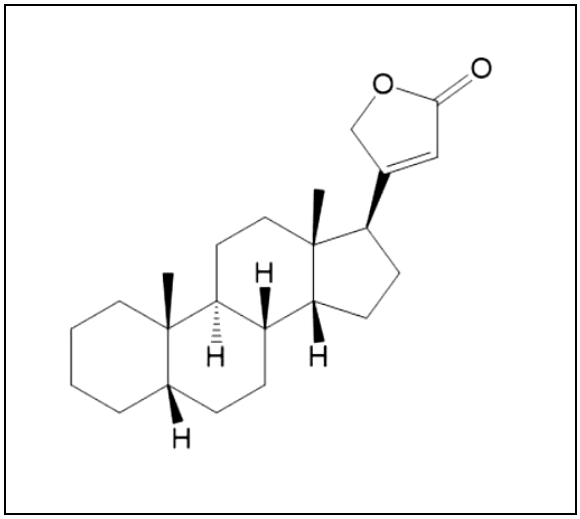

Fig 2: basic moiety of cardenolide.

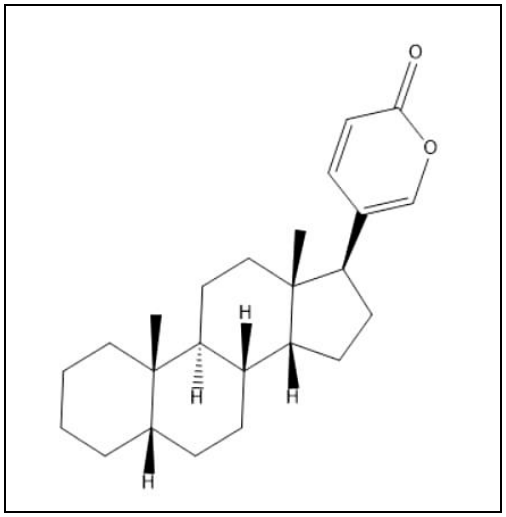

Fig 3: basic moiety of bufadienolide.

Targets of cardiac glycosides as anticancer

Although many studies have been done to evaluate the effects of extracts of cardiac glycosides on tumor cell, the exact mechanism by which cardiac glycosides acts on tumor cell still being investigated. Many theories have been proposed as modulators of observed effects, but no theory sufficiently describe the exact anti-proliferative action of cardiac glycosides as it is too complex. The heterogeneity of mechanism is thought to be due to the use of specific cell types in which the extracts were tested.[7,8]

One of the best theory explaining the antitumor activity is involvement of sodium-potassium ATPase pump. The cardiac glycosides binds to alpha subunit of Na^+/K^+-ATPase pump, that leads to increased Na^+ concentration in the cell and decreased concentration of K^+ ions. As a result concentration of Ca^{2+} in the cytoplasm increased which in turn increase the rate of Na^+/Ca^{2+} exchange in mitochondria. Cardiac glycosides may also interact with non-pumping activity of Na^+/K^+-ATPase pump that leads to activation of intracellular pathways. cardiac glycosides may also interact with the cell membrane through the steroid nucleus, thereby modifying cell membrane fluidity and circuitously affecting the function of several membrane proteins and receptors.[7,9] It is important to discuss that the α-1 subunit is overexposed in several types of cancer, including non-small cell lung cancer (NSCLC), renal carcinoma, glioma, and melanoma, whereas the α-3 subunit is overexposed in colon cancer.[10,11]

Multiple cell death by cardiac glycosides

As discussed so far, the inactivation of Na^+/K^+-ATPase pump, and activation of different intracellular signaling pathways may cause different types of cell death. It is previously known that cardiac glycosides cause apoptosis, immunogenic cell death, autophagy, depending on the properties of the cells.[12,13] The cardenolide UNBS1450 (7), can cause cell death in human leukemic cells.[14] Recently, UNBS1450 was shown to cause a neuroblastoma cell-specific effect leading to apoptosis or necroptosis. In neuroblastoma SH-SY5Y cells, this cardiac glycoside induced mitophagy and a ROS response, causing an procurement of autophagosomes, thereby affecting mitochondrial accumulation and causing apoptosis through oxidative stress-induced lysosomal destabilization. however, the induction of mitochondria autophagosomal clearance cause stromal SK-N-AS neuroblastoma cells more resistant to UNBS1450 treatment, inducing necroptosis at high doses.[15]

CONCLUSION

Historically cardiac glycosides mainly used for the treatment of heart diseases but recent studies demonstrated the anticancer activities of several cardiac glycosides. Depending on these findings cardiac glycosides have been recognized as potential anticancer agents that should be assessed in clinical studies. Primarily cardiac glycosides acts on Na+/K+ ATPase, which has a role in attenuating several signaling pathways linked to cell proliferation, apoptosis and autophagy.

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