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Preclinical Evidence on the Cardio Protective Activity of *Prisniparni* (*Desmodium Gangeticum* (L.) Dc) in Myocardial Ischemia Reperfusion Injury: A Narrative Review.

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ABSTRACT:

Heart failure developed by Myocardial Ischemia and Ischemia reperfusion injury has been a major challenge for medical science with its mortality and morbidity rate, worldwide. The need of the hour is medical interventions that can reduce injury from myocardial ischemia and reperfusion. It's here where herbal medicines can play a pivotal role, as it is used in invention of many commercial drugs. *Prisniparni* (*Desmodium gangeticum* (L.) DC) is a widely used medicinal plant in *Ayurveda* for various ailments especially in cardiac diseases. Medicated milk prepared from *Prisniparni* is advised in *Vatika hridroga chikitsa*. This review highlights the cardio protective activity of *Desmodium gangeticum* (L.) DC seen in several preclinical models of Myocardial Ischemia reperfusion injury. A thorough literature search lead to 6 studies that met the inclusion criteria .Results of these studies pointed out the free radical scavenging activity of the plant *Desmodium gangeticum* (L.) DC during Ischemia and Ischemia reperfusion. Which majorly helped in cardio protection by preserving mitochondrial respiratory enzymes.

Key words: *Desmodium gangeticum*, Myocardial ischemia reperfusion, Herbal medicine, Cardioprotection, Ayurveda

INTRODUCTION

Myocardial infarction (MI) being a large cause of death and disability worldwide as proved by WHO which reported 7,254,000 deaths^[1] worldwide (12.8% of all deaths) as a result of Coronary Heart diseases^[2] and acute myocardial infarction, paints an alarming picture of coronary heart disease worldwide and throws light in to the need for

timely and effective Ischemia reperfusion (IR) procedure by thrombolytic therapy or primary percutaneous coronary intervention as the only way to rescue ischemic myocardium.^{[3][4]} But at the same time IR induces some irreversible injury to cardiomyocytes which ultimately leads to heart failure.^[5] Reperfusion leads to excessive



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formation of Reactive Oxygen Species (ROS) than during ischemia. And the oxidative stress induced by the generation of ROS, during acute reperfusion [6], experimental evidence shows plays a key role in the etiopathogenesis of Reperfusion Injury (RI)[7]. [8] And mortality and morbidity due to heart failure developed as a result of acute myocardial infarction remain substantial irrespective of the sophisticated reperfusion technologies. Measures and interventions that may reduce injury from myocardial ischemia and reperfusion is often neglected medical need. [9] The additive cardio protection, focusing on patients who are really in need is a helpful approach, medically employed at present. Herbal medicines played a pivotal role in the invention of many commercial drug preparations using nowadays including Ephedrine, Reserpine etc. Antineoplastic drug, Paclitaxel, recently discovered from *Taxus brevifolia*, underscores the important role plants play as a resource for modern medicines.[10] Newly reported studies showed the beneficial role of berberine [11] and curcumin [12] in RI. Many preclinical studies reported the beneficial role of the plant *Desmodium gangeticum*(L.) DC in various pathways of RI.[13], [14], [15] So it is the need of time to validate the preventive and curative aspects of herbal drugs explained in the traditional wealth of Ayurveda in this era of Evidence based Medicine.

Desmodium gangeticum (L.) DC (DG) (Family Fabaceae) is a slender, diffusely branched undershrub found throughout India.[16] In Kerala DG is considered as the source plant for the drug *Prisniparni* or *sthira*, which is widely used in Ayurveda for various ailments and known as *Orila* in Malayalam.[17] Roots are the medicinally useful part and said to be useful in vitiated conditions of *tridoshas*. Authentic Ayurveda text books pointed out its *vrushya* (Aphrodisiac) property and effectiveness in the treatment of *Daha* (Burning sensation), *Jwara*(Fever), *Swasa* (Asthma), *Raktaatisara* (bloody diarrhoea) and *Vami*(vomiting).[18] Acharya Vagbhata indicated the use of goats milk medicated with *Prisniparni* for infants in case of *stanya abhava*(deficiency of breast milk).[19] Acharya Susrutha advocated the use of decoction of *Prisniparni* along with some other drugs mixed with milk in seventh month of pregnancy to prevent miscarriage.[20] Acharya Vagbhata also pointed out its use in the treatment of *Ardhavabhedaka* (Migraine).[21] Cardio-protective activity of this plant is described in authentic text books of Ayurveda. Acharya Charaka described the use of *Ksheerapaka* (medicated milk) of *Prisniparni* if *vata* is vitiated in heart. [22] In *chikitsamanjari*, a famous

Malayalam book used widely among vaidyas (traditional medicine practitioners) in Kerala, *ksheerapaka* of the root of *prisniparni* is mentioned in *vatika hridroga chikitsa*(Heart disease due to vitiated *vata dosha*).[23]

The objective of this review is to draw attention towards recent preclinical studies that experimentally addressed the role of DG on several factors known that have led to Myocardial Ischemia Reperfusion injury. Also to highlight the age old ayurvedic concept of *Hridya* (cardioprotective) property of *Prisniparni* in the form of *ksheerapaka*, which is botanically accepted as *Desmodium gangeticum*(L.) DC in Kerala.

MATERIALS AND METHODS

This review relies on an electronic search of databases, hand searches and authoritative text books. We identified articles from Pub Med and Science direct using the search term “*Desmodium gangeticum* and myocardial ischemia reperfusion injury”. A total of 14 articles published between January 1990 up to January 2021 were available. Articles that come under the following inclusion and exclusion criteria were reported in this review. Inclusion criteria: Preclinical studies of various extracts of *Desmodium gangeticum* (L.) DC in myocardial ischemia reperfusion injury. Exclusion criteria: Repeated articles, reviews, and articles which are irrelevant to the topic. Among the 14 articles, 6 articles written in English, either full text or abstracts published between January 1990 up to January 2021 were included in this review.

Results

Different types of extracts of DG root were analysed for its cardio protective effects in IR injury. Experiments were conducted on the basis of its use in various preparations in the treatment of ischemic heart disease in Ayurveda and Indian system of medicines. [24] Kurian et al [25] reported the cardio protective effect of ethyl acetate extract of roots of DG in isolated rat hearts using in vitro and in vivo antioxidant models. Analysis of in vitro antioxidant potential, in terms of hydroxyl radical, lipid peroxide, nitric oxide scavenging activities in several concentrations of extract ranging from 2-1000 ug/ml was done and in vivo antioxidant potential was studied in an isolated rat heart model following the method by Doring H. Further, observing the changes in hemodynamic parameters, functional recovery of myocardium was assessed. Tissue damage and necrosis was analyzed by cardiac enzymes. 42 Rats, were included in three groups- control group, reperfusion group and treatment group. Rats in treatment

group were pre-treated for 30 days, orally. Free radicals were scavenged by the test compounds in a concentration-dependent manner, within the given range of concentration in all models, study showed. Drug-treated rat heart showed a significant ($P < 0.05$) recovery of left ventricular developed pressure compared with control. This is an indicator of physiological recovery of heart from ischemia reperfusion injury. Improvement in rate pressure and mean arterial pressure in ethyl acetate treated rat heart, shows ionic balance recovery for the normal physiological functions of hearts.. Administration of the DG root extract significantly ($P < 0.01$) improved the level of the enzymes Lactate dehydrogenase and SGOT. Improvement was observed in creatine kinase and SGPT also. These are the indicators of recovery from cardiac damage and myocardial necrosis. Lipid peroxidation in drug treated rat hearts were significantly ($P < 0.05$) reduced as compared to normal control hearts. Likewise, antioxidant enzymes got recovered significantly ($P < 0.05$) in drug treated rat heart, compared to normal control.

Another study by Kurian *et al* [26] reported that methanol extract of DG root showed a pharmacological action similar to that of Acetyl choline which will bring about a post-conditioning effect in isolated rat heart. Ischemic post conditioning (POC) may be useful to protect myocardium against ischemia/reperfusion injury by activating various receptors including muscarinic receptors. But the search for alternative therapeutic agents which will mimic the POC effect is gaining momentum because of its practical clinical difficulty. When studied and compared, the POC mimetic action of the extract, was found to act as muscarinic receptor agonist and antagonist- acetylcholine (Ach) and atropine (Atr) respectively. Study was conducted in four groups namely control, reperfusion, ischemic post conditioning and pharmacological post conditioning groups and assessed the effect of the drugs using physiological and biochemical parameters. The results of the study showed an improved working index of rat heart in DG extract post treatment group which is similar to that of recovery by POC and Ach post treatment. The extract also showed a negative chronotropic and inotropic effect in a dose dependent manner which is similar to that of binding of acetylcholine to receptors in the intact heart. They also reported a reversal of the physiological change mediated by Ach/DG in kymogram after addition of Atr, which further strengthen the possibility of action of DG extracts on muscarinic receptor. A good change in lipid peroxidation and antioxidant enzymes in Ach and DG root extract, in post treated groups

when compared to ischemic reperused control hearts , tissue homogenate and mitochondria both, was studied. This finding emphasises the role of DG root extract in the pathogenesis of post-ischemic myocardial dysfunction. They also identified cardio-stimulatory molecules namely 4-[2-(dimethylamino) ethyl] phenol -(Cactine) and 2,5- bis (1,1-dimethyl ethyl) phenol by GS/MS analysis.

Kurian *et al* [27] reported the protective effect of methanol extract of DG root in ischemia reperfusion induced mitochondrial dysfunction. They evaluated the effect of DG root extract on lipid peroxidation and antioxidants in mitochondria and tissue homogenates of normal, ischemic and ischemia-reperfused rats to find out the role of drug in maintaining the mitochondrial respiratory enzymes. Study was conducted in three groups, control, IR group and IR group with drug treatment. Animals of drug group was pre-treated with DG (50 or 100 mg/kg) orally for 30 days following the experimental protocol. Study reported a significant decrease in the level of TBARS in both tissue homogenates and mitochondrial extract in rats pretreated with various doses of DG mg/kg for 30 days. They also observed a significant improvement in the activities of mitochondrial enzymes which is comparable to that of standard drug verapamil. The study shows, volatile compounds Asaron and p-[2- (dimethylamino) presence which are known for their action on cardiac tissues.

Srivats S *et.al* [28] reported, the impact of root extract against ischemia reperfusion injury. Reperfusion injury induced by Langenedroff apparatus, they isolated rat heart and in-vitro antioxidant models that helped to assess the injury. DPPH, super oxide scavenging activity, hydroxide scavenging activity and nitric oxide scavenging activity were employed, which helped an improved antioxidant scale of the myocardium which suggests reduced oxidative stress, they found. Also, a cardiac marker protein was used to assess reduction of infarct size and for investigation of cardio-stimulatory effects by treating it as a pre-conditioning agent.

Kurian and Padikkala [29] reported the effect of aqueous extract of DG in IR rat. In the study they witnessed an RI associated with an increased oxidative stress and depletion in myocardial endogenous antioxidants both in tissue homogenate and mitochondrial fraction of myocardial tissue. Oral administration of DG root aqueous extract for 30 days prevented oxidative stress associated with IRI. They observed an improvement in the activity of catalase and SOD along with decreased level of TABRS in tissue homogenate and mitochondria samples.

Kurian *et.al* evaluated the cardioprotective effect of insulin

mixed with DG through oral and intraperitoneal route in diabetic rats. [30] In a previous study they observed the mediator action of DG aqueous root extract in the absorption of insulin into blood through gastrointestinal tract. [31] A significant recovery in contractile dysfunction in diabetic rat, induced by reperfusion injury, was seen after oral administration of insulin mixed DG. Both oral and intraperitoneal administration of DG mixed insulin was more impactful than the administration of DG root extract or insulin alone. Reperfused diabetic rat hearts achieved protection in ischemia, by the synergic action of DG extract, which acted as vehicle for insulin delivery as well as mediate synergic action with insulin and render cardio protection .

DISCUSSION

Myocardial reperfusion is an optimal therapy for MI to restore blood flow to ischemic region. But it will result into cardiomyocyte death, known as myocardial reperfusion injury, for which there is still no effective therapy. It is a strong inductor of adverse left ventricular extracellular matrix remodelling. [32] Various metabolic stresses resulted by reperfusion lead to calcium overload and massive release of reactive oxygen species which will favour the degradation of mitochondrial integrity, leading to necrotic and apoptotic cell death. [33] The mortality and morbidity associated with acute myocardial infarction generated heart failure remain substantial even after the development of improved methodologies for coronary reperfusion. [34] Evidence suggests, the important role of oxidative stress driven by the release of ROS during reperfusion in the etiopathogenesis of RI. So, a rational method for ameliorating RI is the pharmacologic and non-pharmacologic methods while research are on for a novel cardioprotective intervention .From time immemorial , medicinal plants are used for treatment for various ailments in human beings, as the antioxidants in plants offer a shield of protection , doubling as natural therapeutic agents [35] DG, like a ‘super queen herb’, is a widely used medicinal plant in Ayurveda. It is a component of various formulations and its use as *ksheerapaka* is specifically described in the treatment of cardiac diseases in Ayurveda classics. *Prisniparni* is predominantly having *madhura and tikta rasa*. It is having *Snigdha Guna, Ushna Veerya ,Madhura Vipaka And Tridoshahara* in action. *Madhura rasa and vipaka* of the drug nourishes the dhatus including *mamsadhatu* thereby strengthens *hridaya*. *Tikta rasa* with *lekhana and soshana* property and *ushna veerya* with its

vilayana property helps in *srotosodhana* thereby promoting action on *hridaya*. *Madhura rasa, Madhura vipaka ,Ushna veerya* are having *vatasamana* property which substantiate the role of *prisniparni* in treatment of *hridroga*. This paper reviewed six preclinical studies conducted on various extracts of DG in Ischemia reperfusion injury. Experimental evidence from these preclinical studies points out the promising role of various DG root extracts on cardiomyocytes in myocardial reperfusion injury and supporting the strengthening and *srotosodhaka* effect of *Prisniparni*. All these studies showed the ability of extracts of DG roots to scavenge the free radicals generated during ischemia and ischemia reperfusion thereby preserving the mitochondrial respiratory enzymes that eventually lead to cardio-protection. [36] These studies also reported the presence of two cardio-stimulatory molecules [37] and 2 volatile compounds [38] which have been reported to have action on cardiac tissue. All these findings strongly support the cardio-protective activity of DG described in authentic text books of Ayurveda.

CONCLUSION

The studies and available reviews clearly demonstrate, various extracts of DG could alleviate myocardial Ischemia reperfusion injury and provide cardio protection by free radical scavenging activity. Also, advanced In vivo and clinical studies would further provide strong evidences on the cardio-protective effect of DG. It should also be noted that studies to evaluate efficacy of *Ksheerapaka* of DG in the treatment of cardiac ailments, will largely benefit in validating its traditional use. All these, will open up a path of new discoveries of role of therapeutic agents in various pathologies related to heart, thereby providing healing touch to sores of ailing patients.

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