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Review Article

Evaluating The Therapeutic Efficacy and Safety of Cardiac Glycoside in the Management Of 'Congestive Heart Failure'

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ABSTRACT

When the heart muscle is unable to pump blood as effectively as it should, congestive heart failure develops. Over time, some disorders, such as high blood pressure or coronary artery disease, cause your heart to become too weak or stiff to fill and pump blood effectively. Digitalis, squill, and strophanthus are examples of herbal medications that are frequently used to treat heart conditions. Cardioactive glycosides include glucosyllaren A and scillarenase, which are found in squill and strophanthus, and purpurea glycosides A and B, which are found in digitalis. Cardiac glycoside is found in several plants and in toad skin [Bufotoxin]. Digitalis lanata is the source of Digoxin, the only glycoside currently used. Other like Digitoxin (from Digitalis purpurea) and Ouabain (from Strophanthus gratus), etc., are no longer clinically used or marketed.

INTRODUCTION

Heart failure is a progressive condition marked by a persistent decline in cardiac function. The most prevalent causes of heart failure are coronary artery disease and hypertension. A class of chemical substances known as cardiac glycosides increases the force of myocardial contractions by having a positive inotropic impact on the heart. Their main applications are in the management of cardiac arrhythmias such as atrial fibrillation and heart failure [1].

Congestive Heart Failure - Congestive heart failure is a complicated clinical state that can be brought on by any anatomical or functional cardiac condition that inhibits the ventricle's capacity to fill or empty blood. It is characterised by inefficient heart function, which puts the body's blood supply in danger. Any condition that slows down the flow of blood into the systemic circulation can lead to CHF [2].

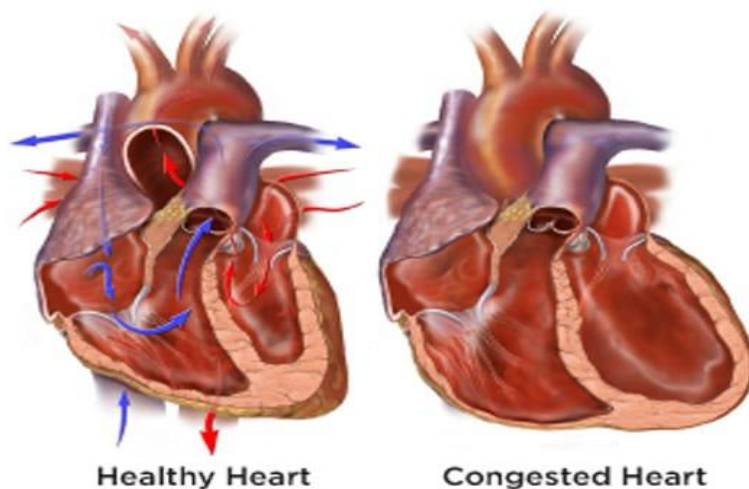
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Coronary artery disease is the most common cause of congestive heart failure (CHF). Atheroma or plug formation in the arteries supplying blood to the heart is a symptom of coronary artery disease (CAD). It lowers blood pressure and reduces the amount of oxygen available [3].

Cardiac Glycoside

By blocking the cellular sodium-potassium ATPase pump, cardiac glycosides are a class of chemical substances that raise the heart's output force and slow down its contraction rate. They are described as naturally occurring medications that can have both positive and negative effects on the heart. CGs are naturally occurring cardiotonic steroids that are frequently used in cardiac and cancer treatments. They are mostly sourced from a variety of plants and amphibians [4,5]. Glycone (sugar) and aglycone (steroid) moieties make up the structural makeup of CG medicines [6]. The presence of a lactone-containing substituent (butyrolactone or α -pyrone) at the β -17 position and a sugar moiety at the β -3 position of the steroidal core define the CG's core structure [7]. The lactone ring of the aglycone moiety controls the functional activity of the CG, which is made up of a steroidal nucleus [8]. Additionally, the CGs' toxicokinetic and toxicodynamic characteristics are controlled by the glycone moiety. Within the glycone moieties, glucose, fructose, galactose, glucuronide, mannose, rhamnose, and digitalose

are the sugars that are most frequently found [9, 10, 11]. The type of sugar that is linked to the steroid affects the CGs' overall potency. It has been observed that adding rhamnose increases the CG compound's efficacy by 6 to 35 times. On the other hand, there was no discernible change in potency [9]. when mannose was added [12]. The two structural categories of CGs are (i) cardenolides and (ii) bufadienolides, which are determined by the R group at position 17. The presence of the doubly unsaturated six-membered α -pyrone ring identifies the bufadienolides (lactone 2-pyrone), while the presence of the unsaturated five-membered butyrolactone ring at position C-17 characterises the cardenolides (lactone 2-furanone).

The Way That Cardiac Glycosides Work:

For many years, CG medications were utilised as emetics, diuretics, and folk remedies in cardiology to treat heart arrhythmia and congestion [11]. By focussing on the cellular Na^+/K^+ ATPase pump, the CG steroids have an impact on heart contractility. Through the action of $\text{Na}^+/\text{Ca}^{2+}$ membrane exchanges, the inhibition of the Na^+/K^+ ATPase pump (Figure 1) causes intracellular retention of Na^+ , which in turn causes the concentration of intracellular Ca^{2+} ions [13]. The heightened intracellular Ca^{2+} concentration results in bradycardia and inotropy. Additionally, the membrane and ventricular ectopy are caused by the buildup of intracellular Na^+ and Ca^{2+} [13].

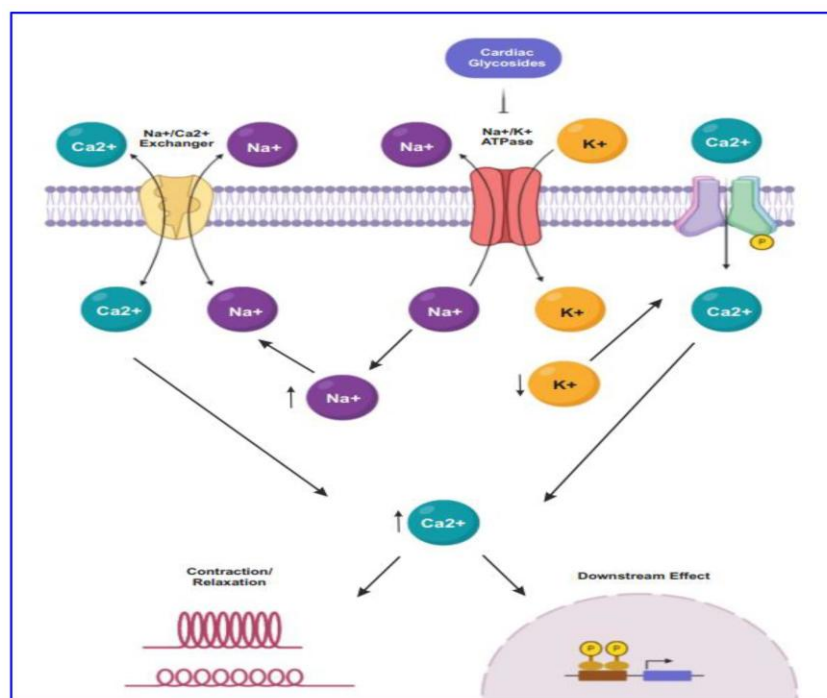


Figure.1

By maintaining the sodium-potassium gradient concentration across the plasma membrane, CGs target Na⁺/K⁺-ATPase in their mode of action against cancer. By attaching itself to the Na⁺/K⁺-ATPase pump and blocking it, CG causes intracellular Na⁺ retention and raises the Ca²⁺ concentration. Consequently, endoplasmic reticulum stress is brought on by decreased Na⁺/K⁺-ATPase expression.

Transcription Factor Activity Modification By Cardiac Glycosides

Over the past several years, research on transcription and its regulators in cancer has resurfaced. According to reports, cancer cells require aberrant gene expression as a basic requirement in order to sustain their increased metabolic and proliferative condition [14,15,16]. Therefore, different disruptors can be used to target these dysregulated cellular processes involving several druggable proteins in the creation of cancer drugs. As a result, we have collected research findings here that demonstrate how CGs regulate these processes through their

regulators, making them prime metabolic targets for cancer treatment. One particular class of pharmacological targets is represented by mutated transcription factors. They are the key regulators that govern the transcriptional process and, consequently, the rate at which genetic material is transcribed [17]. Scientists have recently discovered how to target these variables and control the formation of cancer by preventing the transcription of undesirable or carcinogenic genes. Important transcription factors that contribute to the development of cancer include NF-κB, HIF1, C-Myc, AP-1, STAT3, and others [18]. Increased activity of the transcription factor NF-κB has been reported in a number of malignancies, including thyroid, lung, breast, and colon cancers [19,20,21]. The function of NF-κB and how it regulates other genes involved in cell growth [22], survival, proliferation, and differentiation were demonstrated by Giuliani and his team. Ibrahima and his team recently conducted a thorough investigation that revealed the activating protein's (AP-1) critical involvement in self-sufficient proliferation and migration [23]. They emphasised

the role of the AP-1 family's Fos and c-Jun proteins, as well as the signalling cascade's frequency in human breast and lung cancer [23]. Exciting research by Prassas and Diamandis [24] demonstrated that CG's mechanism of action on Na⁺/K⁺-ATPase can change AP-1's activity and

control transcriptional gene processes. Additionally, by temporarily raising intracellular Ca²⁺, CGs can alter NF-κB and protein kinase (PKC) activity, which in turn influences AP-1, reducing cell division and promoting death in tumour cells [25,26].

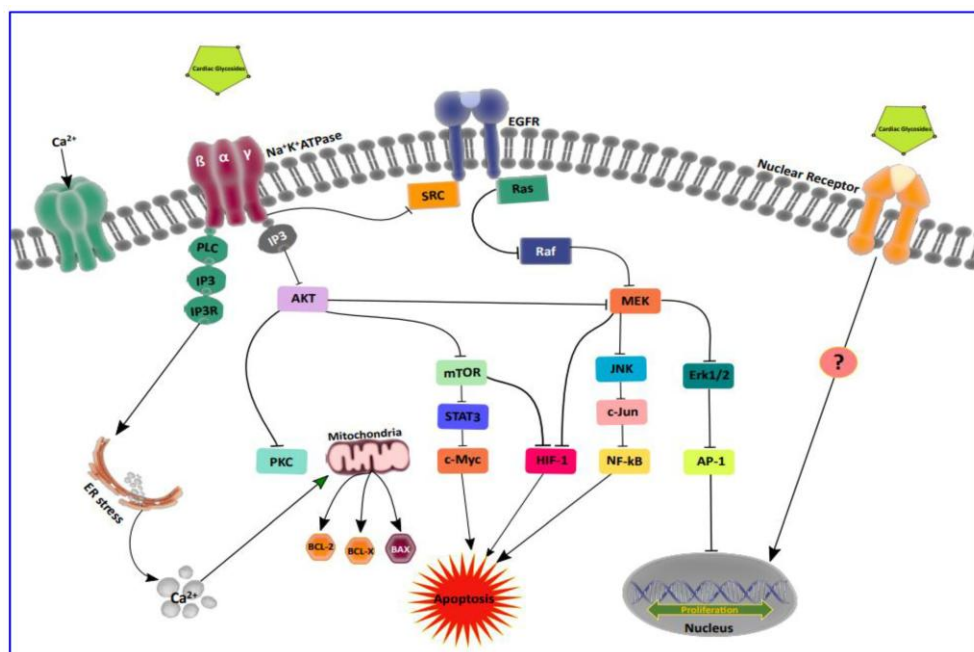


Figure 2

shows how cardiac glycosides block transcription factors that are active in cancer. By binding to the Na⁺/K⁺/ATPase (NKA) channel, CGs reduce the activity of the NKA pump, which in turn down regulates a number of signal transduction cascades, particularly those that target the TF proteins involved in cell growth and proliferation. Figure 2 shows how cardiac glycosides inhibit transcription factors activated in cancer. By sending signals to the transcription machinery, the binding of CGs on the Na⁺/K⁺/ATPase (NKA) channel reduces the activity of the NKA pump, which in turn down regulates a number of signal transduction cascades, including those that target the TF proteins implicated in cell growth and proliferation. The route represents dysregulated TF and its targeted treatment via CG.

Effects of Cardiac Glycosides on Cytotoxicity and Anti-Proliferation

Unchecked cell division is thought to be a key characteristic of cancer cells. Tumour formation and fast expansion are hallmarks of cancer progression, which is characterised by ongoing cell proliferation[26]. The growth and division of cancer cells are independent of external stimuli such as growth factors, in contrast to normal cells[27]. Additionally, growth suppressors and antiproliferative signals can be evaded by cancer cells leading to insufficient cell division and dysregulation of tissue level. Numerous investigations have demonstrated that CG medicines have antiproliferative effects on various cancer cells (Figure 3); bufalin demonstrated antiproliferation against human melanoma BRO cells by stopping them at the G2/M phase[28].

Anti-Proliferative And Cytotoxic Effects Of Cardiac Glycosides

Cancer cells is thought to be unchecked cell proliferation Ongoing cell proliferation that results in tumour formation and quick growth is a hallmark of cancer progression [26]. Cancer cells proliferate and divide independently of extrinsic stimuli such as growth factors, in contrast to normal cells [26,27]. Growth suppressors and antiproliferative signals, which promote insufficient Cardiac Glycosides' Cytotoxic and Anti-Proliferative Effects One important characteristic of cell division and disrupt tissue homeostasis, can also be eluded by cancer cells. The antiproliferative action of CG medicines on various cancer cells has been demonstrated in a number of studies (Figure 3); bufalin demonstrated antiproliferation against human melanoma BRO cells by stopping them at the G2/M phase. Jiang and associates. Cardiac Glycosides' Cytotoxic and Anti-Proliferative Effects One important

characteristic of cancer cells is thought to be unchecked cell proliferation. Ongoing cell proliferation that results in tumour formation and quick growth is a hallmark of cancer progression. Cancer cells proliferate and divide independently of extrinsic stimuli such as growth factors, in contrast to normal cells Growth suppressors and antiproliferative signals, which promote insufficient cell division and disrupt tissue homeostasis, can also be eluded by cancer cells. The antiproliferative action of CG medicines on various cancer cells has been demonstrated in a number of studies (Figure 3); bufalin demonstrated antiproliferation against human melanoma BRO cells by stopping them at the G2/M phase. Jiang and associates.

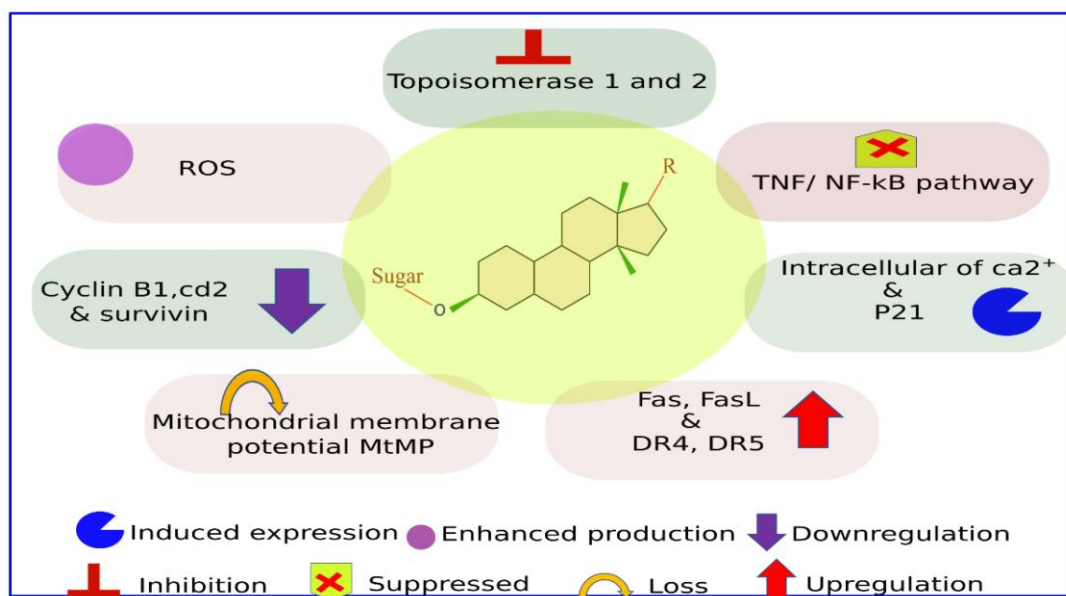
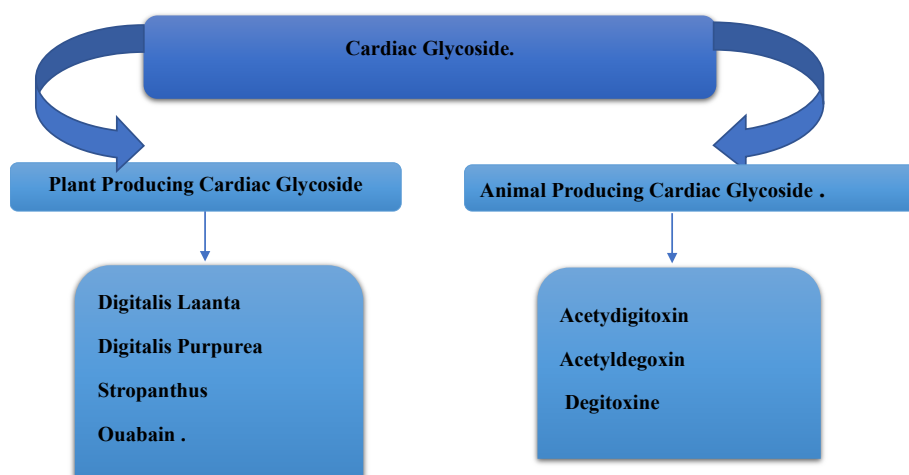


Figure 3: Molecular mechanisms underlying cardiac glycosides' cytotoxic and antiproliferative actions.

Classification of cardiac glycoside :



Plant Producing Cardiac Glycoside:

Digitalis lantana :

Kingdom	Plantae
Class	Tracheophytes
Order	Lamiales
Genus	Digitalis
Species	D. lanta
Biological name	Digitalis lanata
Family	Plantaginaceae



Fig . *Digitalis lanta*

Key Features :

Appearance	A biennial or short-lived perennial with lance Shaped leaves and tubular, pale yellow to brownish flowers dark veins .
Native Range	Southeastern Europe, especially the Balkans .
Habitat	Prefers dry, rocky soils and can grow in full sun or partial shade .

Cultivation	Grown mainly for pharmaceutical purposes. Need well drained soil and moderate watering .
Taste	Faint, Bitter, Characteristics
Colour	Greyish – green due to dense trichomes .
Leaves	Simple, sessile or short petioled, ovalate – lanceolate

Chemical Constituent :

Digitalis Lanta Containing Primary and Secondary Glycoside .

Primary Glycoside

These are directly extracted from plant

Lanatoside A

Lanatiside B

Lanatoside C [Most Important]

Lanatoside D

Lanatoside E

Secondary Glycoside

Formed by hydrolysis of primary glycoside

Lanatoside C [After Removal of Terminal Glucose and Acetyl Group]

Aglycons[Genesis]

Digitoxigenin

Digoxigenin

Gitoxigenin

Flavonoids

Luteolin
Apigenin

Other Constituents

Steroids – Phytosterols such as Stetosterol and stigmasterol.

Saponins – Minor amount, may assist absorption of glycoside

Tanins – Astringent property.

Anthraquinone derivatives – Present in trace

Resins and fixed oil – Present in small quantities

Applications Of Digitalis Lanata In Medicine :

1. Congestive heart failure (CHF) treatment

Action: Increases the force of cardiac muscle contraction by a positive inotropic effect.

Mechanism: Strengthens myocardial contractions by inhibiting the Na^+/K^+ -ATPase pump, which raises intracellular calcium.

As a result, heart failure symptoms including exhaustion and dyspnoea are lessened and cardiac output is increased.

2. Cardiac Arrhythmia Management :

very helpful for atrial flutter and fibrillation.

Action: Slows the heart rate; has a negative chronotropic impact.

Mechanism: Reduces conduction via the AV node and raises vagal tone.

Result: Aids in regulating heart rate and rhythm

3. Treatment Of Supraventricular Tachycardia (SVT)

Can help to restore normal rhythm by slowing AV conduction.

Used under close monitoring due to risk of pro-arrhythmic effects.

Pharmaceutical Applications :

1. Source of Digoxin

Digitalis lanata is the primary commercial source of digoxin, a purified cardiac glycoside.

Preferred over D. purpurea because:

Contains higher concentrations of lanatoside C.

Digoxin is more stable and has predictable pharmacokinetics.

2. Standardized Drug Formulations

Digoxin from D. lanata is formulated as:

Tablets (e.g., 0.25 mg)

Oral solution

Injectables (IV use in emergencies)

Other Possible/Investigational Uses

While its primary use is cardiac-related, studies have investigated potential new roles:

1. Anticancer Potential (Investigational)

Some lab studies suggest digoxin may inhibit certain cancer cell lines via apoptosis and cell cycle arrest.

Not clinically approved for cancer treatment.

2. Antiviral Activity (Experimental)

Preliminary research indicates that digoxin might have activity against viruses like HIV and some coronaviruses through modulation of cellular signaling pathways.

Needs further clinical trials.

Veterinary Use

Occasionally used under veterinary supervision in treating heart conditions in dogs and other animals. Dosage and monitoring are species-specific due to toxicity risks.

Animal Producing Cardiac Glycoside :

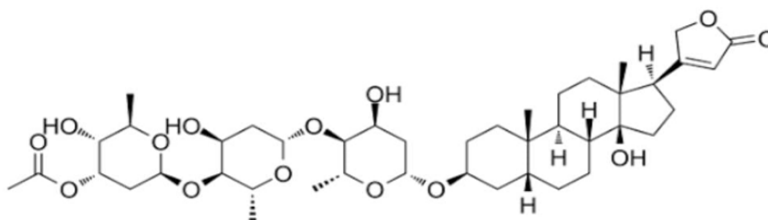


Acetyldigitoxin.

Acetyldigitoxin is cardiac glycoside, a type of compound known for its effects on the heart. It is derived from *digitoxigenin*, a steroid nucleus, and belongs to the family digitalis glycoside.

Chemical Structure and Properties :

Molecular formula	C₄₇H₇₄O₁₈
Molecular weight	911.08 g/mol



Three sugar molecule [digitoxoses] are attached at the 3 – position .

IUPAC Name – 3B[O(Acetyloxy)-digitoxosyl-(14)- digitoxosyl]-digitoxigenin

Pharmacological uses of Acetyldigitoxin:

Acetyldigitoxin primarily affects the heart pharmacologically. Many of the negative effects are caused by extracardiac effects. Its primary effects on the heart are 1) a reduction in electrical impulse conduction at the AV node, which makes it a medication frequently used to regulate heart rhythm during atrial fibrillation or atrial flutter, and 2) an increase in contraction force by inhibition of the Na⁺/K⁺ ATPase pump.

TESTS AND DIAGNOSIS:

The diagnosis of CHF is crucial for understanding or determining the illness or causal factor. It aids in selecting the best medical course of action. Healthcare professionals mostly enquire about your symptoms and medical history. Additionally, medical professionals enquire about:

- 1) Tobacco product use
- 2) The quantity of alcohol consumed.

- 3) Medications taken
- 4) Ancestry

They conduct a physical examination as well. Congestive heart failure can be diagnosed using a variety of tests.

These are listed below.

1] Test for blood: A complete blood count is part of the laboratory test used to diagnose anaemia. In order to rule out liver failure as the source of peripheral oedema, it also involves tests for liver and kidney function. A heart attack can also be diagnosed with the use of a high Sensitivity tryptophan T test .

Additionally, it has the following:

- a) the Brain Natriuretic Peptide Test (BNP Test)
The heart and blood arteries create the protein known as BNP. This test is performed to measure the BNP level, which rises during heart failure. One natriuretic peptide that rises in heart failure is called Pro-BNP (N-terminal pro-B-type natriuretic peptide test). The Pro-BNP level is determined by this test.
- b) The Brain Natriuretic Peptide Test (BNP Test)
is another one of its components. Blood

arteries and the heart both create the protein known as BNP. The BNP level is measured with this test because it rises during heart failure. The N-terminal pro-B-type natriuretic peptide test.

- c) Test of electrolytes Potassium and sodium levels are measured with it. During heart failure, this natriuretic peptide rises.
- d) Test for electrolytes It is employed to determine the sodium and potassium levels.

2) Catheterisation of the heart Congestive heart failure can also be diagnosed with it. Another name for it is coronary angiography. This test involves inserting a catheter—a tiny tube—into a blood vessel in your arm, upper thigh, or groin. It is connected to the heart.

3) X-ray of the chest It is not the main technique used to diagnose CHF. but also employed to detect CHF problems.

4) Echocardiogram It is used to diagnose CHF. It is a common non-invasive test that measures the heart's pumping function, and also evaluates its structure and function.

5) Heart MRI It is a non-invasive imaging technique that accesses the function and structure of the heart. It measures ventricular. Systolic function, assess myocardial

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6) An ECG CHF is diagnosed with it as well. It is a fundamental tool for detecting heart failure,

especially in those with a family history of the condition. An ECG cannot provide a reliable diagnosis of OHF on its own. combination of different exams. Combination art uses additional testing. The echocardiogram A CT scan. MRI and PET The biopsy

Controlling Congestive Heart Failure :

A specific treatment for congestive heart failure does not exist. The primary goals of treatment are to alleviate symptoms and stop CHF from getting worse. The patient's condition, symptoms, heart failure type, and stage all influence the course of treatment.

- 1) non-pharmacological therapy.
- 2) Medication.

Although neither medication cures the illness, it does assist to prevent its symptoms.

1) Non-pharmaceutical therapy among the-

a) Change in Lifestyle Heart failure may result from a number of circumstances related to our everyday lives. These include things like eating poorly, exercising seldom, being obese, smoking, drinking alcohol, and drinking too much water. Congestive cardiac failure can be avoided with a few crucial adjustments. Doctors may suggest that you stay away from caffeine and salt. The patient should only drink a certain amount of fluid.

b) Work out In order to slow the progression of congestive heart failure, exercise is the most crucial element. The main goal of exercise is to lose weight. The blood flow can be improved by exercise. Engaging in physical activity can help maintain heart health and encourage microvascular dilation. The goal of non-pharmacological treatment for CHF has frequently been weight loss and exercise .



2) Pharmacological therapy to control or avoid the symptoms linked to congestive heart failure, pharmacological treatment is employed. CHF cannot be cured; the medications used to treat it only stop its progression. CHF can be prevented using a number of different medications.

They are :-

1) Diuretics :

Diuretics work well to decrease fluid retention and lessen congestion symptoms by lowering preload, but they don't stop the condition from getting worse. Diuretics are medications that promote the production of urine, which helps heart failure patients get immediate symptom relief. Loop diuretics are better medications for severe cases of congestive heart failure, Long-term diuretic usage may also trigger the Renin-Angiotensin System, which speeds up the progression of the illness. So, the extended diuretic therapy is only advised in cases of heart failure that are advanced. For example, hydrochlorothiazide with furosemide.

2) Vasodilators :

These are the medications that widen blood arteries, lowering blood pressure and relieving congestion brought on by congestive heart failure. Vasodilators are utilised for both acute and severe heart failure when they may be administered intravenously. These medications are used for long-term treatment when taken orally.

ACE inhibitors,

a) Such as Ramipril, Enalapril, and Captopril
Mechanism of action: These medications treat congestive heart failure by blocking angiotensin converting enzymes. The transformation of angiotensin I into pharmacologically active angiotensin II is catalysed by ACE. The latter

substance might cause an increase in aldosterone secretion. Vasoconstriction is another effect of antidiuretic hormone.

b) An antagonist of the angiotensin receptor For example, Valsartan and Losartan. These medications relieve congestive heart failure in patients by having an antagonistic impact on the AT-1 receptor in smooth muscle. These medications have a vasodilatory effect because they inhibit the AT 1 receptor in vascular smooth muscle.

The nitrates The main vasodilators are organic nitrates, such as glycerol nitrate and isosorbide dinitrate. By relaxing the venous smooth muscles more than the arterial smooth muscles.

Hydralazine Arteriolar smooth muscles are dilated more than venous smooth muscles by this arteriolar dilator. These medications reduce cardiac afterload and aortic impedance.

Nitropruside Arteriolar relaxation is achieved by this mixed vasodilator. They also have vasodilator properties.

3) B-blockers, including metoprolol and carvedilol, Recently a novel class of medications for heart failure patients has emerged: B-blockers. By blocking a catecholamine's activity at B-adrenergic receptors. Metoprolol and carvedilol are examples of B-blockers. B blockers can lessen the sympathetic nervous system's overstimulating effects. As a result, acute negative effects including tachycardia and elevated myocardial oxygen demand are mitigated. B-blockers also lessen the negative cardiac effects of the renin-angiotensin system.

4) An aldosterone receptor inhibitor Spironolactone is one of its ingredients. By blocking aldosterone's ability to attach to the



receptor, these medications reduce the hormone's effects. Plasma volume and cardiac preload may rise as a result of aldosterone. When potassium and magnesium levels in the blood are lowered, ventricular arrhythmias are more likely to occur, which can cause sudden death in patients with congestive heart failure. You can use spironolactone to block all of the effects of aldosterone.

5) Cardiac Glycosides, such as Digoxin and Digitoxin, are cardiac inotropic agents.

We refer to cardiac glycosides as cardio tonic agents. Without increasing oxygen consumption, they improve the heart's mechanical pump efficiency.

Mechanism of action :

An antagonist of the aldosterone receptor It contains the medication spironolactone. By preventing aldosterone from attaching to the receptor, these medications reduce the effects of aldosterone. Increases in cardiac preload and plasma volume may result from aldosterone. It lowers potassium and magnesium levels in the blood, increasing the risk of ventricular arrhythmias, which can cause sudden death in patients with congestive heart failure.

Digitalis exhibits a positive inotropic effect as its mechanism of action. Digoxin attaches itself reversibly to a location on the extracellular side of the heart's cell membrane's alpha subunit of the Na^+/K^+ ATPase pump. As a result, pump activity is inhibited, myosin's Na^+ level, which in turn promotes the interchange of Na^+ and Ca^{2+} As a result.

B) Inhibitors of phosphodiesterase III Amrinone and Milrinone are among them. These medications deactivate the product 5-AMP by blocking the

phosphodiesterase enzyme, which catalyses the breakdown of cAMP. It raises cAMP levels in the heart, blood vessels, and bronchial smooth muscles. These medications relax the vascular smooth muscles and have a good inotropic effect.

CONCLUSION

Therapeutic efficacy of natural chemicals, especially CGs, to stabilise the aberrant gene functions in cancer was the main emphasis of this review. The importance of CGs as putative inhibitors of a number of oncogenic genes and transcription factors implicated in cancer signalling pathways was underlined. The efficacy of digoxin, strophanthidin, and ouabain against a number of tumor-causing TFs, including HIF- α , NF-Kb, AP-1, and C-Myc, was demonstrated in clinical trials, indicating the strong selectivity of CGs against transcription modification. Important directions for future research are motivated by the review of current articles on CGs and nuclear variables. As a result, this class of biomolecules offers a substitute for chemical and synthetic medications that have serious adverse effects. Its growing significance and acceptance in targeted TF therapy for cancer was also emphasised, as was the development of medicines capable of suppressing the elusive TFs reliance in cancer

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