ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Review Article

CRITICAL REVIEW OF DRUG INDUCED CARDIOTOXICITY W.S.R. TO *GARA VISHA*

Matre Akash T[1]*, Anjankar Meghsham P[2], Nikam Ashwin V[3], Pawade Uday V[4]

*[1]P.G. Scholar, [2]Guide and Assistant Professor, [3]Professor & H.O.D, [4]Associate Professor, Department of Agadtantra, Vyavahar Ayurved Evum Vidhivaidyak, Shri Ayurved Mahavidyalaya, Nagpur, Maharashtra, India.

ABSTRACT

Cardiotoxicity is a condition when there is damage to heart muscles by a toxin. It has many causes but drug induced cardiotoxicity is more common. *Agadtantra* is one of the eight clinical branches of Ayurveda. It deals with *Visha*, their characteristics, manifestations and treatment. Cardiovascular diseases and cancer are the most common causes of death in India. Out of which, heart failure is a major cause. Cardiotoxicity is one reason for heart failure; it may cause due to some common drug categories like anticancer agents, monoclonals, antihypertensives, antidepressants etc. No specific antidote treatment for drug induced cardiotoxicity is available till now. Currently it is managed by using general line of treatment and symptomatic treatment. *Gara visha* (Artificial Poison) is the type of *Samyogaja visha* (Unnatural poison or chemically prepared poison) which is prepared by the combination of either poisonous or non-poisonous substances. Thorough literature review has been conducted on modern aspect of drug induced cardiotoxicity and classical aspect of *Gara visha*. It is found that there is positive correlation between drugs induced cardiotoxicity and *Gara visha*. Hence, it is concluded that various treatment modalities useful in *Gara visha* can be effective in drug induced cardiotoxicity. Present article will be helpful for researchers to explore different dimensions of treatment of drug induced cardiotoxicity.

KEYWORDS: Drug induced Cardiotoxicity, *Gara visha, Samyogaja visha*.

INTRODUCTION

In India the most common causes of death are cardiovascular diseases and cancer, yet heart failure is the prime cause[1]. Cardiotoxicity is defined as a condition when there is damage to the heart muscles by a toxin. Drug induced cardiotoxicity is one of the commonest cause[2]. Common drug categories responsible for cardiotoxicity are anticancer agents, monoclonals, antihypertensives, antidepressants etc. There are two types of cardiotoxicity, Type I irreversible damage category, which is due to cumulative doses and Type II reversible damage, it is not related with cumulative doses[3]. Clinically cardiotoxicity is presents in various forms e.g. Cardiomyopathy, CHF, LVEF, Cell damage etc. The most frequent symptom of such cardiotoxicity is LVEF (left ventricular ejection fraction) reduction which may indicate the development of left ventricular dysfunction and leads to congestive heart failure. Other cardiotoxicity symptoms include arrhythmias, changes in blood pressure or cardiomyopathy. As per report, many patients suffer from drug induced cardiotoxicity as a adverse effect of anticancer treatment in Europe and USA[4]. Occurrence rate of cardiotoxicity in patients on treatment with drugs like Doxorubicin, Trastuzumab and Sunitinib is 3-26%, 2–28% and 2.7-11% respectively[5]. Recent retrospective study on breast and hematological cancer suggests that 6.6% of patients who received chemotherapy has developed heart failure[6]. Statistical information from United Network for Organ Sharing (UNOS) and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) shows that 0.5% to 2.5% patients develop drug induced Cardiomyopathy following with anticancer treatment[7]. Till now there is no established antidote treatment for drug induced cardiotoxicity and is treated symptomatically by using general line of treatment.

In classical review direct reference of drug induced cardiotoxicity is not found but it is considered that, this form of toxicity may be included in *Gara visha* (*Kritrim visha).* Acharya Charaka has divided *Dravaya* into two parts one of these is *Abhaishaj* which is again classified into two categories i.e., *Badhana* and *Saanubadhana*. *Badhan* refers to drugs causing acute toxicity while *Saanubandhana* are the drugs which causes chronic toxicity and acts as causative factor for some

illness[8]. *Charak* has classified *Visha* into *Sthavar, Jangam and Gara visha*[9,10]. According to *Chakrapani* commentary, *Gara visha* is termed as *Nirvisha dravaya samyog krut* while *Kritrim visha* is termed as *Savisha dravaya samyog krut*[11]. The same has been reciprocated by *Vriddhakashyapa*.

Hence, this article aimed to review contemporary aspect of drug induced cardiotoxicity and classical aspect of *Gara visha*. It is an attempt to find correlation between them. This will be helpful in exploring the different dimensions of treatment of drug induced cardiotoxicity.

METHODOLOGY

A) Anatomy and Physiology of Heart[12-26]

Heart is made up of specialized tissues called myocardium and one of the important components of cardiac system. Circulatory system consist of the systemic circulation to and fro the body and the pulmonary circulation to and fro the lungs.

According to Ayurveda, *Nirukti* of *Hridaya* is *Hri* means *Harti* (to receive from), *Da* means *Dadati* (to give), *Ya* means *Yagati* (pulsatile action). It is made out of the essence of *Rakta* and *Kapha. Hridaya* is *Sthana* of *Sira, Dhamani, Chetana Buddhi, Mana, Manasa dosha* and *Prana-Udana-Vyana Vayu, Sadhaka Pitta, Avalambaka Kapha, Rasa-Rakta-Mansa-Meda-Sukra-Oja Dhatu, Pranavaha-Rasavaha, Manovaha Srotasa* etc. It is one of the *trimarmas*, *Sadyopranahara* and *Sira marma. Hridaya* is a *matruja avayava* and one of the members of *Dashapranayatana* and *Ashtakoshthanga.* According to *Sushruta, ahara rasa* made through *pachana* process is brought to *Hridaya* by *Samana vayu* which is then circulated all over the body by *Vyanavayu*. This process is called as *Rasa-Rakta vikshepana kriya.* According to *Sharangadhara, Prana vayu* brings *Ambar-Piyush* (Oxygen) existing in the atmosphere, inside the body by every inspiration and *Vyana* circulates this *Ambar-Piyush* into the body through *Rasa-Rakta*.

B) Modern Aspect of Cardiotoxicity

The term Cardiotoxicity is a generally used to define toxicity to heart[27]. Clinically, drug induced cardiotoxicity is defined as, "fulfillment of either criterion like- reduction of LVEF, presence of signs or symptoms associated with heart failure, reduction in LVEF from baseline ≤5% in the presence of signs or symptoms of heart failure or reduction in LVEF ≥10% to <55% without signs or symptoms of heart failure"[28].

C) Drugs causing cardiotoxicity[29]

Table 1: Drug induced congestive heart failure

Sr. No.	Class	Drugs
1	Anticancer	Doxorubicin
		Paclitaxel
		Daunorubicin
		Idarubicin
		Cyclophosphamide
		Fluorouracil (5fu)
		Mitomycin
		Imatinib
		Sunitinib
		Mitoxantrone
		Ifosfamide
2	Monoclonal antibodies	Trastuzumab
3	Antihypertensive	Minoxidil
	Calcium channel Three group a)Polyethyalamine b)Dihydropyramidin c)Benzothiazepine	 Verapamil Nifidipin Diltiazem
4	Antidepressant	Tricyclic-Antidepressant
5	Non-selective beta-adrenoreceptor agonist	Isoproterenol
6	Potassium channel Activator	Diazoxide
7	COX inhibitor	NSAIDs
8	Antifungal	Ketoconazole

Table 2: Drug Induced Cardiomyopathy

Sr. No.	Class	Drug
1	Antiretroviral	Zidovudine
2	Signaling Protein	Intertron
3	Immunosuppressant	Cyclosporine
4	CNS stimulant	Amphetamine and Methamphetamine
5	Atypical antipsychotic	Clozapine
6	Platelet reducing agent	Anagrelide
7	Androgenic stimulant	Ephedrine
8	Addictive psychoactive	Ethanol

Table 3: Symptoms and signs of cardiotoxicity [30]

Dyspnoea	Cachexia and muscle wasting
Orthopnoea	Tachycardia
Paroxysmal nocturnal Dyspnoea	Pulses alternant
Reduced exercise tolerance	Elevated jugular venous pressure
Nocturnal cough	Displaced apex beat
Wheeze	Right ventricular heave
Ankle swelling	Crepitation or Wheeze
Anorexia	Oedema
Lethargy	Hepatomegaly
Fatigue	Ascites

Table 4: Management of cardiotoxicity [31]

Cardiotoxicity	Management
Heart failure	Avoid risk factor, Diuretic, BB, MRA, ACEIs or ARBs, CRT or ICD
Ischemic heart disease	Nitrate or nitroglycerine, Anti platelet agent, anticoagulation, BB, CCB, ACEIs or ARBs, Lipid-lowering agents, Coronary revascularization (surgery)
Hypertension	Diuretic, BB, DHP-CCB, ACEIs or ARBs
Arrhythmia QT prolongation :- Atrial fibrillation :-	Avoid risk factor, ICD in cases of, VT or VF Rhythm control:- Cardio version Rate control:- BB, Digoxin, non DHP-CCB
Pericarditis	Aspirin, NSAIDs, Colchicine

C) Gara Visha Vivechana

Visha is defined as a substance which when enters in the body, vitiates *Dosha-Dhatus* and produces ill effects or death of an individual[32]. According to Ayurved *Samhitas*, it has three types- *Sthavar, Jangam* and *Gara visha. Sthavar visha* is of plant origin*. Jangam visha* is of animal origin*. Gara visha* (Artificial Poison) is the type of *Samyogaja visha* (Unnatural poison or chemically prepared poison) which is prepared by the combination of either poisonous or non-poisonous substances*.* According to *Chakrapani* commentary *Gara visha* is termed as *Nirvisha dravaya samyog krut* while *Kritrim visha* is termed as *Savisha dravaya samyog krut. Dushi visha* has not been separately classified. It is a part or traces of *Sthavar, Jangam* or *Gara visha* which becomes less potent after treatment and its effects are not completely nullified due to which it resides in the body is known as *Dushi visha. Gara visha* though having sever fatality can be act as *Dushi visha* depending upon the potency of the combination of poisonous drugs [33,34]. *Hridpradhaman (Hridroga)* is one of the symptoms of *Gara visha*[35].

Table 5: Manifestations of *Gara visha*

Sr. No.	*Gara visha*
1	*Pandu*
2	*Krushata*
3	*Alpagni*
4	*Hridpradhaman*
5	*Aadhmana*
6	*Hastapada Shotha*
7	*Udara*
8	*Grahani*
9	*Rajyakshma*
10	*Kshaya*
11	*Jwara*
12	*Gulma*

E) *Visha Roga samprapti vivechana (Samanya samprapti)*[36]

When *Visha* enters into the body, initially it causes *Rasa-Rakta Dushti* then causes *Tridosh Dushti* and *Dosha Ashaya Dushti.* Lastly, *Visha* enters into the *Hridaya* causing death.

F) Probable *Vishajanya Hridroga samprapti (Vishesh samprapti)*

When *Visha* enters into the body, it vitiates *Rasa-Rakta dhatu.* Vitiated *Rasa-Rakta dhatu* then enters into the heart causing imbalance in the function of heart (as *Visha* has *Guna* opposite to that of *Oja*) resulting into *Vishajanya Hridroga*.

G) Treatment of *Vishajanya Hridroga*

As direct references of *Vishajanya Hridroga* are not available in *Samhitas* hence in this condition treatment modalities in *Visha Chikitsa* can be applicable. When the *Visha* is in the form of *Gara Visha* then fundamental treatment modalities of *Gara Visha Chikitsa* can be applied. The specific treatment modalities mentioned in *Samhitas* for *Gara Visha* are as follows.

Table 7: *Shodhana Chikitsa* in *Gara Visha*

Sr. No.	Type of *Visha*	Type of *Shodhana*	*Shodhan Dravya*	References
	Gara visha	*Sadya Vamana*	*Sukshma Tamraraja* with Honey	*C.Chi.23/238-239* *AAS.Ut.40/15* *AH.Ut.35/55*

Table 8: *Shamana Chikitsa* in *Gara Visha*

Sr. No.	*Shamana Yoga*	References
1	*Mrutsanjivan Agada* *Sanjivan Agad*	*C.Chi.23/54-60* *AS.Ut.40/81-89*
2	*Kshara Agad*	*C.Chi.23/101-104*
3	*Yapan Agad*	*AS.Ut.40/90-94*
4	*Bilwamuladi Agad*	*AS.Ut.42/91-92* *AH.Ut.36/84-85*
5	*Jivan Agad*	*AS.Su.8/29*
6	*Vajra Agad*	*AH.Ut.36/82-83*
7	*Kalyanaka Ghrita*	*S.Ka.6/8-10*
8	*Ajeya Ghrita*	*S. Ka. 2/47-49* *AS.Ut.40/165-168*

9	*Nagdantyadi Ghrita*	*C.Chi.23/241-242* *AS.Ut.40/164*
10	*Amrut Ghrita* No.1 *Amrut Ghrita* No.2	*C.Chi.23/242-249* *AS.Ut.40/168-169* *AS.Ut.40/170-176*
11	*Haridra Ghrita*	*AS.Ut.40/162*
12	*Jati Ghrita*	*AS.Ut.40/162*
13	*Nakuli Ghrita*	*AS.Ut.40/162*
14	*Tanduliyakamuladi Ghrita*	*AS.Ut.40/163*
15	*Tiktak Ghrita*	*AH.Chi.19/2-7*
16	*Mahatiktak Ghrita*	*AH.Chi.19/8-11*
17	*Hemachura Prayoga*	*C.Chi.23/239* *AS.Su.8/133-134* *B.P.N.7/11* *AH.Su.7/28*
18	*Tapyasuvarna Yoga*	*AS.Ut.40/154* *AH.Ut.35/56*
19	*Vrushyanimbadi Yoga*	*AS.Ut.40/161*
20	*Palash Kshara Yoga*	*AS.Ut.40/189-193*
21	*Mantra prayoga*	*AS.Ut. 40/194-196*
22	*Kiratatiktadi Yoga*	*AS.Ut.46/40-41*
23	*Dantiharitaki Yoga*	*AH.Chi.14/92-97*
24	*Patha*	*B.P.N.3/192*
25	*Trapvadi Gana*	*S. Su. 38/62-63*
26	*Abhayarishta*	*AH.Chi.8/64-68*
27	*Narayan Churna*	*C. Chi.13/125-132* *AH.Chi.15/14-21*

DISCUSSION

Cardiotoxicity is one of the major complications while using chemotherapeutic agents. Table no.1, 2, 3 and 4 shows causative drugs, manifestations and treatment protocol of drug induced cardiotoxicity. As per Ayurveda, *Hridroga* is the condition which disturbs the functions of heart. As *Hriday* is one of the *Trimaramas*, this may cause fatal consequences on slight injury. General causative factors mentioned by *Acharya* do not show direct reference of *Aushadhijanya hridroga* but they mentioned cardiac disturbances as a side effect of improperly prepared medicine. This proves that they were well aware of drug induced cardiotoxicity.

Hriday is one of the vital organs which has important role in *Visha samprapti* (as explained in *Visha samanya samprapti vivechana*). When *visha* causes *Hridroga* it can be termed as *Vishajanya hridroga samprapti*. When the *Visha* is in the form of *Gara Visha* then this *Samprapti* can be termed as *Gara Vishajanya Hridroga Samprapti*. In *Gara Visha*, *Hridpradhaman* is one of the manifestations and can be correlated with manifestations of drug induced cardiotoxicity. This shows association between *Gara visha* and drug induced cardiotoxicity. Hence treatment protocol of *Gara visha* can be applicable for the treatment of drug induced cardiotoxicity. Table no.7 and 8 provides *Shodhana* and *Shamana Chikitsa* for *Gara Visha*. Out of these *Abhayarishta, Dantiharitaki, Narayan Churna, Tiktak Ghrita, Mahatiktak Ghrita, Tapya Suvarna Yoga* and *Patha* are indicated in both *Gara Visha* as well as *Hridroga Chikitsa*. It is recommended that further clinical trials should be conducted in this regards.

CONCLUSION

From the above discussion it is concluded that there is positive correlation between drug induced cardiotoxicity and *Gara visha*. Various treatment modalities useful in *Gara visha chikitsa* can

be effective in drug induced cardiotoxicity. This will be helpful for researchers to explore different dimensions of treatment of drug induced cardiotoxicity. Further clinical trials should be needed in this context.

ABBREVIATIONS

C:- Charka

S:- Sushrut

AS:- Ashtanagsangrha

AH:- Ashtanghridayam

Su- Sutarsthan

Ni- Nidanstana,

Chi- Chikitsasthan,

Ka- Kalpstana,

Ut- Uttarsthan

B.P.N:-Bhavprakash Nighantu

BB:- Beta blocker

MRA:- Mineral corticoid receptor antagonist

ACEIs:- Angiotensin converting enzyme inhibitors

ARBs:- Angiotensin receptor blockers

CRT:- Cardiac resynchronization therapy

ICD:- Implantable cardioverter defibrillator

CCB:- Calcium channel blocker

DHP:- Dihydropyridine

VT:- Ventricular tachycardia

VF:- Ventricular fibrillation

NSAID:- Non-steroidal anti-inflammatory drug.

REFERENCES

1. The Leading Causes of Death in India. Sheth, Khushboo. World Atlas. [cited on 2017April 25]. Available from: http//www. worldatlas.com/ articles/the-leading-causes-of-death-in-india.html.
2. Marica F, Mircea C, Dragos V. Chemotherapy Induced Cardiotoxicity. Maedica a Journal of Clinical Medicine. 2013; 8(1): 59-67.
3. Csapo M, Lazar L. Chemotherapy Induced Cardiotoxicity: Pathophysiology and Prevention. Clujul Med. 2014; 87: 135-142.
4. Araujo-gutierrez R, Ibarra-cortez SH. Incidence and Outcomes of Cancer Treatment Related Cardiomyopathy among Referrals for Advanced Heart Failure, Cardio-oncology. 2018; 4: 3.
5. Yeh ET, Bickford CL. Cardiovascular Complications of Cancer Therapy, J Am Coll Cardiol. 2009; 53: 2231-47.
6. Clark RA, Berry NM, Chowdhury MH, et al. Heart Failure Following Cancer Treatment Characteristics Survival and Mortality of a Linked Health Data Analysis. Intern Med J. 2016; 46:1297–1306.
7. Liveira GH, Qattan MY, Al-Kindi S & Park SJ. Advanced Heart Failure Therapies for Patients with Chemotherapy Induced Cardiomyopathy, Circ Heart Fail. 2014; 7(6):1050–1058.
8. Shukla Vidhyadhar. Charka Samhita Vol. II (Chikitsa Sthana 1/4). Delhi; Chaukhamba Prakashana; 2015. p. 5.
9. Shukla Vidhyadhar. Charka Samhita Vol.II (Chikitsa Sthana 1/6). Delhi; Chaukhamba Prakashana; 2015. p. 538.
10. Jadavaji Trikamji Acharya. Charka Samhita Tika Vol.II (Chikitsa Sthana 23/14). Delhi; Chaukhamba Prakashana; 2015. p. 571.
11. Jadavaji Trikamji Acharya. Charka Samhita Tika (Chikitsa Sthana 23/14). Delhi; Chaukhamba Prakashana; 2015. p. 571.
12. Shastri Ambikadutta. Sushrut Samhita Vol. I (Sharir Sthana 4/30). Delhi, Chaukhamba Prakashana; 2015; p.33.
13. Gupta. A. Ashtang Hridayam (Sharir Sthana 3/18). Varanasi, Chaukhamba Prakashana. 2015; p. 252.
14. Gupta. A. Ashtang Hridayam, (Sharir Sthana 3/39). Varanasi, Chaukhamba Prakashana. 2015; p. 254.
15. Shastri Ambikadutta. Sushrut Samhita Vol. I (Sharir Sthana 4/33). Delhi, Chaukhamba Prakashana; 2015; p.34.
16. Shastri Ambikadutta. Sushrut Samhita Vol. I (Shari Sthana 3/30). Delhi, Chaukhamba Prakashana; 2015; p. 26.
17. Shastri Ambikadutta. Sushrut Samhita Vol. I (Sharir Sthana 6/26). Delhi, Chaukhamba Prakashana; 2015; p.55.
18. Gupta. A. Ashtang Hridayam (Sutra Sthana, 12/ 4, 5,7,13,15). Varanasi, Chaukhamba Prakashana. 2015; p. 120-122.
19. Gupta. A. Ashtang Hridayam (Sutra Sthana, 11/ 37, 39) Varanasi, Chaukhamba Prakashana. 2015; p199.
20. Shukla Vidhyadhar, Charka Samhita Vol. I (Viman Sthana 5/7) Delhi, Chaukhamba Prakashana; 2015; p.587
21. Shukla Vidhyadhar, Charka Samhita Vol. I (Nidan Sthana 7/4) Delhi, Chaukhamba Prakashana; 2015; p.531
22. Shastri Ambikadutta. Sushrut Samhita Vol. I (Sharir Sthana 6/26). Delhi, Chaukhamba Prakashana; 2015; p.55.
23. Shastri Ambikadutta. Sushrut Samhita Vol. I (Sharir Sthana 3/31) Delhi, Chaukhamba Prakashana; 2015; p.27.
24. Yadavji Trikamji Acharya. Charka Samhita Tika (Sutra Sthana 29/4). Delhi, Chaukhamba Prakashana; 2015; p. 181.

25. Shastri Ambikadutta. Sushrut Samhita (Chikitsa Sthana 2/12) Delhi, Chaukhamba Prakashana; 2015; p. 25.
26. Shastri Ambikadutta. Sushrut Samhita (Sutra Sthana 14/3). Delhi, Chaukhamba Prakashana; 2015; p.46.
27. Marica F, Mircea C, Dragos V. Chemotherapy Induced Cardiotoxicity. Maedica a Journal of Clinical Medicine. 2013; 8(1):59-67.
28. Seidman A, Hudis C, Pierri MC. Cardiac Dysfunction in the Trastuzumab Clinical trials Experience. J Clin Oncol. 2002; 20;1215–1221.
29. Ashif Iqubal. Clinical Updates on Drug Induced Cardiotoxicity, IJPSR. 2018; 9(1); 6-26.
30. Watson R D S. Clinical Features and Complication. BMJ, 2000 Jan 22; 320(7229); 236-239.
31. Hyungseop Kim. Diagnosis Treatment and Prevention of Cardiovascular Toxicity Related to Anti-cancer Treatment in Clinical Practice an Opinion Paper From The Working Group on Cardio-oncology of The Korean Society of Echocardiography. J Cardiovascular Ultrasound. 2018; 26(1); 1-25.
32. Shastri Kashinath, Charka Samhita Vol. II (Chikitsa Sthana 23/1-2). Delhi, Chaukhamba Prakashana; 2015; p.538.
33. Shukla Vidhyadhar. Charka Samhita Vol. II (Chikitsa Sthana 23/14). Delhi, Chaukhamba Prakashana; 2015; p. 540.
34. Shastri Ambikadutta. Sushrut Samhita Vol. I (Kalpa Sthana 2/25). Delhi, Chaukhamba Prakashana; 2015; p. 32.
35. Shukla Vidhyadhar. Charka Samhita Vol. II (Chikitsa Sthana 23/ 234-237). Delhi, Chaukhamba Prakashana; 2015; p. 572.
36. Gupta. A. Ashtang Hridayam (Uttarsthan 35/9-10). Varanasi, Chaukhamba Prakashana. 2015; p. 785.

Cite this article as:
Matre Akash T, Anjankar Meghsham P, Nikam Ashwin V, Pawade Uday V. Critical Review of Drug Induced Cardiotoxicity W.S.R. To Gara Visha. International Journal of Ayurveda and Pharma Research. 2020;8(3):31-37.
Source of support: Nil, Conflict of interest: None Declared

***Address for correspondence**
Dr. Matre Akash T
P.G. Scholar
Department of Agadtantra, Vyavahar Ayurved Evum Vidhivaidyak,
Shri Ayurved Mahavidyalaya, Nagpur, Maharashtra, India.
Email: akashmatre037@gmail.com
Mobile no: 07875803350