A CRITICAL REVIEW ON HRIDYA (CARDIOTONIC) ACTION OF DADIM (PUNICA GRANATUM LINN.) WITH SPECIAL REFERENCE TO AYURVEDIC AND MODERN ASPECT

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ABSTRACT

Cardiovascular diseases pose an alarming threat to global health. Heart disease is still the leading cause of death in India, killing 1.7 million Indians in 2016. According to Ayurved, Hriday or Heart is a vital organ as any type of damage to this organ leads to loss of life. Hridya mahakashaya (group of cardiotoxic drugs i.e. drugs having beneficial action on the heart) possessing sour taste has been explained in Charak Samhita. These drugs are useful in maintaining cardiac health and also mental health. Dadim (Punica granatum Linn.) means Pomegranate is one of the Dravyas explained under Hridya group. By means of its virtues, Dadim performs Agnideepan, Rasa-Dhatwagnideepan, Pittashamana, Vatanuloman and the Hridya function; and strengthens heart moreover nourishes brain. Hriday is one of the sites for Mana (psyche). Amla rasa of Dadim performs Tarpana karma of Hriday, satiates mind and improves mental strength. In this review the antioxidant, anti-inflammatory, anti-hypertensive, Anti-stress, thrombolytic, anxiolytic and anti-depressant actions of Dadim have been focused which are the key factors in treatment of cardiovascular diseases. This is an attempt made to explain the Hridya action of Dadim according to Ayurvedic as well as modern aspect. This article spreads a hopeful array for the researchers working on cardiovascular diseases.

KEYWORDS: Dadim, Amla, Hridya, Cardiotoxic, Punica, Pomegranate.

INTRODUCTION

The current status of heart disease in India is alarming; with projections suggesting that by the year 2020, the burden of cardiovascular diseases in India will exceed that of any other country in the world. It is estimated that 17.5 million people die each year in India from cardiovascular diseases, amounting to a staggering 31% of all deaths worldwide. 80% of all cardiovascular deaths are due to heart attacks and strokes, 74% of urban Indians are at risk of cardiovascular diseases. There are estimated 40 million heart patients in India. Out of which 19 million reside in urban areas and 21 million in rural areas. This suggest heart diseases are fast becoming an epidemic in rural India and a structured solution is needed for combating the issue.[1] Although many types of cardiovascular diseases are enlisted in contemporary science, only a few explanations are available in Ayurvedic classics. The synthetic drugs like organic nitrates, calcium antagonist and beta blockers are recently used to treat the cardiovascular diseases but they are not free from side effects like hypotension, bradycardia and dizziness etc.[2] Herbal medicines are increasingly gaining greater acceptance from the public and medical profession, the common belief that, herbal formulations are safer than modern drugs has lead to increasing use of herbal preparations.[3] The role of plant based bioactive compounds or phytochemicals has attracted much attention due to their unique cardioprotective activity. Several epidemiological studies suggest that dietary patterns characterized by relatively high intakes of fruits and vegetables are significantly associated with reduced risk of coronary heart disease and stroke.[4-7] Fruits and vegetables present a heart-healthy and colorful array of phytochemicals including carotenoids and polyphenols like flavonoids, resveratrol, ellagitannins, isothiocyanates and organosulfur compounds.

Phytochemicals are potent antioxidants and anti-inflammatory agents, thereby counteracting oxidative damage and inflammation which underlie the pathogenesis of CVD.[8-11] Keeping continuously increasing scenario of CVD in mind and as fruits are possesses a heart healthy and colorful array of phytochemicals it is necessary to focus on the fruits which are helpful to keep the heart healthy and protect from CVD. In this review we have focused on Hridya action i.e. cardiotoxic action of the fruit Dadim which is commonly known as Pomegranate (Punica granatum Linn.) and used as an edible fruit.
Pomegranate juice is rich in tannins, possesses anti-atherosclerotic properties, has anti-aging effects, and potent anti-oxidative characteristics. As some antioxidants have been shown to reduce blood pressure, Pomegranate juice consumption may reduce systolic blood pressure, inhibits serum ACE activity, and is convincingly a heart-healthy fruit. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Pomegranate juice flavonoids inhibit low density lipoprotein oxidation and cardiovascular diseases. Pomegranate juice has shown considerable anti-atherosclerotic, anti-hypertensive, antioxidant, and anti-inflammatory effects in human subjects and mouse models. The principal mechanisms of action of pomegranate juice may include decreased systolic blood pressure, thus causing an overall positive effect on the progression of atherosclerosis and the ensuing potential development of coronary heart disease.

In this review an attempt has been made to explain the Hridya (cardiotonic) action of Dadim according to Ayurvedic as well as modern aspect. Dadim is the cheapest and easily available dietary fruit and lot of research had proved that Dadim reverses plaque buildup in the arterial walls. This fruit appears to have more potential as a health supplement rich in natural antioxidants and merits further intensive study.

Methodology

Literary review of Dadim was taken from an Ayurvedic classical texts viz. Samhita and Nighantas, different textbook of Dravyagunavidnyan for comprehensive information of the drug Dadim. The research work done by scholars on this herb regarding related pharmacological activities was also compiled.

OBSERVATIONS

Vernacular Name [21]
Sans.-Dadim; Eng.- Pomegranate; Hind.- Anar; Ben. & Mah.- Dalimb; Punj.-Daru; Guj.-Damad; Can-Dalimbay; Tel.- Dadima, Dalimba; Tam.-Madalai, Madalam; Mal.-Madalam, Fr.- Grenadier cultivate; Ger.-Granate baum.

Taxonomical Classification [22]
Kingdom- Plantae; Subkingdom- Viridiplantae; Infrakingdom- Streptophyta; Superdivision-Embryophyta; Division-Tracheophyta; Subdivision- Spermatophyta; Class- Magnoliopsida; Superorder - Rosanae; Order - Myrtales; Family - Lytheraceae; Genus - Punica L; Species - Punica granatum L.

Habitat and Morphology [23-28]
Pomegranate is considered as an excellent tree for growing in arid zones for its resistance to drought conditions. It is now widely cultivated in Mediterranean, in tropical and subtropical areas. It is native from the Himalayas in northern India to Iran but has been cultivated and naturalized since ancient times over the entire Mediterranean region. It is also found in India and more arid regions of South-east Asia, the East Indies, and tropical Africa. Pomegranate plants require full sun, tolerate our alkaline soils, summer heat and winter lows to 10 degrees. It is adaptable to deep, loamy, well drained soils which are preferred but it has some tolerance to less than ideal drainage and to mild alkaline condition up to pH 7.5.

The Pomegranate tree typically grows 12 to 16 feet, has many spiny branches, and can be extremely long lived. The leaves are glossy and lance shaped, and the bark of the tree turns gray as the tree ages. Heterostylyous funnel shaped red flowers are characteristic to this plant and are found either in singles or in clusters of up to five, flowers are large, red and have tubular calyx that eventually becomes the fruit. The ripe Pomegranate fruit can be up to five inches wide with a deep red, leathery skin, is grenade-shaped, and crowned by the pointed calyx. The fruit contains many seeds separated by white,
membranous pericarp and each surrounded by small amounts of tart, red juice.

**Pharmacological uses** [29-36]

Dadim is considered as "a pharmacy unto itself" in Ayurvedic medicine and is used as an antiparasitic agent, a blood tonic, to heal ulcers, also possesses anticancer, anti-inflammatory, antioxidant, anti-viral, neuroprotective activity, hepatoprotective, reproductory function, anti-atherogenic effect, hypoglycemic and antiglycemic effect. Along with this many researches has proved that pomegranate effectively used in the treatment of prevention of cancer, cardiovascular diseases, diabetes, dental conditions, stomach disorders, anaemia, erectile dysfunction, bacterial infections, antibiotic resistance, and ultraviolet radiations-induced skin damage. Other potential applications include infant brain ischemia, male infertility, Alzheimer's disease, arthritis and obesity. Bhavprakash has stated its use in Daha (burning sensation), Jwara (fever). And the pharmacological actions include Balya- Balapradam (providing strength), Medhya (brain tonic), Shukralam (having aphrodisiac effect), Hridya (cardiac tonic).

**Phytochemicals** [25, 37]

Fruits are believed to be a potential source of natural phenolics that have been associated with reducing the risk of cardiovascular diseases. Phytochemical analysis of Punica granatum indicated the presence of alkaloids, flavonoids, phenolic compounds, tannins, lignins, fats and oils, inulin, cardiac glycosides and carbohydrates. These classes of compounds were responsible for antioxidant and free radical scavenging effect of plant material. It also chelates iron and possesses reducing power. The beneficial Pomegranate constituents are ellagic and gallic acid, ellagitannins, punicic acid, flavonoids, anthocyanidins, anthocyanins and estrogenic flavonols and flavones.

**DISCUSSION**

In different Ayurvedic texts and Nighantus, regarding references of Dadim, variation in the rasas is generally observed. Aacharya charak has mentioned the three Rasas of Dadim such as Amla, Kashaya, Madhura whereas Aacharya Sushruta stated that Dadim possesses the Madhura and Amla rasa, whereas Bhavaprakash Nighantu reveals Madhura, Kashaya, Amla rasa of Dadim.

Some Aacharya has explained the three types of Dadim according to their Rasas viz. 1) Madhura 2) Madhuramula and 3) Amla. [36, 38, 39, 40]

**Ayurvedic aspect of Hridaya**

The word Hridaya is composed of three syllables, i.e. hri+da+ya=hridaya. The first syllable denotes the suction activity of Hriday (Hridayam i.e. venous return), second points out the pumping activity of Hriday (Samvardhanam i.e. supply of oxygenated blood) and lastly the third syllable means control of these above two functions (Yama). The etymological derivation of the word Hriday consists of three verbs viz. Hri Aaharane- to extract, accept from Da Daane- to give, return to and 

In Gatau- to be in motion

Thus Hriday is that organ in the body which receives, gives out and in a state of motion, the indication is to the organ Heart. The Hriday is vital for all the normal mental and physical activities because the entire sense, perception representing the life or movement of the body depend on the Hriday. Furthermore, the Hriday is the substratum of Rasa, Vyana vayu, Buddhi, Indriya, Atma and Para oja. Charak has stated that heart is the seat of consciousness which is primarily a function of the brain. [41] Susruta has mentioned that heart is placed in the thoracic cavity between both nipples and extends up to the end of stomach [42] Both Acharyas have mentioned that only Hriday is the seat of Chetana and anatomical heart in the body. The heart harbours Chetana (Atman, soul or spirit). Atman is enclosed in the body and inseparably connected with Manas, Indriya etc. Heart is the site of origin of cardiac impulse, therefore it also harbours the Aatmik Gunas (like Dnyan, Vidnyan, Ichccha, Dwesh, Sukhh, Dukhh and Prayatna). Atman is the driver behind this mind-body complex; it expresses various desires which are gratified by the mind-body apparatus.

Heart evolves from the clear part of Rakta and Kapha. Hriday is the only organ that has distinction of being the origin or seat (Moolsthan) of two equally important Srotasas i.e. Pranavaha and Rasavaha srotas [43] and is one among the three important Marmas (vital spots) in human body [44] Rasavaha srotas is responsible for converting the Aahar Rasa to Rasa Dhatu and providing nourishment to all other body constituents and Pranavaha srotas is responsible for uninterrupted supply of the Ambarapeeyoosh (oxygen) through breathing. Rasa Dhatu is the first tissue emerging out of the nutritive fluid Aahar Rasa. Rakta circulars with Rasa all over the body and is responsible for Jeevan Karma, sustaining the life processes by supplying Pran to all body constituents. Rasa-rakta complex is essential for continuation of life. The human body is nourished by Shuddha rakta circulated by Hriday with the help of Vyvanavayu.[45]

The functioning of heart is a complex phenomenon. All the Vayu types are involved in it.
Prana is responsible for dilatation and relaxation of chambers, valves etc. and acceptance of Rasa-rakta complex in the heart (Aadan). Udhan is related with the contraction of same part (Visarga); the resultant Vyayam is accountable for pushing the Rasa-rakta complex for circulation along the aorta, (Vikshep). The synchronization among all the moving parts is significant for the sustenance of life process (Yogkshem). Saman indirectly influences the heart by providing it the first nutritive fluid resulting from the digestive process in the gut. Sadhak Pitta resides in the heart and drives its nourishment from Pachak Pitta. It is responsible for mental faculties like intellect (Buddhi, Medha) and ego (Ahamkar). Tactful use of these modalities to get his or her work done under the purview of Sadhak Pitta. Hence in some stages of Hridroga mental signs and symptoms are observed. Pachak Pitta is situated in Pachyamashaya (small intestine) and its chief function is digestion and generation of Aahar rasa. It also imparts nourishment and strength to other Pitta types spread all over the body. Avalambak Kapha is situated in the heart itself and it is responsible for smooth functioning of heart by maintaining its nourishment level. For this, it receives the essence of Aahar rasa (anna veerya) and its own potency. Agni is the converter per excellence in internal milieu. Aahar rasa is capable of generating all the seven Dhatus while Rasa Dhatu has a function of Preenan (i.e. to maintain the fluid level and balance of the body by circulating along the vessels) attributed to it.

Aacharya Charak has mentioned the five types of Hridroga (cardiac disorders) nearly 2500 years ago. The etiological factors of Hridaya roga are - Ativiyayama (physical exertion), Atisara (purgation), Chhardi (vomiting), Ama and Aghata (injury). The other factors which are responsible for Hridroga are Murchha (fainting), Jwara (fever), Kasa (cough), Shwasa (dyspnoea), Chinta (anxiety), Bhaya (fear), Trishna (thirst), Atiutsaha (excitement), Bhrama (mental confusion), and Aruchi (anorexia). Charak discusses about the role of improper exercise, stress, physical and mental trauma, excessive use of Tikshna Ashara (pungent and spicy foods) and Amadosha (Undigestible substances which act as toxin) as a causative factors of Hridroga. Manas is the seat of various emotions and stressful conditions producing mental symptoms like agitation etc. Psychological factors like prolongs stress, anxiety, fear, grief etc. affect Rasa adversely. These various factors affect the Agni function first which results in generation of Ama which is contaminating and toxic in nature and it exhibits a special capacity to cause occlusion of various spaces and channels in the internal environment. The presence of Ama leads to contamination of Rasa and vitiation of Doshas. This contaminated rasa and vitiated Dosha complex reaches the heart. This complex is incapable of nourishing the heart as a normal Rasa does in combination with Avalambak Kapha. This leads to malnourishment of the heart which manifests as Hridroga. The predominance of Dosha, involvement of particular Dhatu and Rasa lead to variation in symptomatology, severity and prognosis. The principles useful to treat Hridroga are twofold i.e. to maintain Rasa-rakta circulation (Preenan and Jeevan) and to ensure smooth beating of heart (by generation and conduction of cardiac impulse).

**Hridya action of Amla rasa**

In the ancient literature of Ayurveda, many herbs are described as Hridya. It is generally stated that Hridya is the drug which is excellent for the heart.

The other quote explains that Hridya means the drug beneficial for mind as stated in Commentaries by Gangadhar & Yogratnakar on Chapter 4 of Sutrasthan of Charak Samhita. Amla rasa is good for heart.

Amla rasa is also claimed to nourish the heart. This view is further sustained with the description of group of ten plants which are good for heart (Hridya Dasaimani). Under this group, only the plants possessing sourness are quoted. These are beneficial to increase the threshold of stress as well as lessen the hazardous effects of stress in the body. These herbs help to repair the body tissue particularly CVS against the harmful damages caused by stress. Hridya group of drugs are Amla Rasa Pradhana (dominating) and rich source of vitamin C. Vitamin C is proved to be a potent antioxidant in addition to good stress buster. It is very much obvious that Hridya property had a wide spectrum of application in Ayurveda.

Amla Rasa is one among the Shadrasas, which consists of Agni and Prithvi Mahahbhutas, allied with Gunas like Snigdha (unctuous), Laghu (light) etc. It is Hridya (good for heart and mind) and Ushna (hot) in potency. It supports digestion and has a mild warming effect on the body as a whole. Indriya bodhana (stimulates sense organs), Rochana (improves taste), Brumhana (produces stoutness), Tarpana (satisfaction), Preenan (nourishment), Kledana (creating moistness), Anulomana (brings the Vata in the normal direction) etc are other Karmanas performed by Amla Rasa. Its specific action on Doshas can be listed out as Vatahara (alleviates Vata), Pittaslepkara (augments Pitta and Kapha) and Raktakrut (increases Rakt). It alleviates Vata by Ushna and Snigdha Gunas. One of the most important properties of Amla rasa is Anulomana of Vata.

**Dodim** (Punica granatum Linn.) has been illustrated as ‘Hridya’ in Ayurvedic texts.
Dadim possesses Amla, Madhura, Kashaya rasa, Madhura vipaka, Anushna veerya and Snigdha guna. Dadim (Panica granatum L.) breakdowns the pathophysiology (Samprapti) of Hridroga by means of its virtues as described above. The general properties of Amla rasa shows that Amla rasa is Pittaprapokapa (vitiates Pitta) but Acharya Vagbhta has mentioned Dadima as an exception for this property. Amla rasa of Dadima doesn’t vitiate Pitta, but instead of that it helps to alleviate Pitta (due to its Madhur vipak and Anushna veerya). This is the characteristic property of Dadim.

As Amla rasa is composed of Tej (Agni) and Prithvi Mahabhutas, it is Agneya in origin. Due to this it performs the function of Rasadhavani-deepana (stimulates Rasadhavagni) and also helps to bring Samana vayu in its normal state and pathway. This Samana vayu in its healthy state executes the task of Agni-sandukshana and helps to breakdown the pathophysiology of Hridroga by means of Deepan karma (stimulating Agni). Because of proper functioning of Agni, the process of digestion of food occurs correctly resulting in the formation of healthy Aahar-rasa which helps in generating all the seven Dhatus. Thus it encourages the organic metabolism by Agnideepan and Dhatwagnideepan action resulting in improved structural & functional form of Dhatu. As the first tissue emerging out of the nutritive fluid Aahar Rasa i.e. Rasa Dhatu is of improved quality, it promotes and strengthens the health of all tissues of the body. The ‘Rasadhavatu’ has an effect on the health of other successive Dhatus (tissues) of the body since these Dhatus develop sequentially and nourish further Dhatu. Thus Dadim acts at level of Rasa by enriching the nutritional value of the Rasa (circulating plasma) which in turn facilitate the synthesis and nourishment of the best quality of successive Dhatu. The next Dhatu is Rakta. Dadim is a best haematinic used in anaemia, grossly the colour and shape of its seed is as that of RBCs. Rakta and Amla Rasa comes under the similar category i.e., both have the domination of Agni Mahabhuta and in this manner Amla Rasa can be the absolute solution in Rakta Kshaya. Amla Preeti (desire for sour taste) is one of the prominent features of Rakta Kshaya commenting on this explains the cause for this longing of sour taste. Rakta kshaya sequentially leads to the Vridhhi of Vata and to pacify this Vata the desire for Amla Rasa is created by the body itself; in that way the balance of the system can be restored.

In Hridroga the predisposing factors in generation of Aam, contamination of Rasa and vitiation in Doshas creating obstruction in Rasavaha srotasa leading to provocation of Vata. This also results in diminished supply of nourishment and Pranvayu to Hriday. By means of Vatanulomana property of Amla rasa, Dadim brings Vata in normal direction. There is a requirement of clear Srotasas for tissue perfusion. Dadim helps in the opening of channels by its Agnaya property of Amla rasa and Angideepan (stimulating Agni) and Aampachan (digesting Aam) Karma (action); and activates microcirculation. The clear channels facilitate Dhatu Poshana (Tissue Nutrition) by nourishing Dhatu which finally results in production of excellence of tissues and boosts Ojas (immunity). After proper digestion and assimilation of food or drug, the respective Dhatu (tissue) get enriched with the nutrition (essence) and carry out their respective functions in optimum power. Therefore Dadim performs the functions of Hridya (nourishing heart), providing strength (Balapradam), nourishing brain (Medhyam) and having aphrodisiac effect (Shukralam). Its Madhur vipaka supports the Dhatuposhan (nourishing tissues) Karma (action).

Amla rasa is beneficial for Mana (psychye) and in Ayurveda it has mentioned that Hriday is one of the site for Mana (psychye), by means of this property Amla rasa Dadim performs the Tarpana (nourishing) karma (action) of Hriday, satiates mind (Manasadasana) and improves mental strength.

Dadim is mainly useful to get rid of Symptoms of Pittaj Hridroga like Ooshma (feeling of warmth), Daha (burning sensation), Chosha (sucking sensation in cardiac region), Hriday Klam (fatigue of heart), Dhoomayan (feeling of hot air or fumes emerging from external orifice especially mouth), Trisna (thirst), Moorcha (fainting), Sweda (sweating in cardiac region, Mukshshosh (dryness of mouth) etc. Modern Aspect of Hridya action

Antioxidant property

Treatment of cardiovascular diseases (CVD) in elderly is not easy and need prolonged treatment and there is a need for the safer drugs to use them for longer period. Ayurveda offers satisfactory management strategies for CVD through preventive and curative approaches. Most of the degenerative diseases are caused by free radicals. Antioxidants are the agents responsible for scavenging free radicals. Antioxidants are phytochemicals, vitamins and other nutrients that protect our cells from damage caused by free radicals. Oxidative stress is responsible for many of today’s diseases that results from an imbalance between formation and neutralization of pro oxidants. Oxidative stress is initiated by free radicals, which seek stability through electron pairing with biological macromolecules such as proteins, lipids and DNA in healthy human cells and cause protein and DNA damage along with lipid peroxidation. These changes contribute to the pathogenesis of many diseases.
cardiovascular diseases. Plants are the important source for free radical scavenging molecules. Various synthetic antioxidants are on the use, but they are suspected to be carcinogenic. [62] Natural antioxidants therefore, have gained importance. Most of the fruits, vegetables, culinary herbs and medicinal herbs contain high levels of antioxidants. [63] Fruit possesses a spectrum of phytochemicals that could be the accountable factor for its varied biological activities, including the antioxidant potential.

*Punica granatum* fruit rind extracts showed good antioxidant effect, which could be due to the available phytoconstituents. *Punica granatum* rind is more potent scavenger of superoxide radical. Superoxide anions are highly toxic to cellular components. [37] *Punica granatum* is the rich source of flavonoids, these flavonoids are effective antioxidants mainly because they scavenge superoxide anions [64] According to a research study stated in American journal of clinical nutrition, *Punica granatum* being rich in antioxidants can prevent the oxidation of LDL ‘bad’ cholesterol. [65] Studies have confirmed the suspicion that the flavonoids in pomegranate comprise a potent antioxidant with additional enzyme inhibition properties which make preparations of the juice and oil potential dietary supplements for promoting longevity and preventing heart disease. [66] Pomegranate extract have been shown to scavenge free radicals and decrease macrophage oxidative stress and lipid peroxidation in animals [67] and increase plasma antioxidant capacity in elderly humans. Pomegranate peel juice exhibited significantly decreased plasma carbonyl content (a bio-mark for oxidant/ antioxidants barrier impairment in various inflammatory diseases) [68] A clinical trial demonstrated pomegranate juice inhibits serum angiotensin converting enzymes (ACE) and reduces systolic blood pressure in hypertensive patients. [69] Studies have shown that pomegranate contains more antioxidants than green tea, cranberries and even red wine. Pomegranate in our daily diet can improve blood flow, help to prevent heart diseases such as heart attacks, stroke or clogged arteries and it also promote healthy blood pressure levels and low cholesterol. [65] It contains vitamin C and flavonoids like Punicalgin which act as antioxidant [70,71] Antioxidants are body guards for the heart vessels which prevent them from clogging. [72]

**Anti-inflammatory property:** Atherosclerosis, a major degenerative disease of arteries involves a series of inflammatory and oxidative modifications within the arterial wall [73] Emerging research shows that obesity, hypertension, dyslipidemia, diets rich in saturated fats and reduced physical activity are the risk factor for atherosclerosis, which is also characterized by inflammation and oxidant burden. [74-82] Oxidative stress, an imbalance between free radical formation and antioxidant status, is the major contributor to CVD, and inflammation is a manifestation of oxidative stress. Oxidative stress induces inflammation by acting on the pathways that generate inflammatory mediators like adhesion molecules and pro-inflammatory cytokines. [83,84]

Recent human studies have shown significant positive associations between oxidative stress and inflammation and indicators of vascular damage, like impaired endothelial function [85] and arterial function. [86-88] Oxidative stress and inflammation lead to endothelial dysfunction by reducing nitric oxide (NO) bioavailability due to the formation of peroxy nitrate, which is cytotoxic. [85,89,90] Thus, both oxidative stress and inflammation initiate, participate in, and enhance the process of atherosclerosis, and are the principle targets of therapeutic interventions with dietary phytochemicals, in preserving the endothelium or reversing atherosclerosis. [91-98]

Pomegranate fruit has been rated to contain the highest antioxidant capacity in its juice, when compared to other commonly consumed polyphenol rich beverages in the United States. [99,100] The principle antioxidants polyphenol in pomegranate juice include the ellagitannins and anthocyanins. [101] Ellagitannins account for 92% of the antioxidant activity of pomegranate juice and are concentrated in the peel, membrane and piths of the fruit. [102] Nitric oxide plays an important role as an antioxidant and anti-inflammatory agent in the endothelial cells and thereby attenuates the progression of atherosclerosis. [103] Pomegranate juice has also been shown to prevent oxidative destruction of nitric oxide and enhance its antioxidant and anti-inflammatory functions. [104] In short the principle mechanism of action of pomegranate juice may include- increased serum antioxidant capacity, decreased plasma lipids and lipid peroxidation, decreased oxidized-LDL uptake by macrophages, decreased intima media thickness, decreased atherosclerotic lesion areas, enhanced biological actions of nitric oxide, decreased inflammation, decreased angiotensin converting enzyme activity and decreased systolic blood pressure, thereby causing an overall favourable effect on the progression of atherosclerosis and the subsequent potential development of coronary heart disease.

**Anti-stress**

Stress may be classified as physical, emotional and social etc. where long time stressful condition lead to various complications like hypertension, atherosclerosis and other similar disorders which can be compiled under life style.
disorders. High levels of cortisol can also raise heart rate and increase blood pressure and blood lipid (cholesterol and triglyceride) levels. Increases risk factors to both heart attacks and stroke. Vitamin C is found to increase HDL and reduce LDL to considerable levels. Cortisol is a hormone secreted by the adrenal glands in response to stress. Earlier studies demonstrated that vitamin C abolished secretion of cortisol in animals that had been subjected to repeated stress. The vitamin helps to decrease both the physical and psychological effects of stress on people. Treatment with high-dose sustained-release ascorbic acid palliates blood pressure, cortisol, and subjective response to acute psychological stress. Vitamin C has potent antioxidant properties i.e. it is able to lessen the damage caused by oxidizing chemicals, such as free radicals. These oxidizing chemicals, sometimes called reactive oxygen species, or ROS, are the normal by-products of the cellular reactions which take place inside the body. Vitamin C decreases this damage by directly binding to oxidizing chemicals and converting them to less harmful molecules. Reducing oxidative damage can have several benefits for the body, including reducing stress and heart disease.

**Anti-hypertensive action**

Angiotensin II is a key regulator of blood pressure (BP). Several actions leading to an increase in BP are elicited by Ang II via the angiotensin AT1 receptor (AT1R), including vasoconstriction, renal sodium reabsorption (directly or through the release of aldosterone), vasopressin release, and facilitation of sympathetic nerve activity. The pressor responses to Adr, NA, PE, Ang II and 5- HT were significantly (p<0.05) increased in Ang II treated hypertensive rats as compared to control rats. The pressor responses to Adr, NA, PE, Ang II and 5- HT were significantly (p<0.05) reduced in case of Ang II treated rats that received PJ extract (100 and 300 mg/kg/day, p.o.) for 4 weeks as compared to only Ang II treated rats. Also reduction in ACE activity may contribute to lowering blood pressure. It is known that reactive oxygen species (ROS) contribute to the pathogenesis of numerous cardiovascular diseases including hypertension, atherosclerosis, cardiac hypertrophy, heart failure, NAD(P)H oxidase being the predominant source of ROS. Activation of this enzyme leads to a variety of intracellular signaling events. Ang II, via activation of the AT1 receptor, stimulates NAD(P)H oxidases activity in vascular smooth muscle cells increasing superoxide anion formation and nitric oxide inactivation, effects associated with the pathogenesis of hypertension. SOD, CAT and GSH are the three primary antioxidant enzymes among the endogenous systems for removal of reactive oxygen species. Pre-treatment with pomegranate juice (PJ) restored the antioxidant enzyme level which in turn indicates the protective effect of PJ against oxidative stress. Increased serum ACE activity is associated with enhanced susceptibility to lipid peroxidation and hence the inhibitory effect of pomegranate juice on serum ACE activity can further contribute to an antioxidant environment. In-vitro study using chronic administration of PJ (100 and 300 mg/kg/day, p.o.) for 4 weeks in Ang II treated rats, proved the inhibitory effect of PJ on Ang II receptors. Thus, pomegranate juice significantly reduced mean arterial blood pressure, vascular reactivity changes to various drugs, and prevented oxidative damage in angiotensin model of hypertension. The antioxidant activity, serum ACE inhibition activity and blockade of angiotensin receptor may be partly responsible for its antihypertensive action.

**Thrombolytic potential of Punica Granatum Linn.**

Platelet count was found to increase when a thrombus was formed and subsequently increased when treated with both the Pomegranate fruit extract and standard streptokinase. The increase in the level of platelets when treated with the extracts were lower when compared with that of the drug, streptokinase. This marginal increase could be credited for the reocclusion, a major drawback in thrombolytic therapies. Studies reported that streptokinase activates platelets, thereby limiting its efficiency as a thrombolytic agent. In contrast, the level of platelets did not increase significantly when treated with fruit extracts, proving its safety and thrombolytic efficiency in vivo. During reperfusion, oxidative stress reaches higher peaks and has a more sustained duration than other pathogenic mechanisms of ischemic cell death, the risks and hurdles associated with the currently used thrombolytic agents such as tPA overshadows the supposed benefits as thrombolytic agent, demanding an urge for sources with both antioxidant and thrombolytic property. In- vivo study using Punica granatum in experimental rats reported that the fruit extract conferred good antioxidant protection against the oxidative stress that was found to be peaked during the thrombus formation and lysis. The fruit Punica granatum has an augmentive effect on thrombolysis by rendering good oxidative protection with its numerous antioxidants.

**Anxiolytic, Anti-depressant and CNS stimulant activity**

Different studies suggest that natural products, such as polyphenolic and alkaloids compounds that isolated from plants potentially delayed the neurodegeneration and also improve......
memory and cognitive function. Plants and their constituents play their protective roles via increased SOD and catalase levels, restoration of GSH, decreased MDA levels and also protects of neurons against ROS as antioxidant activities. Anti-inflammatory properties of plants and their constituents as well as due to their interactions with pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and mediated by over expression of BCl-2 which is inductive nitric oxide synthase (iNOS). Some protective effects of these natural compounds may be due to reduction of Ca2+., Na+ and enhancement of K+ level or ‘anti-glutamatergic’ effect. Furthermore, neuroprotective action of plants and their components occur via inhibition of the acetylcholinesterase (AChE) activity and decreased MDA levels in the neural system via modulating GABAergic and glutamatergic neurons, and also increasing amount of amino acids and serotonin (5-HT) in the neurotransmitters systems or as ligand for some receptors like 5-HT2A, α2, β and D2.[117] Pro-inflammatory cytokines including IL-1β, TNF-α and IL-6 have been reported to be significantly elevated in the cerebro-spinal fluid or plasma of Alzheimer's disease patients.[118-119] The mechanism of the reduction of IL-1β, TNF-α and IL-6 by pomegranates is uncertain, since its multiple active components such as anthocyanins, ascorbic acid, ellagic acid, gallic acid, fumaric acid, caffeic acid, catechin, EGCG, quercetin, rutin, tannins, alkaloids and flavonoids, have multifunctional action, thus making it pharmacologically complex. Our current results, in agreement with previous reports, suggest that pomegranates in diet indeed decreased the cytokine levels.[120-125] Some studies suggest that the anxiolytic-like effect of Pomegranate is dependent on interactions with both GABAergic (related to Mg) and serotonergic (5-HT1A) systems.[126]

When oxidative stress causes anxiety, antioxidants may have therapeutic potential in the meantime. The production of reactive oxygen species (ROS) dominates the defence system of the brain, the lipid-rich brain structure can be susceptible to lipid peroxidation that creates a chain reaction of free radicals, which can reduce membrane fluidity and damage membrane proteins leading to the loss of receptors, enzymes, and ion channels and eliminating the membrane integration that ultimately causes cell death. In addition to oxidative damage to proteins, lipids, and nerve cell membranes (neurons), oxidation can also occur in other sensitive sectors and transmitter of biological nucleic acids. As a result, oxidative stress can change neural transmission, neuronal function, and overall brain activity.[127] Polyphenols have shown their ability to relieve anxiety-related behaviour in rodents.[128] Some polyphenols have medicinal conditions that show a minor conflicting activity, which may show effects such as anxiety reduction without side-effects.[129] Pomegranate juice is rich in phenolic compounds, which is higher than many other fruit juices. Phenolic compounds form an important group of plant compounds as secondary metabolites that are produced in response to the environmental stress. Due to having hydroxyl groups, these compounds could neutralize free radicals and act as electron or hydrogen donors.[130] Oral administration of hydro-alcoholic extract of pomegranate seeds, once a day for 14 days, significantly improved the disorder caused by cerebral ischemia on stress and anxiety behaviours. Since PGSE contains phenolic compounds including ellagic acid in free and bond forms as well as other flavonoids, subsequent disorders of ischemia disorders can be improved using the method of sweeping oxidants and free radicals produced by the brain's ischemia.[131]

Several studies on behaviours of rats showed significant decrease in the duration of immobility in fast swimming test (FST), increase in the distance travelled, number of central entries in open field test (OFT) and number of entries in open arm in elevated plus maze test (EPM) by Punica granatum in dose dependant manner. The antidepressant action might be due to the presence of flavonoid.[132] Major flavonoid found in Punica granatum is ellagic acid, since ellagic acid is reported to produce anxiolytic action.[133] These results of Punica granatum may be due to presence of testosterone in it.[134] Since there is evidence that testosterone could attenuate immobility in healthy rats and act as antidepressant by increasing central dopaminergic and 5-hydroxytrptaminergic metabolism.[135] Another study suggests that anti-depressant like effect might be due to the estrogen which is an important component of Punica granatum.[136] Hence role of estrogen or estrogen like compound as anti-depressant have been well documented.[137] From above discussion it may be concluded that Punica granatum is most effective for its CNS stimulant, anxiolytic and antidepressant effects.

CONCLUSION

The mortality and morbidity rates due to cardiovascular diseases become a worldwide issue. Researches on organ targeting and low toxic effects drugs are the need of time. Dadima is the cheapest and easily available dietary fruits possess an antioxidant capacity more than green tea and red wine, due to this Dadima plays a major role in the treatment of heart diseases as oxidative stress is the main cause for CVD. Also by means of Amla rasa Dadima
performs the function of Agneesandhukshana and Dhatwagnideepana it helps to bring the vitiated Vayu in its healthy states and pacifies Ama and breakdown the pathophysiology of Hridroga. In Ayurvedic classics Hriday is mentioned as one of the site for Mana (psyche) and Amla rasa is beneficial for mind, so that Amla rasatmaka Dadima perform the function of Hriday tarpana, satiates mind and improves mental strength. Pomegranate juice is rich in Vitamin C, flavonoids like Punicalgin, tannins, possesses anti-atherosclerotic action, and has an anti-aging effects and potent anti-oxidant properties. Pomegranate juice has also been shown to prevent oxidative destruction of nitric oxide and enhance its antioxidant and anti-inflammatory functions and prevent the oxidation of LDL ‘bad’ cholesterol. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Pomegranate juice has shown considerable anti-atherosclerotic, anti-hypertensive, antioxidant, and anti-inflammatory, anti-stress, anxiolytic and CNS depressant activity in human subjects and mouse models.

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