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Assessing Cardiac Risk: A Comparative Review of Herbal and Allopathy Medicines.

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Abstract

The study examines the cardiac risks associated with certain herbal medicines compared to conventional allopathy drugs. Herbal remedies such as *Citrus aurantium*, *Ephedra sinica*, *Aristolochia fangchi*, *Glycyrrhiza glabra*, *Corynanthe yohimbe*, and *Aconitum spp.* are reviewed for their potential to cause adverse cardiac effects, including arrhythmias, hypertension, and cardiomyopathy. These risks are compared to allopathic drugs like digoxin, doxorubicin, and cyclophosphamide, which are known for their cardiotoxic profiles. Citrus aurantium and Ephedra sinica are noted for their stimulant properties that can lead to elevated blood pressure and increased heart rate, potentially resulting in cardiac arrhythmias. *Aristolochia fangchi* poses risks of nephrotoxicity and cardiotoxicity due to aristolochic acids. *Glycyrrhiza glabra* can cause hypokalemia, leading to arrhythmias, especially when used in high doses or for prolonged periods. *Corynanthe yohimbe* contains yohimbine, which may increase blood pressure and heart rate, heightening the risk of cardiovascular events. *Aconitum spp.*, known for its potent alkaloids, can cause severe cardiac arrhythmias and hypotension. The study highlights the importance of awareness among healthcare providers and patients regarding the potential cardiac risks of both herbal and allopathic medications. It emphasizes the need for careful consideration of the patient's cardiovascular status when prescribing or consuming these substances, as well as the necessity of rigorous clinical trials and pharmacovigilance to better understand and mitigate these risks.

1. Introduction:

Cardiotoxicity, defined by the National Cancer Institute, refers to any form of poisoning or harmful effect on the heart. This can include direct impacts on the heart muscle or function, changes in hemodynamic flow, or any type of thrombosis that is related to medical intervention. Remarkably, data from the National Health and Nutrition Examination Survey indicates that 33% of long-term cancer survivors experience heart disease [1]. Additionally, approximately 10% of medications introduced globally over the past 40 years have been withdrawn due to heart-related safety issues, including drugs such as sibutramine, tegaserod, and rofecoxib [2]. Despite significant efforts to identify cardiotoxicity stay at the forefront of the drug inventory during the preclinical phase, safety issues, mostly because of an insufficient comprehension of the fundamental mechanics for the development of cardiotox-

icity [3]. and also, the herbal remedies to address a variety of health issues [4], [5], has become more and more significant. Research indicates that 80% of individuals worldwide cure various disorders [6], [7] with a combination of standard therapy and complementary and alternative medicine (CAM).

Additionally, a number of studies have shown that there are roughly 20,000 herbal medicines available in various markets worldwide [8]. Many people also rely on medicinal plants and use herbal remedies in addition to conventional medication to treat a variety of diseases, which raises the possibility of herb-drug interactions [9], [10], [11] According to research, using natural goods and allopathy medicines causes some injuries, such as disorders to the kidneys [12], neurological systems [13], liver [14], skin [15], and hearts [16].

Drug-induced cardiotoxicity significantly restricts drug development and the clinical management of existing drugs [17]. One critical safety concern is the risk of inducing potentially lethal arrhythmias through direct interactions with cardiac electrophysiology. Recent studies have revealed that many drugs can also impair cardiac function by disrupting myocardial metabolism and altering cardiac structure. Examples include anticancer therapies associated with myocardial apoptosis, [18] neurodegenerative disease agents posing a severe risk of fibrotic valvular heart [19] disease, and antibacterial [20] and antiviral [21] antidiabetic and antiobesity treatments causing mitochondrial damage. Cardiotoxicity, in general, is the phenomenon of heart damage by different substances such as certain herbs and medicines. The cardiotoxicity occurring in the heart is caused by various substances, including both herbs and drugs.

The path of cardiotoxicity is multifaceted and complex. Oxidative stress is defined as the dominant pathway and this pathway is characterized by the imbalance of positive and negative ions which results in the cellular destruction as compared to antioxidants. Further, this oxidative injury can affect the heart muscle cells leading to arrhythmias, heart failure as well as a heart attack. Other than that, the interruption of various ion channels, mainly calcium and potassium, which are the effectors of normal cardiac pathways and positively regulate heart contractility, is the mechanism behind it. Some substances can also impair mitochondrial function in a way that there is an increased lack of energy in the heart cells leading to apoptosis or necrosis. Additional, cells damaged by cardiotoxic agents can initiate inflammatory responses or fibrosis making the heart function worse. These mechanisms are the key and must be understood in the course of developing strategies for the prevention and relief of the cardiotoxic effects of certain herbs and drugs.

The common pathway for this is oxidative stress, which is characterized by a deficit in the concentration of reactive free radicals and antioxidants as well as conversion by cellular constituents. This oxidative damage can impair myocardial cells, leading to arrhythmias, heart failure, or myocardial infarction. Another pathway is ion channel interference that controls calcium and potassium among others. Some substances as well can impair mitochondrial function which doesn't allow energy production in heart cells and they start to die because of apoptosis or necrosis. Also, cardiotoxins can provoke the inflammatory response or fibrosis and thus worsen heart function. Understanding of these mechanisms is crucial to the establishment of prevention and therapeutic strategies for the certain herbs and drugs-induced cardiotoxicity.

1.1 The Herbal Medicines May Lead to Cardiotoxicity:

Herbal drugs have therapeutic uses, but they may also cause adverse effects, such as cardiotoxicity like cardiac arrhythmias and heart rate. It is important to be aware about the possible threats, especially with herbs that have more physiological effects. Table 1 provides some examples of herbal medicines, emphasize their therapeutic uses and also the cardiotoxic effects.

1.1.1 Solanaceae:

Atropa belladonna, *Mandragora officinarum*, and *Datura stramonium* which belong to Solanaceae family, are well known for their diverse alkaloids with various therapeutic effects. *Atropa belladonna*, well known as deadly nightshade, which is used to treat bradycardia. A case study involving a 49-year-old woman treated by ingestion of A. *belladonna* resulted from an adverse effect of anticholinergic toxic syndrome and irregular heart rate [22]. some research has also indicated that there is potential to cause tachycardia and other side effects [23].

Mandragora officinarum, contains chemical compounds such as flavnolides, tropane alkaloids (scopolamine and hyoscyamine), and coumarins. The root of M. *officinaru* has various therapeutic applications and research showed that consumption of M. *officinaru* led to supra-ventricular tachycardia [24]. Similarly, Datura stramonium, which is used as antipyretic and used to treat rheumatism, alkaloids that can cause tachycardia, as observed in animal studies [25]. Some clinical studies shows that consumption flower, leaf, and seed of *D.stramonium's causes* instances of tachycardia. [26], [27], [28].

1.1.2 Dioscoreaceae:

Dioscorea bulbifera, belong to the family of Dioscoreaceae, is a herbal drug used in traditional medicine for treating various disorders like wounds, rectal carcinoma, sore throats, and gastric cancer [29]. Some Research has shown that consumption extracts from its rhizome can cause adverse effects like cardiotoxicity due to the accumulation of pirarubicin, which

leads to necrosis and muscle fiber damage [30]. During the cancer treatment, *Dioscorea bulbifera* interacts with doxorubicin (DOX), causing accumulation of DOX and resulting in cardiovascular injuries such as necrosis and damage to cardiac muscle fibers [31].

1.1.3 Ephedraceae:

Ephedra distachya, commonly known as sea grape, belongs to the family of Ephedraceae which is used as traditional medicine in treating colds, bronchitis, asthma, and low blood pressure [32]. Research revealed that consumption of ephedra alkaloids from *E. distachya* have adverse effect on cardiovascular and cerebrovascular systems [33]. Ephedra sinica, another member belonging to Ephedraceae family, is traditionally used for treating respiratory disorders, asthma, and colds [34]. Research shows combination of *E. sinica* with caffeine can lead to cardiotoxicity effects [35]. Additionally, other research studies have shown that the combination of caffeine with ephedrine can damage the cardiovascular system and cause cardiotoxicity effects [36], [37].

1.1.4 Hypericaceae:

Hypericum perforatum belongs to the family of Hypericaceae ,has been used traditionally to treat burns, anxiety, and viral disorders. Several research studies have also shown that *H. perforatum* has anti-cancer activity [38], [39]. Many investigations showed that consumption of *H. perforatum* resulted many side effects like cardiotoxicity arrhythmia, hypertension, and herb-drug interactions. [40].

1.1.5 Cupressaceae:

Juniperus oxycedrus belongs to Cupressaceae family its herbal medicine mainly used for treating a wide range of infections and respiratory disorders and it is commonly known as prickly juniper or cade juniper. *Juniperus oxycedrus* is native to the Mediterranean region and parts of Asia. Traditionally it is used for treating dermatological infections and respiratory disorders and also act as antiseptic [41], [42]. The extracts of *Juniperus oxycedru* is associated with potential adverse effects. Research showed that on exposure to *J. oxycedrus* lead to symptoms of fever, tachypnea, and tachycardia [43], [44].

1.1.6 Apocynaceae:

Nerium oleander, or just Nerium, is a Prominet decorative and landscaping plant that is grown extensively across many different areas. It is a member of the Apocynaceae family. *N. oleander* has long been used to treat ringworm infections, eczema, gastrointestinal issues, and opthalmia [45]. The consumption of *N. oleander* has been linked to some negative effects, including nervous system disorders and the irregular heartbeat known as bradycardia [46]. Oleander poisoning can cause arrhythmia and other adverse effects, according to a study [47].

1.1.7 Piperaceae:

Piper methysticumis belongs to Piperaceae family. It is well known as kava. *Piper methysticum* is traditionally used for treating anxiety, restlessness, and psychological disorders [48], [49]. Multiple research projects shows that *P. methysticum* can interact with psychiatric drugs, increasing the risk of potentially fatal herb-drug interactions. Additionally, it has many adverse effects on cardiovascular system, leading to circulatory irregularities and cardiac arrhythmia [50].

1.1.8 Ranunculaceae:

Aconitum napellus, *Aconitum kusnezoffii*, and *Aconitum carmichaeli* belongs to Ranunculaceae. The Ranunculaceae family comprises of more than 2200 species of flowering plants including *Aconitum napellus*, *Aconitum kusnezoffii* and *Aconitum carmichaeli* the plants of this family are widely used in folk medicine more in cancer therapy [51], [52]. Aconitum kusnezoffii commonly known as Kusnezoff's monkshood, with known antimicrobial and analgesic effects [53], the legume has known negative impacts upon the cardiac system: tachyarrhythmias, ventricular tachycardia, and fibrillation [54]. *Aconitum napellus* commonly used in Analgesic [55] is associated with severe cardiotoxic effects like ventricular tachycardia, arrhythmia, cardiac arrest on ingestion [56]. *Aconitum carmichaeli*, with established activities on wound healing and anti-inflammatory, has been found associated with aconitine toxicity in myocardial necrosis. They include diterpenoid alkaloids including aconitine and mesaconitine that has been causing cardiovascular toxicity to the species [57].

1.1.9 Ginkgoaceae:

Ginkgo biloba commonly referred to as ginkgo, belongs to family Ginkgoaceae, and is widely used as a traditional medicine to treat several diseases such as asthma, cognitive diseases, circulation problems, and vertigo. Few research revealed that consumption of *Ginkgo biloba* has mild adverse effects causing heart palpitations [58]. A study shows that many people use ginkgo to reduce the platelet aggregation [59].

On the other hand, going by different studies, it was found that ginkgo can interfere with, warfarin, and consequently, the likelihood of bleeding [59]. On the other hand, a brief data review from randomized blind controlled trials revealed that ginkgo may not have the ability to interact with warfarin [60], [61]. Another study pointed out that the patient who concurrently consume ginkgo and warfarin faced an elevated level of bleeding adverse effects and therefore patients should be wary of herb and drugs interaction [62].

1.1.10 Fabaceae:

Glycyrrhiza glabra commonly known as Licorice belongs to the Fabaceae family which is extensively used in traditional medicine to cure many ailments. Respiratory disorders, GERD, liver diseases, fever, excessive thirst, rheumatism, TB, erectile dysfunction, and infection can be treated with it due to its anti-inflammatory properties, antimicrobial, and immunomodulatory properties. However, some dangers can cause cardiovascular problems. Research has revealed that taking licorice calms down the heart and consequently triggers what is known as arrhythmias, spasms of the coronary arteries; this results in major problems such as cardiac arrhythmias and pulmonary edema if taken in products like candies [63], [64].

Due to this dual role of licorice, it must be taken with precautions, particularly for those with COPD and other cardiac issues. This paper highlights that knowledge of the pharmacological effects of licorice is the key to using it appropriately. This study examines the use and therapeutic effects of *Glycyrrhiza glabra* and its cardiovascular side effects for the development of guidelines for safe consumption [65].

Table 1. Thermal cycle conditions of the FimH gene.

S.No	Plant Name application	Family	Potential therapeutic	Type of adverse effect	Pictures of plant	Reference
1.	Atropa belladonna	Solanaceae	Treat of asthma, cough, and hay fever	Flushed and Tachycardia		[22], [23]
2.	Datura stramonium		Treat of wounds, inflammation and rheumatism	Tachycardia		[66], [25], [26], [27], [28]

3.	Mandragora officinarum,		Fever, ulcers, wounds, toothache, rheumatism, and bronchitis	Tachycardia		[67], [68], [69], [70], [24]
4.	Aconitum napellus	Ranunculaceae	Treat of high fever	Tachyarrhythmias,		[55]
5.	Aconitum kusnezoffii		Treat of sore throat, gout and rheumatism	Tachyarrhythmias, ventricular tachycardia and fibrillation		[54]
6.	Aconitum carmichaeli		Pain relief	Cardiotoxicity		[57]

7.	Dioscorea bulbifera	Dioscor-eaceae	Treat of syphilis, ulcers, cough, leprosy and diabetes	Accumulation of THP in heart tissue		[29]
8.	Ephedra distachya	Ephedraceae	Weight loss and obesity	Cardiovascular system and cerebrovascular effects		[33]
9.	Ephedra sinica		Treat of asthma, bronchitis, and hay fever	Serious cardiovascular adverse effects		[36]
10.	Digitalis purpurea	Plantaginaceae	Treat of asthma, epilepsy and tuberculosis	Heart Failure		[47]
11.	Ginkgo biloba	Ginkgoaceae	Cognitive disorders and dementia	Increasing the bleeding tendency, heart palpitations		[58]
12.	Glycyrrhiza glabra	Fabaceae	Respiratory disorders , hyperdipsia and fever	Cardiac arrhythmias, Pulmonary edema		[63]

13.	Hypericum perforatum	Hypericaceae	Anxiety and depression	Arrhythmia, hypertension		[38], [39]
14.	Juniperus oxycedrus	Cupressaceae	Anti-inflammatory and antimicrobial	Tachycardia		[41], [42]
15.	Nerium oleander	Apocynaceae	Cancer, painful menstrual periods	Arrhythmia		[46], [47], [48]
16.	Piper methysticum	Piperaceae	Fever and respiratory disorders	Cardiovascular abnormalities, Arrhythmia		[48], [49]

2. Drugs that Have the Potential to Cause Cardiotoxicity:

Numerous medications carry a significant risk of negatively impacting the heart. Some cytotoxic medicines and their cardiotoxic effects are compiled in Table 2. The next part will cover the key medicines that cause cardiotoxicity.

2.1 Antiobesity:

Phentermine, an antiobesity drug, shares its mechanism of action with amphetamines, primarily targeting the release of noradrenaline [71]. Unlike amphetamines, phentermine selectively promotes noradrenaline release, which plays a significant role in appetite suppression and weight reduction. Despite its stimulant properties, phentermine does not typically increase blood pressure; however, it can cause an increase in heart rate. The combination of phentermine with topiramate, a combination approved in 2012, has demonstrated similar outcomes in weight management. Notably, this combination can lead to a significant reduction in arterial blood pressure, likely due to the associated weight loss. While an increase in heart rate is observed with phentermine use, studies to date have not identified any substantial cardiovascular risks associated with its use. This overview underscores the effectiveness of phentermine, both alone and in combination with topiramate, in promoting weight loss and highlights its relatively safe cardiovascular profile [72].

2.2 Endogenoeus Catecholamines:

In intensive care units, the endogenous catecholamines dopamine, noradrenaline, and adrenaline are frequently administered to treat shock symptoms related to acute cardiovascular problems. Regarding their selectivity for adrenergic receptors, they differ significantly from one another. While noradrenaline acts on - and 1-adrenergic receptors but has a low affinity for 2-adrenergic receptors, adrenaline often activates both - and -adrenergic receptors. The use of prolonged infusions or high doses of adrenaline (epinephrine) or noradrenaline (norepinephrine) is generally, avoided due to the potential for direct cardiotoxic effects, including, apoptosis (programmed cell death) and necrosis (cell death) of, cardiomyocytes [73], [74] (heart muscle cells). Such cardiotoxicity can also occur with the rapid intravenous (i.v) administration of insufficiently diluted adrenaline solutions. This risk underlines why the intramuscular (i.m.) route of administration is often preferred in clinical practice, especially in emergencies like anaphylactic reactions, as it is inherently safer for the heart.

When adrenaline is administered intravenously in a clinical setting, a ”fractionated” administration approach or slow injection is recommended to mitigate the risk of cardiotoxicity and acute hemodynamic complication [75], [76]. Additionally, the production of reactive oxygen species (ROS), either through adrenoceptor activation or autoxidation of catecholamines, contributes to the cardiotoxic effects of adrenaline.

2.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

The NSAIDs are widely used for pain relief. Their primary mechanism of action involves blocking cyclooxygenases 1 and 2 (COX-1 and COX-2). The most common issue with nonselective, or traditional, NSAIDs is the risk of peptic ulcers and gastrointestinal bleeding, primarily due to COX-1 inhibition. The development of selective COX-2 inhibitors (coxibs) aimed to reduce gastrointestinal side effects [77], [78]. However, coxibs were later found to cause cardiovascular side effects [79].

Two primary mechanisms have been identified for these cardiovascular complications:

1. **Imbalance between Proaggregatory and Antiaggregatory Agents:** The inhibition of COX-1 leads to decreased production of proaggregatory thromboxane A2 by platelets. Meanwhile, the inhibition of COX-2 reduces the production of antiaggregatory prostacyclin by endothelial cells. This imbalance can promote cardiovascular issues.

2. **Blockade of Prostaglandin E2 Synthesis in the Kidney:** Both COX-1 and COX-2 are constitutively expressed in the kidneys, and their blockade can reduce the synthesis of prostaglandin E2. This reduction affects renal function, contributing to cardiovascular problems [80], [81], [82]. The involvement of COX-2 in cardiovascular effects is clear, as all known NSAIDs, except for low-dose aspirin, potentially block this pathway. Consequently, NSAIDs can increase blood pressure and exacerbate heart failure [77], [83], [84], [85],

2.4 Anticancer Drugs:

Anthracyclines are pivotal chemotherapeutic agents widely used in the treatment of breast cancer, sarcoma, and various blood cancers88. Despite their substantial efficacy in targeting rapidly dividing cancer cells, anthracyclines pose a significant risk of cardiotoxicity, which can manifest either acutely or chronically. Acute cardiovascular complications, occurring within two weeks of dosing, may include electrocardiographic abnormalities, arrhythmias, and inflammatory conditions such as pericarditis and myocarditis [86], [87], [88].

The mechanism behind anthracycline-induced cardiotoxicity is multifaceted, involving the generation of reactive oxygen species (ROS) and the inhibition of intracellular antioxidant systems. A key metabolite, acrolein, exacerbates oxidative and nitrosative stress by inhibiting critical antioxidants like Glutathione (GSH) and superoxide dismutase (SOD), while increasing levels of malondialdehyde (MDA), leading to cell membrane damage.

Anthracyclines exhibit anti-cancer activity by inhibiting topoisomerase IIα in cancer cells, due to which it prevents DNA replication and that leads to cell death. However, they also suppress topoisomerase IIβ in cardiomyocytes, thus leading to DNA strand breaks and ROS formation. This leads

to the activation of apoptotic pathways thus making the cardiomyocytes to die. The cardiotoxic effects of anthracyclines are an issue of concern, and the advancement of cardiomyopathy symptoms in patients who have been treated with these agents ranges from 3-9%. This toxicity is mainly due to the generation of ROS, disruption of mitochondrial functions, and apoptosis of cardiomyocytes. Also, doxorubicin, an exemplary of anthracycline, escalates the level of cell death receptors stimulated by tumor necrosis factor and, therefore, augments cardiomyocyte apoptosis [87].

Surprisingly, although there is evidence of cardiotoxicity linked to anthracyclines, some manufacturers argue that specific variants of the compound are not toxic to the heart. Few drugs like amrubicin, which is used in lung cancer treatment since 2011 by the US FDA, have been said to be free from cardiotoxicity implications hence calling for a change in the chemical composition of anthracyclines to curtail their toxicity effects. This has called for more studies to design safer anthracycline derivatives and effective cardiopreventive measures.

2.5 Antimetabolites:

The fluoropyrimidines include 5-fluorouracil (5-FU) and capecitabine, which are important parts of the chemotherapy regimens; 5-FU is the third most used chemotherapy worldwide for solid tumors. [87] However, it is also described as the second most common cause of drug-induced cardiotoxicity next to anthracyclines [88]. It has been reported that of all fluoropyrimidines-related cardiovascular disorders, chest pain and acute coronary syndromes including myocardial infarction that is the most common [89]. Other less common manifestations include arrhythmias that are rare in fulfillment but not in subfulfilment hepatic failure [90], myocarditis, pericarditis, and heart failure [91]. The administration of 5-FU initiates oxidative stress by generating superoxide (O2), which activates cascades of caspase reactions, ultimately culminating in apoptosis. Few research indicates that an increase in reactive oxygen species (ROS) due to 5-FU correlates with a decrease in glutathione (GSH), a critical ROS scavenger. This imbalance leads to elevated lipid peroxidation and reduced matrix metalloproteinase (MMP) activity together with mitochondrial dysfunction and caspase-3 activation [92]. Moreover, fluoroacetate, a metabolite of 5-FU that inhibits the TCA cycle enzyme aconitasen [93], causes dysfunction of mitochondrial energy metabolism via inhibition by disrupting tricarboxylic acid (TCA) cycle substrates further leading to overload oxidative phosphorylation, finally culminating in decreased ATP production and also increased ROS. Additionally, the accumulation of autophagosomes and lysosomal membrane permeabilization in 5-FU-treated human cardiomyocytes suggest that autophagic cell death also contributes to 5-FU-induced cardiotoxicity [94], [95].

2.6 Alkylating Agents:

Cisplatin, the best-known mechanism of chemotherapy, was introduced by the platinum-based ones and is used for the effective treatment of different types of cancer [96]. Even though the rate of cisplatin-induced cardiotoxicity is not definite yet, research proves that about 6% of people who are treated with cisplatin and 5-fluorouracil (5-FU) develop cardiotoxicity, whereas 1.6% of them are affected if they are treated with 5-FU alone [97]. Cisplatin has been able to result in both acute and cumulative cardiotoxic side effects, to a greater extent, by interfering with caspase-3 activation that in effect causes apoptosis in the myocardium. New write-ups indicate a strong connection between the production of ROS and the emergence of platinum-induced cardiomyocyte apoptosis. Cisplatin cause lipid peroxidation, reduces glutathione (GSH) levels and inhibits superoxide dismutase (SOD) activity, which are all signs of oxidative stress. Furthermore, cisplatin can also damage the DNA present in the nucleus and the mitochondria [98], [99], [100]. This is also linked to the increase in thromboxane A2 (TXA2) synthesis and the formation of thrombi, which is a risk factor for heart diseases like ischemic heart disease. Cisplatin contributes to its cardiotoxic effects by utilizing electrolyte imbalances that are the main cause of gastrointestinal toxicity.

(CP) Cyclophosphamideis an active substance used for treating leukemia, lymphoma, and autoimmune disorders that can cause heart problems, especially at high doses. The proportion of patients suffering from CP-induced cardiotoxicity is from 7% to 28%, with acute Heart failure recorded in 7% to 33% of cases. Symptoms usually appear within a week after administering doses of more than 150 mg/kg [101] Acrolein is the major by-product in CP-induced cardiotoxicity and this leads to cardiac muscle cell death [102]. In recent studies, these results are associated with the increased level of oxidative stress, lipid peroxidation, and breakdown of the mitochondrial function, decreasing ATP production, decreasing caspase-3, and finally apoptotic signaling [103], [104].

2.7 Monoclonal antibodies:

Trastuzumab (TZP), a humanized monoclonal antibody marketed as Herceptin®, is a recently developed and widely utilized medication targeting the extracellular domain of the human epidermal growth factor receptor-2 (EGFR-2, HER2) [105]. Despite its therapeutic benefits, TZP has been associated with numerous cardiotoxic side effects, posing a serious risk to patients. Similar to other cancer treatments, TZP use has been linked to various heart problems, including arrhythmias, acute coronary syndrome, pericardial disorders, left ventricular ejection fraction (LVEF) reduction, congestive heart failure (CHF), vasospasm, dilated cardiomyopathy, and elevated blood pressure [106]. It was hypothesized that TZP's negative regulation of tumor protein (p53) and murine double minute 2 (MDM2) could contribute to cardiotoxicity.

TZP-induced cardiac cell death has been associated with

inflammatory infiltration, with Toll-like receptor 4 (TLR4)-mediated chemokine expressions of TNF and MCP-1 contributing to the inflammatory response. Combination therapies, including TZP, are frequently used in cancer treatment but are associated with a higher risk of cardiotoxicity compared to single-drug regimens. Combining TZP with doxorubicin (DOX) has been shown to increase antioxidant enzyme depletion and mitochondrial damage [107].

2.8 Microtubuler Inhibitors:

The most commonly utilized alkaloids extracted from the Periwinkle plant are vinca alkaloids, including vinblastine, vinorelbine, and vincristine [108]. These medications are employed in the treatment of testicular cancers, choriocarcinoma, and Hodgkin's lymphoma due to their anti-microtubule and anti-mitotic characteristics. Vinblastine acts by binding to tubulin, halting cell division during the metaphase stage and inducing tumor cell death. However, the use of vinca alkaloids [109] has been associated with cardiotoxicity. Vinblastine, for instance, has been linked to myocardial ischemia and infarction [110]. Vincristine, on the other hand, can cause cardiac arrest and coronary spasm [111]. Moreover, paclitaxel and docetaxel, classified as taxoids, can induce bradycardia, ischemia, and heart failure by promoting microtubule assembly and inhibiting microtubule depolymerization [112].

2.9 Tyrosine Kinase Inhibitor:

Tyrosine kinase inhibitors (TKIs) induce cardiotoxicity through various mechanisms. Imatinib-associated cardiotoxicity is primarily linked to B cell lymphoma 2 release-induced mitochondrial damage [113]. Sunitinib and imatinib have been shown to increase reactive oxygen species (ROS) generation, leading to decreased viability of cardiac cells [114]. Dasatinib and nilotinib may also induce cardiotoxicity, possibly by blocking vascular endothelial growth factor (VEGF) signaling [115].

2.10 Antiviral Drug:

Zidovudine, an antiviral medication belonging to the class of nucleoside reverse transcriptase inhibitors, is commonly used to treat HIV-1 infection [116]. However, long-term use is limited by adverse effects such as elevated blood pressure and heart conditions. Zidovudine accumulates reactive oxygen species (ROS) and peroxynitrite, damaging single strands of DNA and ultimately depleting mitochondrial energy in a manner dependent on NAD+ [117].

2.11 Antidiabetic Drugs:

Thiazolidinedione is a class of medications used to treat type II diabetes mellitus; it was formerly thought to be a cardioprotectant [118]. But as their use increased, it was discovered that pioglitazone and rosiglitazone have harmful side effects on the heart, including HF and myocardial hypertrophy [119]. As mediators of cardiac cell death, sphingomyelinase and ceramidase [120] are upregulated by pioglitazone [121]

2.12 Comparison of Herbal and Allopathic (Conventional) Medicines:

Both herbal and allopathic (conventional) medicines are involved in causing threatening of the heart, though, it is said to have their own diverse mechanisms to such happenings. The traditional plant medicines as Atropa belladonna are the cause of tachycardia and hernia but can be used as heart stimulants. Mandragora officinarum, usually for fever and rheumatism, can provoke supraventricular tachycardia. Datura stramonium can treat wounds and rheumatism but may also cause an increase in heart rate and tachycardia. Dioscorea bulbifera is good for sore throats and cancer treatment but it can bring heart attack via death of cells and muscle fiber damage. Such plants as Ephedra species, which are responsible for the healing of cold and asthma, have the potential to lead to cardiovascular effects, especially when they are combined with caffeine. Fortunately, Hypericum perforatum, a plant that is used for burns and anxiety is sending signals to higher blood pressure and arrhythmia, and Nerium oleander, on the other hand, being used for gastrointestinal issues and eczema may cause bradycardia and irregular heart rhythms. On the other hand, allopathic medicines, while rigorously tested and regulated, can also have cardiotoxic side effects. chemotherapy drugs like doxorubicin are well-known for their potential to cause cardiotoxicity effects, including heart failure. Some non-cardiac drugs, such as antibiotics and psychiatric medications, can also have cardiac side effects. The key difference lies in the regulation and monitoring of these medicines; allopathic medicines undergo several clinical trials and continuous post-market surveillance to identify and mitigate risks. In contrast, the cardiotoxic risks of herbal medicines are often less well-documented and regulated, leading to a potentially higher risk of unrecognized adverse effects.

3. Conclusion:

Since the beginning of time, people have looked for novel drugs to treat a variety of illnesses. Self-medication with herbal medicine is a concern that has become an obsession for people all over the world and has various negative impacts. The present review compiled and outlined all documented herbal remedies that cause cardiotoxicity, indicating that herbal remedies have to be taken under the supervision of medical professionals. A serious adverse effect of several medications, including anticancer ones, is cardiotoxicity. The most frequent causes of cardiac cell death are mitochondrial damage, lipid peroxidation, and the production of ROS.

Table 2. Thermal cycle conditions of the FimH gene.

No	Class	Drug	Potential Therapeutic Application	Cardiotoxic effect	Reference
1.	Antiobesity	Phentermine	Lessens appetite	Tachycardia	[71], [72]
2.	Endogenoeus catecholamines	Dopamine, noradrenaline, and adrenaline	Shock symptoms	Cardiotoxic effects, including including ,apoptosis and ,apoptosis necrosis ,cardiomyocytes	[73], [74], [75], [76]
3.	Anti-inflammatory	Nasids Eg. Aspirin	Relief pain	Hypertension and arterial thrombosis	[79], [80], [81], [82], [122], [83], [84], [85]
4.	Anthracyclines	Doxorubicin	Breast cancer, sarcoma, lung cancer, bladder, gastric tumor, prostate tumor, leukemia, lymphoma	Left ventricular dysfunction, hear failure, arrhythmia	[86], [87]
5.	Alkylating agents	Isofosfomide Cisplatin Cyclophosphamide	To treat cancer	Arrhythmia, ischemia, venous thromboembolism, hypertension ,heart failure	[96] [97] [123], [101], [102], [103], [104]
6.	Antimetabolites	Capecitabine 5-fluorouracil	Breast cancer, colon, gastric tumor, pancreatic cancer	Coronary vasospasm ischemia arrhythmia left ventricular dysfunction, myocarditis	[88], [89] [90], [91] [92], [93] [94], [95]
7.	Antimicrotubular agents	Vinblastine	Breast cancer, ovarian cancer, lung cancer.	Left ventricular dysfunction, heart failure, arrhythmia ischemia brady arrhythmia	[108], [109]
		Paclitaxel	Hodgkin's lymphoma, choriocarcinoma, and testicular tumors	Myocardial ischemia and infarction	[110], [111], [112]
8.	Monoclonal antibodies	Trastuzumab	Breast cancer, gastric tumor, gastroesophageal tumor	Left ventricular dysfunction), heart failure	[105], [106], [107]
9.	Tyrosine kinase inhibitors	Lapatinib	To treat renal tumor, thyroid cancer, sarcoma, git stromal tumor, pancreatic neuroendocrine tumor	Left ventricular dysfunction, heart failure	[113]
10.		Imatinib	To treat breast cancer	Left ventricular dysfunction, heart failure, hypertension, venous thromboembolism, aortic thromboembolis.	[114]
11.		Sunitinib	Leukemia	Systolic heart failure, heart failure, left ventricular dysfunction	[115]
12.	Hormonal therapy	Anastrozole	Breast cancer	Hypertension, ischemia, thromboembolism	[107]
13.	Antiviral drug	Zidovudine	Hiv pressure,	Increases blood	[116], [117]
14.	Antidiabetic drugs (thiazolidinedione)	Rosiglitazone and pioglitazone	Diabetes mellitus,	Myocardial hypertrophy and heart failure	[118], [119], [120], [121]

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تقييم مخاطر القلب: مراجعة مقارنة للأدوية العشبية والطب التقليدي

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الخلاصة

تتناول الدراسة المخاطر القلبية المرتبطة ببعض الأدوية العشبية مقارنة بأدوية الطب التقليدي. العلاجات العشبية مثلا أورانتيوم الحمضيات، والإيفيدرا سينيكا، وأريستولوتشيا فانغتشي، وجليسيرهيزا جلابرا، وكوريناثي يوهمبي، والبيش. لمعرفة مدى قدرتها على التسبب في آثار قلبية ضارة، بما في ذلك عدم انتظام ضربات القلب وارتفاع ضغط الدم واعتلال عضلة القلب. تتم مقارنة هذه المخاطر بالأدوية الطبية التقليدية مثل الديجوكسين والدوكسوروبيسين و السيكلوفوسفاميد، والتي تشتهر بخصائصها السامة للقلب. تشتهر *Citrus aurantium* و *Ephedra sinica* بخصائصهما المنشطة التي يمكن أن تؤدي إلى ارتفاع ضغط الدم وزيادة معدل ضربات القلب، مما قد يؤدي إلى عدم انتظام ضربات القلب. تشكل *Aristolochia fangchi* مخاطر السمية الكلوية والقلبية بسبب الأحماض الأرستولوشية. يمكن أن يسبب عرق السوس نقص بوتاسيوم الدم، مما يؤدي إلى عدم انتظام ضربات القلب، وخاصة عند استخدامه بجرعات عالية أو لفترات طويلة. يحتوي يوهيمبي الكوريانثي على يوهيمبين، والذي قد يزيد من ضغط الدم ومعدل ضربات القلب، مما يزيد من خطر الإصابة بأمراض القلب والأوعية الدموية. يمكن أن يسبب *Aconitum spp.* ، المعروف بقلوياته القوية، عدم انتظام ضربات القلب وانخفاض ضغط الدم الشديد. تسلط الدراسة الضوء على أهمية الوعي بين مقدمي الرعاية الصحية والمرضى فيما يتعلق بالمخاطر القلبية المحتملة لكل من الأدوية العشبية والطبية التقليدية. وتؤكد على الحاجة إلى النظر بعناية في حالة القلب والأوعية الدموية للمريض عند وصف أو تناول هذه المواد، فضلاً عن ضرورة إجراء التجارب السريرية الدقيقة واليقظة الدوائية لفهم هذه المخاطر والتخفيف منها بشكل أفضل.

الكلمات الدالة: سمية القلب، الطب التكميلي، الطب العشبي، تلف العضلات.

التمويل: لايوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوطة أو تقديمها لمجلة أخرى، كما أنها ليست قيد المراجعة.