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Review Article

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 cardiotonic 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*, Cardiotonic, 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 poly-phenols 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. cardiotonic action of the fruit Dadim which is commonly known as Pomegranate (*Punica granatum* Linn.) and used as an edible fruit.

Punica granatum Linn. belonging to the family Lytheraceae, although previously placed its own family Punicaceae recent Phylogenetic studies have shown that Punica belongs in the family Litheraceae.[12] Pomegranate is recognized as grenade by the French, granada by the Spanish, and literally translates to seeded ('granatus') apple ('pomum').[13] It is commonly known as Pomegranate. Aacharya charak has placed *Dadim* in the *Hridya mahakashay* [14] and Aacharya Vagbhata has placed it in *Amla gana* in Sutrasthana chapter 10/25, 26. [15] *Amla rasa* or sour taste is said to be good for heart in Ayurved.[16] *Hridya* means Cardiac tonic, the drugs which are helpful in maintaining the cardiac and mental health are called as *Hridya*.[17] Also the medicines or herb that give strength to *Hriday* are called *Hridya dravyas*. Cardiotonic drugs are substances that increase the contracting mechanism within the heart, thereby causing more blood to be pumped throughout the circulatory system. These drugs usually affect intracellular calcium levels in the heart muscle to achieve the desired increase in muscle action.[18] According to Ayurved, *Hriday* or heart is not just an organ but is a vital organ (*Marma*), the physical, physiological and emotional damage can leads to loss of life. If *Hriday* does not function properly, the other organs and tissues are also affected and damaged due to lack or inadequate supply of nutrition and oxygen. [19]

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.[20] 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 *Nighantus*, 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**.-Dadam; **Can**-Dalimbay; **Tel**.- Dadima, Dalimba; **Tam**.-Madalai, Madalam; **Mal.**-Madalam, **Fr.**- Grenadier cultive; **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. Heterostylous 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, reproductive 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) *Madhuramla* and 3) *Amla*. [36, 38, 39, 40]

Ayurvedic aspect of *Hridaya*

The word *Hriday* is composed of three syllables, i.e. hri+da+ya=*hriday*. 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] *Sushruta* 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 *Pranvaha 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 *Vyanavayu*.[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*). *Udan* is related with the contraction of same part (*Visarga*); the resultant *Vyan* 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 *Hridrog*, mental signs and symptoms are observed. *Pachak pitta* is situated in *Pachyaman-ashaya* (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 *Hridrog* (cardiac disorders) nearly 2500 years ago. The etiological factors of *Hriday roga* are - *Ativyayama* (physical exertion), *Atisara (*purgation*), Chhardi* (vomiting)*, Ama* and *Aghata* (injury). The other factors which are responsible for *Hridroga* are *Murccha* (fainting)*, Jwara* (fever), *Kasa* (cough)*, Shwasa (*dyspnoea), *Chinta* (anxiety), *Bhaya* (fear)*, Trishna* (thirst), *Atiutsaha* (excitement), *Bhrama* (mental confusion), and *Aruchi* (anorexia).[46] Charak discusses about the role of improper exercise, stress, physical and mental trauma, excessive use of *Tikshna Ahara* (pungent and spicy foods) and *Amadosha* (Undigested substances which act as toxin) as a causative factors of *Hridrog*.[47] *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 *Aam* 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 *Hridrog*. The predominance of *Dosha*, involvement of particular *Dhatu* and *Rasa* lead to variation in sympomatology, severity and prognosis. The principles useful to treat *Hridrog* 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 [11] 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.[8] *Amla* rasa is also claimed to nourish the *heart*.[9,10] 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* [52], which consists of *Agni* and *Prithvi Mahabhutas* [53], allied with *Gunas* like *Snigdha* (unctuous)*, Laghu* (light) etc. [54] 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)*, Preenana* (nourishment)*, Kledana* (creating moistness)*, Anulomana* (brings the *Vata* in the normal direction) etc are other *Karmas* performed by *Amla Rasa*. Its specific action on *Doshas* can be listed out as *Vatahara* (alleviates *Vata*)*, Pitta-sleshmakara* (augments *Pitta* and *Kapha*) and *Raktakrut* [55] (increases *Rakta*). It alleviates *Vata* by *Ushna and Snigdha Gunas*. One of the most important properties of *Amla rasa* is *Anulomana* of *Vata*.

Dadim (*Punica granatum* Linn.) has been illustrated as '*Hridya'* in *Ayurvedic* texts [14,52,56-58]

Dadim possesses *Amla, Madhura, Kashaya rasa*, *Madhura vipaka*, *Anushna veerya* and *Snigdha guna*[52] *Dadim* (*Punica 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 *Pittaprakopaka* (vitiates *Pitta*)[59] but Aacharya 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*) [60] This is the characteristic property of *Dadim*.

As *Amla rasa* is composed of *Tej* (Agni) and *Prithvi Mahabhutas*, it is *Agneya* in origin [59] Due to this it performs the function of *Rasadhatvagni-deepana* (stimulates *Rasadhatvagni*) 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-sandhukshana* 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 *Dhatus.* 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 '*Rasadhatu'* has an effect on the health of other successive *Dhatus* (tissues) of the body since these *Dhatus* develop sequentially and nourish further *Dhatus*. 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 *Dhatus*. 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*[61] *Dalhana* commenting on this explains the cause for this longing of sour taste. *Rakta kshaya* sequentially leads to the *Vriddhi* 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 [61]

In *Hridroga* the predisposing factors causes 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 *Agneya* 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 *Dhatus* 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* (pschye) and in Ayurveda it has mentioned that *Hriday* is one of the site for *Mana* (pschye), by means of this property *Amla rasa Dadim* performs the *Tarpana* (nourishing) karma (action) of *Hriday*, satiates mind (*Mana prasadana*) and improves mental strength.

Dadim is mainly useful to get rid of Symptoms of *Pittaj Hridrog* 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), *Trishna* (thirst), *Moorcha* (fainting), *Sweda* (sweating in cardiac region, *Mukhshosh* (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

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 oxidization 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-marker 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.[105] 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[106] 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.[107] 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.[108] 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.[109] 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.[110, 111] SOD, CAT and GSH are the three primary antioxidant enzymes among the endogenous systems for removal of reactive oxygen species.[112,113] 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[114] 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 [108] 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. [115] 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. [116]

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 inducible 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 acetyl-cholinesterase (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 flavanoids, 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 anxyolitic-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. *Dadim* 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 *Hridrog*. 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 oxidization 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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