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A Critical Review on Drug Induced Cardiotoxicity and its Treatment Modalities in Perspective of Ayurveda

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ABSTRACT

Hriday is one of the important marma among *Trimaramas*, which may leads to fatal consequences even on the slight injury. There is not any direct reference of *Aushadhijanyahridroga* in our ancient textsbut our ancient Acharyas explained the cardiac disturbances as the side effect of medicines which are not prepared properly. This shows that they were well known about the drug induced cardiotoxicity. In Agadtantra, *Garavisha* is explained as a one of unique concept which artificially prepared by the mixture of various substances responsible for various disorders. Itis the vast aspect mentioned in our ancient literature, which can be compared with various sources of exposure of toxins through our daily life activities in which we can include various drugs and chemicals used in modern medical science are also produced toxic effects like Paracetamol, aspirin, erythromycin, oral contraceptives etc. Such a way Cardiotoxicity occurs due to many chemotherapeutic agents and other drugs can also be understood under the concept of *Garavisha.* The aim of this article is to review contemporary aspect of cardiotoxicity induced by drugs and classical aspect of *Garavisha*. It is an attempt to find correlation between them. This will be helpful in exploring the different treatment modalities associated with of drug induced cardiotoxicity.

Key Words *Garavisha, Hridroga, Cardiotoxicity*

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INTRODUCTION

Cardiotoxicity is also described as the harmful effect on the heart mediated by various toxins (drugs) which leads to weakness of heart. Thus heart becomes inefficient in the pumping and circulation of blood. In Cardiotoxicity there is electrophysiology dysfunction of heart or damage of heart muscle. National Cancer Institute defines Cardiotoxicity as 'toxicity that affects the heart' this definition limits the direct effect of drugs on the heart. Chemotherapeutic agents leads to harmful effect on both vascular system and heart[1]. These agents responsible for cardiac complications like variation in blood pressure, arrhythmias, pericarditis, electrophysiological changes in heart muscles, myocarditis,

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cardiomyopathy, left ventricular dysfunction or heart failure[2]. Some of the common drug categories which are responsible cardiotoxicity includes monoclonal, antihypertensive, antidepressants, anticancer agents, etc. Due to cardiotoxicity, heart becomes unable to pump blood effectively throughout the body. Other symptoms like shortness of breath, fatigue, and anemia are also seen in these cases. These signal that the heart is having difficulty in maintaining its essential functions. If there is symptoms likechronic coughing, swelling of the ankles and feet, and weight gain, indicates the risk of cardiotoxicity. These signal shows that the heart is not beating correctly. The cardiac events like slight change in blood pressure, arrhythmias, thrombosis, pericarditis, myocardial infarction, myocarditis, cardiac failure (left ventricular failure) and electrocardiographic changes and eventhe congestive heart failure may be occurs[3]. However, chronic administration of drugs is the major problem because cardiotoxicity is generally seen after the accumulation of the drug or its metabolites since long duration.

*Garavisha*is one of the unique concept explained in our classics and traditional books of Ayurveda. It artificially prepared by the mixture of various substances and leads to various diseases. Sinceit does not cause instantaneous death buttakes some time to metabolize such type of poison and after that these produce their harmful effects. In the current scenario of fast lifestyle, due to the influence of environmental pollutants, fast foods, adulteration, pesticides, etc. Improper use of all these resources cause endogenous or exogenous toxicity. Most of causative factors that responsible for *garavisha* mentioned in ancient texts can be correlated to our daily used resources. The alarming increase of severe diseases like cancer, stroke, heart attack etc can also be attributed to the toxic effect due to toxic components present in our daily goods like food, drinks, medicines, cosmetics, etc. The substances that causes a toxic effect may be pesticides, insecticides or drugs like Steroids, NSAIDs, or any chemical substance that present in the environment of an individual can be included in it. Itis the vast aspect mentioned in our ancient literature,which can be compared with various sources of exposure of toxins through our daily life activities in which we can include various modern drugs. Thus cardiotoxicity due to modern medications can also be correlated with the ancient concept of garavisha.

OBJECTIVES:

1) To elaborate concept of cardiotoxicity due to modern medications on the basis of their mechanism of toxicity, risk factors and diagnostic criteria.

2) To discuss the concept of *garavisha* in ayurveda classics.

3) To elaborate the correlation between drug induced cardiotoxicity and *garavisha* and suggest the possible management protocol in perspective of ancient toxicology.

METHODOLOGY

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A) CONCEPT OF "HRIDAYA" IN AYURVEDA: [4]

1) Anatomy:

As per our ancient texts *"Hridaya"* is most important *pranayatana* (vital organ) of our body and also one of the most important marma among the*trimarma (Hridaya, Basti, Nabhi)* explained in ayurveda. As per modern medical science, heart is important organ of both respiratory and circulatory system. It's important to know anatomy and physiology of heartin modern terms for understanding of pathology of heart diseases and then we can provide the ayurvedic treatment for heart diseases in today's era. According to ancient ayurvedic texts, myocardium can be correlated with *mamsadhatu* and rhythmic heart contraction are due to vayu.

The word *"Hridaya"*is derived from "*hru"* i.e. *Harati* (to receive from) and "*da*" i.e. *Dadati*(to give) and *"ya"* i.e.*Yagati*(to control). The normal functioning of heart perform in the body continuously due to Vayu, especially *Pran* and *Vyanvayu. Vatadosha* in *prakrut*condition is responsible for normal *vatagati,* due to *chalguna.* Along with this*hridaya* is considered as *sthana*of *Sadhak pitta, Avalambakkapha, Oja* and *Mana.*

2) Physiology

According to Ayurveda, *Samanvayu* takes*aahar rasa* towards*hridaya*and then *vyanvayu* circulate this to all over body in all *dhatus*and finally brings back to the heart. On the other hand*Sadhak pitta*present in heart is responsible for normal functioning of body's important constituents*Buddhi, Medha, Prana and agni.* Also,*AvalambakKapha*in heart plays the important role of *Dharan*(holding) and *Avalambana* (lubricating and Shock absorption) property. According to *ayurveda Hruday-utpatti* is from *Prasad-ansha* of *Rakta*and *Kaphadhatu* and hence considered as *"siramarma"* because *sira* are the considered as *upadhatu* of *Raktadhatu.*

3) Pathology

All of the coronary artery diseases can be classified under *Siradushti*which is *Raktavikruti*because *sira*and *kandara* are the *upadhatu* of *rakta.* If there is any *Raktavikruti* due to *pitta dosha,* the permeability of*sira* increases due to *laghu, ushna, visraguna* then hemorrhagic disorders occurs. If there is any*Raktavikruti*caused due to*kaphadosha,* it leads to increase in coagubility of blood while due to *guru, manda*and *sthira*propertyof *kapha* atherosclerotic diseases occurs. While if*Raktavikruti* is caused due to *vatadosha,* then it mainly affected the rhythm of heart. So there is development of cardiac arrhythmia or impulse conduction disorders like BBB, heart block, etc. V*atadosha* can also causes congenital heart diseases like VSD, ASD, PDA or Tetralogy of fallot, Coarctation of Aorta due to*vibhajana* is karma of *vata* and defective *vibhajana*.

B) MODERN ASPECT OF "CARDIOTOXICITY"

Cardiotoxicity is commonly seen as a side effect of many drugs like anticancer drugs, specificallysevere cardiotoxicity seen as side

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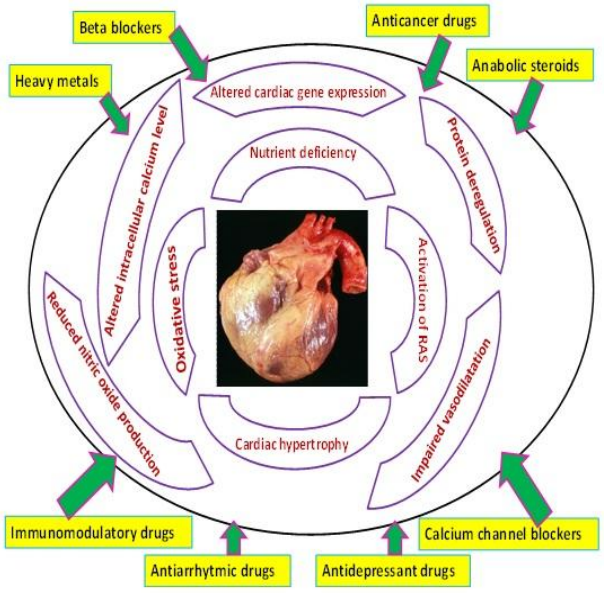
effect of drugsbelongs to class anthracycline. Other drugs like amphetamine, zidovudine mitomycin, and paclitaxel also leads to cardiotoxicity. The common mechanism which causing cardiotoxicity are oxidative stress, generation of free radicals and hypoxia. Long-term exposure to such cardio-toxic drugs further leads to apoptosis & deregulation of myocontractility. Cardiotoxicity of drugs occurs in two ways i.e. (1) Affecting the cardiac muscles performance which leads to cardiac injury OR (2) by altering the ion channels and pump (voltage-gated Na^+ and K^+ channel and Na^+ - K^+ ATPase pump). Exposure to such drugs can leads to prolonged cardiac repolarization (increased QT interval) and also causes arrhythmia (Torsades de pointes) [5].



Cardiotoxicity can be mainly classified into 2 Types:

1) Type I: irreversible damage caused due to the cumulative doses and

2) Type II: reversible damage which is not related with cumulative doses.

Clinically cardiotoxicity is of various types e.g. Cardiomyopathy, CHF, LVEF, Cell damage etc. In these LVEF (left ventricular ejection fraction) reduction is the most frequent symptom of such cardiotoxicity, in which there isdysfunction of left ventricle and leads to congestive heart failure. Arrhythmias, changes in blood pressure or cardiomyopathy are also the symptoms of cardiotoxicity[6].

The chemotherapeutic agents in cancer treatment and psychiatric drugs are the major causes of cardiotoxicity. As per the data of National Health and Nutrition Examination, 33% long cancer survivors die due to cardiac diseases. Along with this, about 6.6% of patients of breast and hematological cancer which are on chemotherapy has developed heart failure[7]. Patients of psychiatric illness,taking specific antipsychotic and antidepressants drugs responsible for extensive chances of cardiovascular mortality. These drugs leads to cardiovascular complications, especially cardiac arrhythmias. For example, Clozapine which is commonly used and most popularly known as a most effective drug for resistant schizophreniais responsible for life-threatening complications like cardiomyopathy andmyocarditis. Myocarditis caused due to clozapineleads to the mortality in 24% of individuals. If there is already coexistence of a heart disease in these patients, then it leads to complications in the management of mental illness and worsens the course of illness. The co-occurrence of psychiatric disorders in the patients with cardiac disorders

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might affect the clinical outcome and morbidity. Cardiotoxicity induced by drugs is generallyseen in the form of cardiac muscle dysfunction that may leads to heart failure which represents as a important adverse effect of some common traditional antineoplastic agents likecyclophosphamide, taxanes, anthracyclines, 5 fluorouracil and also newer agents such as biological monoclonal antibodies, e.g., nivolumab, bevacizumab, trastuzumaband; tyrosine kinase inhibitors, e.g., nilotinibandsunitinib; antiretroviral drugs, e.g., zidovudine; antidiabetics, e.g., rosiglitazone; as well as some illicit drugs such as cocaine, methamphetamine, alcohol, and synthetic cannabinoids.

1) Cardiotoxic Drugs.

The various agents responsible for cardiac complications like variation in blood pressure, arrhythmias, pericarditis, physiological changes in heart muscles, myocarditis, cardiomyopathy, left ventricular dysfunction or heart failure, etc are given in **Table 1** and **Table 2**

Table 1 Cardiotoxic Chemotherapeutic Agents[8]

Sr. No.	Class	Drug	Cardiotoxic effects
1	Anthracyclines/ Anthraquinolones	Doxorubicin/ daunorubicin	LV dysfunction Myopericarditis
		Epirubicin	LV dysfunction, Supraventricular tachycardia
		Mitoxantrone	LV dysfunction Arrhythmias
2	Alkylating agents	Cisplatin	LV dysfunction, Myocardial ischemia Heart blocks
		Cyclophosphamide	Hemorrhagic myopericarditis, Acute heart failure, Arrhythmias
3	Antimetabolites	Cytarabine	Pericarditis, Angina
		5-Fluorouracil	Myocardial spasm, Ischemia Ventricular arrhythmias
4	Antimicrotubules	Paclitaxel	Ventricular tachycardia, AV block and bradycardia
		Vinca alkaloids	Myocardial ischemia, Myocardial infarction
5	Biologic response modifiers	Interferons	Hypotension/LV dysfunction
6	Topoisomerase inhibitors	Etoposide	Hypotension, Myocardial ischemia
7	Differentiation agents	All-*trans*-retinoic acid	Pericardial effusion, Pulmonary edema
		Arsenic trioxide	Prolonged QT, Torsades de pointes
8	Monoclonal antibodies	Trastuzumab	LV dysfunction
		Rituximab	Hypotension, Arrhythmias

Table 2 Some other Cardiotoxic drugs[9]

Sr. No.	Class	Drug	Cardiotoxic effects
1	**Antidepressant**	(1) tricyclic antidepressant (TCA) (more common) e.g. amitriptyline, amoxapine, desipramine, doxepin, imipramine (2) selective serotonin reuptake inhibitor (SSRIs) (3) monoamine oxidase inhibitor (MAO inhibitors)	postural hypotension, altering atrioventricular conduction, prolongation of the duration of QRS interval, altered cardiac rhythm and myocardium contractility, Sudden death
2	**Calcium Channel**	(1) benzothiazepines e.g. diltiazem	negative ionotropic effect, rennin-angiotensin

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	Blockers	(2) dihydropyridines e.g..nifedipine, and (3) Phenylethylamine like.verapamil.	system activation and alteration of membrane Ca^{2+} transport while in patients of Chronic heart failurecauseshemodynamic alteration
3	**Antiarrhythmic drugs**		increased risk of CHF
4	Signaling Protein	**Interferon**	cardiomyopathy and cardiac ischemia
5	CNS stimulant	**Amphetamines / Methamphetamines**	acute coronary syndrome, cardiomyopathy, cardiac hypertrophy, necrosis, myocarditis, inflammation, left ventricular dysfunction and left ventricular dilatation
6		**Cocaine**	tachycardia and increased blood pressure, Chronic use: myocardial ischemia Acute administration: arrhythmia, prolongation of PR, QRS and QT duration that result into arterial fibrillation and tachycardia
7	**Anabolic - Androgenic Steroids**	testosterone and its derivatives	hypertension, atherosclerosis and impaired contraction-relaxation, myocardial necrosis, cardiac steatosis, coagulation and coronary atheroma
8	Addictive psychoactive	**Alcohol**	left ventricular dysfunction and cardiomyopathy, affects the myocardial contractility and abnormal rhythm
9	heavy metals	lead, cobalt and cadmium,	altered myocardial contraction, cardiac cells changes structurally and deregulation of some essential enzymes in heart muscles

2) Signs and Symptoms: [10]

In cardiotoxicity heart is not able to pump blood efficiently throughout the whole body and shows symptoms like shortness of breath, fatigue, and anemia. These symptoms shows that, heart has difficulty in maintaining its essential functions. If there is risk of cardiotoxicity, it leads to the symptoms like chronic coughing, swelling of the ankles and feet, and weight gain. These signal that the heart is not beating in a proper way and failing cardiac events. It produces mild changes in blood pressure, arrhythmias, myocardial infarction, myocarditis, changes in electrocardiograph, pericarditis, thrombosis, left ventricular failure and congestive heart failure. These may occur during or after treatment or within some days or weeks or months or sometimes years after the completion of chemotherapy.

3) Diagnosis: [11]

The most sensitive & specific method for diagnosis of the drug induced cardiotoxicity is Endomyocardial biopsy which describes the structural alterations in microscopic level to the myocardial tissue. But its use is limited because of its high invasiveness of the procedure. Electrocardiographic (ECG) changes are also seen during the treatment with cancer drugs. These changes include decrease in QRS voltage and also changes in ST-T wave. The commonest finding is the prolongation of QT corrected (QTc) interval. It measures the complete time duration of the myocardial depolarization and repolarization. Prolonged QT indicates the increased risk of ventricular arrhythmias, particularly torsades de pointes, and sudden death.

Imaging methods like echocardiography are more often used to determine CICM (chemotherapy-

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induced cardiomyopathy). Left ventricular ejection fraction (LVEF) evaluated by two-dimensional echocardiography (2D-ECHO) is the standard parameter to assess the cardiotoxic effect of chemotherapy. According to Cardiac Review and Evaluation Committee (CREC), for diagnosis of such toxicity, least one of the following criteria must be present:

1) In cardiomyopathy, there is decrease in Left ventricular ejection fraction (LVEF) of heart which was either global or more severe in the septum;

2) Symptoms of congestive cardiac failure;

3) Associated signs of congestive cardiac failure, including but not limited to S3 gallop, tachycardia, or both; and

4) Decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive cardiac failure, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.

4) Risk factors for drug-induced cardiotoxicity: [12]

- Age at time of exposure (less than 4 years and old age are more prone)
- Female gender
- Physical inactivity
- Smoking
- Genetic predisposition
- Black ethnicity
- History of cardiac disorders or left ventricular dysfunction
- Hypertension
- Obesity
- Diabetes
- Dyslipidemia
- Chemotherapeutic agent category
- Total cumulative dose
- Concomitant radiotherapy/cardiac irradiation
- Abnormalbiomarkers levels or cardiac imaging

5) General management of cardiovascular toxicity

As per the modern medical science, the management of various symptomslike Cardiac failure, IHD, Hypertension, arrhythmia,etc arises due to cardiotoxicity are given in **Table 3**

Table 3: Management of cardiovascular toxicity

Toxicity	Management
Cardiac failure	Avoid risk factors
	Diuretics, MRA, BB, ARBs or ACEIs
	ICD or CRT
Ischemic heart disease (IHD)	nitroglycerine or Nitrate
	CCB, BB, ARBs or ACEIs
	Antiplatelet agent, anticoagulation
	Lipid-lowering agents
	Coronary revascularization (intervention or surgery)
Hypertension	Diuretics, BB, DHP-CCB, ARBs or ACEIs
Arrhythmia	
QT prolongation	Avoid risk factors, ICD in cases of VT or VF
Atrial fibrillation	Rhythm control: cardioversion
	Rate control: BB, digoxin, non-DHP-CCB
Acute pericarditis	Aspirin, NSAID, colchicine
Pericardial effusion	Pericardiocentesis, pericardiotomy
Pulmonary hypertension	Iloprost, Ambrisentan
Venous thromboembolism	Anticoagulation

C) "GARAVISHA" & DRUG INDUCED CARDIOTOXICITY

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1) Ancient Aspect

.The word*gara* derived from गृ (Root Word) and अच् (Suffix) which means to diglute or in liquid form [13]. It is classified under *kritrima*or *samyogajavisha*by Acharyas.

"*Garasamyogajamvishamgarasamjamgadapradamkaalantaravipakitwatnatadaasuharatyasoon*" [14].

*Garavisha*is one of unique concept explained in our ancient Ayurvedic texts. Itis artificially prepared by the combination of various substances and responsible for various disorders. But as it takes some time for its metabolizing inside the body, it does not cause instantaneous death of an individual. Now a days, due lifestyle changes, adulteration, fast foods,environmental pollutants, increased use of pesticides, peoples gets exposed to various toxins from many, which one day become intolerable as far as health is concerned. Such non-systematic use of these resources further leads to exogenous or endogenous toxicity. Incompatible drugs in a medicinal formulations and those *vishayogas*which are having lower potency can also be incorporated into gravisha.

G*aravisha*can be classified into 2 main types: [15]

1) *Nirvishadravyasamyogakrtam:*These are combination of two nonpoisonous substances.

eg:*virudhahara* which can be considered as *gara.*

2) *Savishadravyasamyogakrtam:* Combination of poisonous materials also known as*kritrimavisha*.

According to *Acharya Charaka*, *Gara* is the toxic combination of substances which exerts toxic effects after the interval of sometimes and which does are not causes the death of the patient instantly [16]. According to *Acharya Vagbhata*, *Garavish* is included in *krutrimvisha* (Artificial poison) formed by the combinations of various drugs. Its action may be acute or chronic and produces the disorders like *Shopha*(edema), *Pandu* (anaemia),*Udera*(ascites) etc.[17]. In *Garavisha* due to the impairment of *Agni*, by*srotorodha*due to accumulation of toxins as it cannot beproperly metabolized and eliminated from the body, improper metabolism, accumulation of toxins at different tissue level, impairment of organs[18].

2) Correlation between Gravisha and Drug Induced Cardiotoxicity:

Now a days, the chemical induced diseases are increasing paradoxically and in recent years to become a major health problem. As per the Ayurvedic perspective we can incorporate these chemicals as a concept of *garavisha.* In today's world there are ample references of *garavisha.* Thus it has got contemporary relevance. In recent years everything has undergone a change – life style, habits of people, diseases and its manifestations etc. In case of *garavisha* also, whatever have been described in our ancient classics are not exactly the same in today's society but it relevant in most of the cases of toxicities. *Gara* is toxic combination of substances which are non-poisonous in nature or

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whichexerts toxic effects after interval of time and such does not kill the patient instantly. Gara is formulation of different organs of insects or their waste products, *Viruddhaaushadhi* (incompatible drugs), *Bhasmas* (ashes) and less potent poisons [19]. According to Charak samhita, *Garavisha* (Artificial poisons) causes disorders like *Pandu, Krushata, Alpagni, Hridpradhaman, Aadhmana, HastapadaShotha, Udara, Grahani, Rajyakshma, Kshaya, Jwara* and *Gulma*[20]. Here the symptom *Hridpradhamana* can be associated with the concept of cardiotoxicity in the current scenario of drug induced toxicity due to *garavisha.*

*Garavisha*can be any food material which mixed with the substancesthat are harmful to the body i.e. insects body parts, wastes etc. The substances that causes a toxic effect may be pesticides, insecticides or drugs like Quinine, NSAIDs, Steroids or any other chemical substances which are present in the environment of an individual can be included in it. The exposure of these toxins through our daily life responsible for harmful effects in the body. For example, aspirin can cause acute and chronic overdose effects. Here the acute effects of aspirin may be accidental or intentional while chronic effects may occurs in day normal daily dose build up in the body. Use of Aspirin in viral illness inhibit the fat metabolism which may further increase the risk if Reys syndrome. Similarly, Paracetamol overdose causes liver and kidney damage. In this way Cardiotoxicity occurs due to many chemotherapeutic agents and other drugs can also be understood under the concept of *Garavisha*.

3) *Samprapti* (Pathophysiology)

*Visha*enters into body

⇩

Vitiates *Rasa-Raktadhatu*

⇩

Enters into the heart

⇩

Imbalance in the function of heart

⇩

*Visha*has *Guna*opposite to that of *Oja*

⇩

VishajanyaHridroga

4) *SamhitoktaChikitsa* (Treatment)

Direct reference of*VishajanyaHridroga*are not available in any of our ancient texts. But still pathophysiology and manifestation of drug induced toxicology can be correlated with the concept of in ayurveda. So the fundamental treatment modalities for management of *garavisha*can be useful in treatment of drug induced cardiotoxicity.The specific treatment modalities mentioned in *Samhitas*for *Garavisha*are as follows:

Shodhana:

Instantaneously, the patient of*garavisha* (Concocted poison) should be given *Vamana*(Emesis). He should be given the fine powder of *Tamra* (copper) along with honey for cleansing the heart (here it means stomach). After the heart is cleansed, the patient should be given *one Shana* quantity of the *SwarnaBhasma* (fine

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powder of gold) [21]. When poisoning due to *Garavisha*is diagnosed in any person, it should be treated immediately.

After the patienttreated with *Vamana* (Emesis) &*Virechana* (Purgation), he should be given fine powder of *Tamra* (copper) mixed with honey, at the right time (i.e. after *Samsarjana karma*) which helps in detoxification process of*Hridaya* (here it means the stomach) [22]. After this detoxification of*Hridaya*, the individual to be administrated with one *Shana* of goldpowder (1 *Shana* i.e. 4 *Masha* i.e. 24 *Ratti*(about 3gm approximately), But thisdoseis practically too large and should not employed on patient. So, the *Swarnabhasma* should be preferably used in therapeutic dose i.e. 1/8 ratti to ¼ ratti (which is about 15-30 mg approximately)[23]. The gold powder responsible to reduce the effect of poison and also act as a Hridya[24].*Vagbhata* also describe the use of *dipan-pachan* treatment for *mandagni*caused by *Garavisha* (Concocted poison). [25]

SukshmaTamra-raja churna (fine powdered copper) suggested that it should not be *Shodhita* (the purified and calcined one). It is because, if we use*ShodhitaTamrabhasma*, it does not cause emesis which is intended here for cleansing the heart [26].*Nirmalikrita* (Filtered) *SukshmaTamra-raja* can also be used here for emesis as it also possesses emetic property. As its use is also safe over *AshodhitaTamrabhasma*[27].

Properties of *Tamra*[28]

Tamra is widely used from the ancient period in various Ayurvedic formulations in the bhasma form. The action of tamra due to its rasa, guna, virya, vipaka and prabhava known as rasapanchaka given in Table 4

Table 4: Rasapanchaka of Tamra

Rasa	*Tikta, Kashaya, Madhura&Amla*
Guna	*Snigdha*
Virya	*Ushna*
Vipaka	*Katu*
Karma	*Vishahara, Saraka, Lekhana, Dipana, Rochaka, Aayuvardhaka,* ***Vamak****&Virechaka*
Doshaghnata	*Pittaja, Kaphaja& Pitta-Kapahaja*
Rogaghnata	*Krimihara, Kushtha, Kasa, Shvasa, Kshaya, Pandu, Arsha, Grahani, Sthaulya, Jvara, Vrana,* ***Garavisha****, Shula, YakrutplihaVisuchika, Akshepa, Amlapitta,Chardi, , Udara, Agnimandya, Parinamshula, Khalliantrashosha, Apasmara*

TREATMENT (as per ancient texts):

As the modern medication for the cardiotoxicity has harmful effects on the other organs along with the general complication. So it is need of time to find the possible alternatives for the cardiotoxicities arises in current scenario of lifestyle. So in ancient Ayurvedic texts, there are various treatment modalities explained for such toxicities. The collection of treatment protocol as per Acharya *Charaka*, *Vagbhata* and *Yogratnakara*are given in **Table 5**

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Table 5 Treatment modalities as per different acharyas

Acharya Charaka[29]	Acharya Vagbhatta[30]	Yogratnakar[31]
1. ***Vamana (Emesis)***: administration of fine powder of copper along with honey for cleansing the heart. *(hrudayashuddhi)* **2.** ***Swarnaprashana:*** one *shana*of the powder of *swarna*[gold]. *Swarna*controls all poisons and poisonous combinations. Poison does not stay in the body on taking *suvarna*like water on lotus leaf. **3.** ***Agadpana*****-** buffalo ghee cooked with *nagdanti ,trivitit, dantidravanti,* milk latex of *snuhi*and *madanfala*along with one *adaka*of cow‟s urine is useful incuring patients suffering from the poisons of snake‟s bite, insects and from *gara.*	**1.Vaman** **2. Sharkarasuwarnadileha** **3. Suwarnamakshika** and***suwarnabhasma***when given with sugar and honey cure *garvisha.* **4. Treatment of *mandagni*** The powder of *murva, amruta, tagar, pipli, patol, chavya, chitrak, vacha, musta, vidanga*mixed with either butter milk, warm water, water of curds, meat soup or sour liquid should be consuming by the patient having *Mandagni,* destroyed by artificial poisoning. **5. Treatment of pain**, *trishna, kas, shwas, hikka, jwarupdrava-ghrita*and *trifala*juice with *makoy*shake-*shwas kasnashak*. -decoction prepared from the meat of the pigeon, *shathi*and *pushkarmul*cooled and consume.31 **6. Treatment in damaged skin** Apply *lepa*of*renuka, chandan, priyangu,kha*son skin. **7. Treatment of ojkshaya** *Ubtan*of *manjishta, apamarg, neem, haldi, papal* and *chandan.* **8. Milk** and **ghee** is supposed to be the best diet in *garavisha.* **9. Nagdantyadighrit**	**1. *sharkarasuvarnadileha.*** **2. *PutrajivmajjaYog*.** **3. Grihdhumadigrita.** **4. Paravatadihima.** **5. *Garnashanras.***
AgadKalpa in Charak Samhita: *MrutsanjivanAgada (C.Chi.23/54-60)* *KsharaAgad (C.Chi.23/101-104)* *NagdantyadiGhrita (C.Chi.23/241-242)* *AmrutGhrita*No.1 *AmrutGhrita*No.2 *(C.Chi.23/242-249)* *Hemachura Prayoga (C.Chi.23/239)* *Narayan Churna (C. Chi.13/125-132)*	***AgadKalpa in AshtangSamgraha:*** *JivanAgad (AS.Su.8/29)* *AjeyaGhrita (AS.Ut.40/165-168)NagdantyadiGhrita (AS.Ut.40/164)* HaridraGhrita (AS.Ut.40/162) JatiGhrita (AS.Ut.40/162) NakuliGhrita (AS.Ut.40/162) TanduliyakamuladiGhrita (AS.Ut.40/163) Vrushyanimbadi Yoga (AS.Ut.40/161) PalashKshara Yoga (AS.Ut.40/189-193) Mantra prayoga (AS.Ut. 40/194-196) Tapyasuvarna Yoga (AS.Ut.40/154) Kiratatiktadi Yoga (AS.Ut.46/40-41) ***AgadKalpa in AshtangHridya:*** *Vajra Agad (AH.Ut.36/82-83)* TiktakGhrita (AH.Chi.19/2-7) MahatiktakGhrita (AH.Chi.19/8-11) Tapyasuvarna Yoga (AH.Ut.35/56) Dantiharitaki Yoga (AH.Chi.14/92-97) *Abhayarishta (AH.Chi.8/64-68)*	

DISCUSSION

In current scenario of modern medications, cardiac complications are increasing day by day. Polypharmacy approach of these medications usually leads to occurrence of various secondary diseases likearrhythmia, hypertension, etc. There are so much drugs which are co-administered along with the existing therapy which may be responsible for the worsening of the cardiac complications. Now a days,generally all the physicians commonly uses calcium channel blockers, beta-blockers, anti-arrhythmic

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drugs,anticancer drugs, and immunomodulatory drugs in their practice, thus there must be proper monitoring for the use of such drugs. Especially in patients who are having left ventricular dysfunction, all extensive precautions must be taken to prescribe medicines for cardiac toxicity. There are about 10% of drugs which have been withdrawn from the worldwide market in the last 40 yearsdue to cardiovascular safety issues, e.g., sibutramine, rofecoxib, and tegaserod. In such drugs, there is great effortshas been taken to reveal cardiotoxicity of these drugs in the preclinical trail phase of development of medicinal products, still cardiotoxicity is still greatest safety concerns mainly due to the lack of sufficient knowledge of the mechanisms of cardiotoxicity. Also even if cardiotoxicity occurs by these drugs, there is no specific established antidote treatment for such toxicity and it is treated symptomatically by using general treatment protocol.

According to Ayurveda, *Hridroga* is the condition which disturbs the functions of heart. As *Hriday* is one of the marma among *Trimaramas,* explained in ancient Ayurvedic texts, Therefore even the slight injury responsible for fatal consequences. General causative factors explained in Ancient Ayurvedic texts does not shows direct explanation of *Aushadhijanyahridroga*but there is explaination about cardiac disturbances which produced as a side effect of medicines which are not prepared properly. This shows our ancient acharyas were well known about the cardiotoxicity due to drugs.

In *GaraVisha*, *Hridpradhaman*is one of the manifestations and can be correlated with manifestations of drug induced cardiotoxicity. This shows association between *garavisha*and drug induced cardiotoxicity. Hence treatment protocol of*garavisha*can be applicable for the management of drug induced cardiotoxicity. In Ayurveda, there is treatment modalities including both *Shodhan*and*ShamanChikitsa*should be use for *Garavisha*. Out of these treatment modalities *Narayana Churna,MahatiktakGhrita, TiktakGhrita, TapyaSuvarna Yoga,Abhayarishta, Dantiharitaki* and *Patha*are indicated in the management of both *Garavishachikitsa*and*HridrogaChikitsa*. Still there is scope of further clinical trials to be conducted for validation of such medication at global level.

CONCLUSION

From the given article, it is finally concluded that there is positive correlation between drugs induced cardiotoxicity and *garavisha*. Thus various treatment modalities can be useful in *garavishachikitsa*can be effective in drug induced cardiotoxicity in the current scenario. Thus it is helpful for researchers to explore different dimensions of treatment of drug induced cardiotoxicity. Further preclinical and clinical trials should be required to bring these product into market and global acceptance.

RESEARCH OUTCOME:

In last few a years, the demands of Indian traditional medicines has been increased in the

medical world. Ayurveda is although highly effective in the various disorders in the today's world also but there is not proper exploration of pharmacology, pharmacodynamics, pharmacokinetics and pharmacovigilance of various Ayurvedic drugs. Therefore, advancements in the current situation of ongoing research methodology is need of time for the promotion of Ayurveda at the global platform. In the current article the ancient concept of *Garavisha* along with its relation with cardiotoxicity due to modern medications. Thus it helps for reestablishing the fact that, the treatment modalities used by our ancient acharyas can also be used in current scenario of cardiotoxicity. This helps the researchers to conduct preclinical and then clinical trials for the validation of results of Ayurvedic medications and gives the confidence to clinicians to prescribe these treatment modalities in drug induced cardiotoxicity. It also helps industries to look forward for manufacturing of formulation prescribed under the*Garavisha* concept in our ancient texts and this brings evolution for the globalization of Ayurvedic medications in drug induced toxicities due to modern drugs.

SCOPE OF FUTURE RESEARCH:

As the given article is review contemporary aspect of drug induced cardiotoxicity and classical aspect of *Garavisha*. It is an attempt to find correlation between them. This will be helpful in exploring the different dimensions of treatment of drug induced cardiotoxicity. Further clinical trials should be needed in this context.After preclinical as well as clinical research of these treatment modalities validate their efficacy and acceptance of our ancient medications in the global platform.

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