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# EMERGENCE OF EPIGENETICS IN AYURVEDIC PREVENTIVE CARDIOLOGY: THE LONG ROAD AHEAD

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## ABSTRACT

Industrialization of economy with a resultant shift from physically demanding to sedentary jobs along with technology driven culture may explain the steady increase of cardiovascular diseases during the last few decades. Since past few decades, public preventive strategies had always relied on managing environmental factors that contribute to cardiac disorders. Recently, understanding the contributory role of genetics in cardiovascular development has become more relevant as researchers have began to link genetics with disease and its response to therapy. Epigenetics deals with virtually everything that happens to the expressed genes in the phenotype during phases of lifespan like diet, lifestyle, stress and other environmental factors that impact gene expression. This review is to convey the relevance of understanding *Charyas* (practices) mentioned in ayurvedic classics in the field of preventive cardiology using the science of epigenetics as well as to express how genes can predispose individuals to cardiac disorders and applying this knowledge to more comprehensive preventive strategies in future.

**KEYWORDS:** Epigenetics; Ayurveda; Preventive Cardiology; Diet and Lifestyle Modification.

## INTRODUCTION

The 5 major Cardiovascular diseases which include Ischemic heart disease, Cerebrovascular disease, Hypertension, Inflammatory heart disease & Rheumatic heart disease are linked to over 17.9 million deaths annually representing 32% of the global deaths, says 2019 WHO reports.[1] The burden of the diseases like Coronary artery disease is gravely increasing in the Indian population and is almost endemic in the Indian society. The excess burden of

premature coronary artery disease is due to the genetic susceptibility mediated through a metabolic syndrome which consisted of hypertension.With growing evidence that cardiovascular diseases have a sizable hereditary component; more emphasis is being given to the genetic predisposition which leads to cardiovascular disease development.

## AIM

1. To study the role of epigenetics in the pathogenesis and management of cardiovascular diseases.
2. To study the role of *Pathya Ahara* and *Vihara* (conducive diet and regimen) in the management of epigenetic modification in the field of preventive cardiology.

## MATERIALS AND METHODS

Classical texts of Ayurveda viz. *Charaka Samhita, Sushrutha Samhita, Ashtanga hridaya* were consulted as research references for the concept of *Prakrithi* and *Dravyoushadhis*. Literature available regarding the concept of epigenetics and its role in cardiovascular development were also collected. These references from both streams of knowledge were compared and analyzed.

## DISCUSSION

### Role of Genetics in CVD Development

A review article by the HTN & Rehabilitation Unit at university of Leuven in Belgium discusses the key polymorphisms are being looked as the major player in the onset of cardiovascular disease.[2] The study states that the M235T polymorphism of angiotensinogen gene induces hypertension.[2] The review also states that A1166C polymorphism of angiotensinogen II type I receptor gene induces hypertension which later on interacts with D/1 polymorphism of angiotensin converting enzyme that results in Coronary heart disease.[2]

**M235T polymorphism of angiotensinogen gene ⟶ HTN**

**A1166C polymorphism of angiotensin II type I receptor gene ⟶ HTN + D/1 polymorphism of angiotensin converting enzyme ⟶ Coronary heart disease**

Epigenomics is the concept that will address the gaps in the current knowledge of interaction between nature and nurture in cardiovascular disease development. The term epigenetics describes the concept itself, as ‘epi’ means above in greek, but it was Conrad Waddington who in 1940 provided 1st operational definition of epigenetics as causal interaction between

genes and their products which the phenotype into being.[3] Some authors have proposed a definition of epigenetics as the molecular factors and processes around DNA that are mitotically stable and regulate genome activity independently of DNA sequence. Epigenetics refers to the external modification of DNA that turns genes ON & OFF, affecting gene expression & this phenomenon occurs without changes in the basic structure of DNA & can have transgeneration effects & can be transmitted to the progeny.

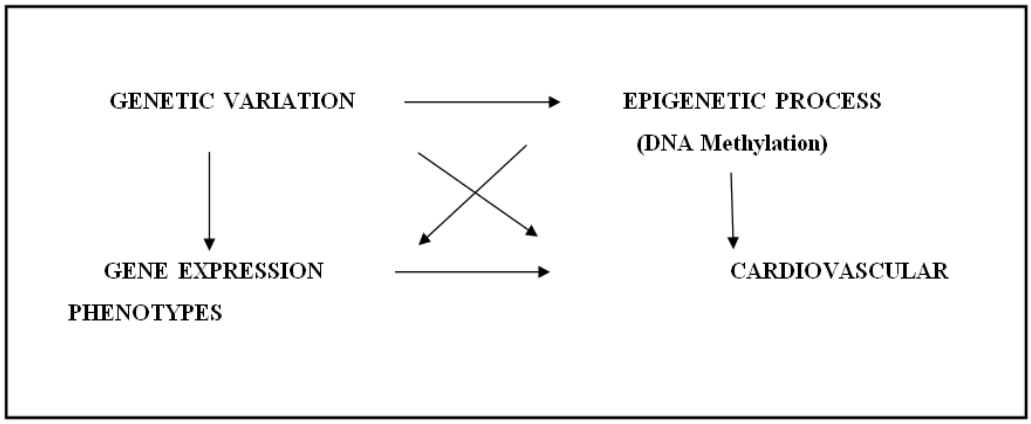
In brief, DNA methylation, histone modification, chromatin remodeling & micro RNA are involved in modifying gene expression that collectively enables the cells to respond to the environmental changes. Individual variation in the epigenetic modification of genes can explain a larger part of phenotypic variation observed in humans than differences in genotype alone. The factors that cause epigenetic changes are:

- Lifestyle and behavior
- Diet and digestion
- Stress
- Environmental factors[4]

Ayurveda addresses these factors that affect the *Deha* which corresponds to phenotype & indirectly the *Prakrithi* which corresponds to genotype. The ayurvedic understanding that *Deha Prakrithi* has a genetic basis has been explained by current scientific research. Phosphoglucomutase 1 [PGM1] gene has been correlated to *Pitta Prakrithi*. Research on human leukocyte antigen (HLA) gene polymorphism showed a reasonable correlation between HLA type and *Prakrithi* type.[5]

- Messenger RNA corresponds with ⟶ Vata [transmission of information]
- TRNA corresponds with ⟶ Pitta [transformation]
- Protein corresponds with ⟶ Kapha [structure]

Transcriptional profiles of pooled RNA from *Vata, Pitta* and *Kapha* revealed difference in core biological processes between *Prakrithi* that overlapped with biochemical pathways and biochemical profiles, signifying the existence of genetic variations and their cellular manifestation as mentioned in Ayurveda.[6] *Swasthavritta* plays a pioneer role when it comes to the field of preventive cardiology as it is a prevention oriented system that provides detailed recommendations that are personalized for individual based on their *Prakrutha* & *Vaikruthavastha*.




**An integrated perspective on genomic variation, gene expression & epigenetic modification in cardiovascular phenotypes.**[6]

Several studies have focused on the relationship between epigenetics and CVD risk factors, including homocysteine, the biomarker most directly implicated in epigenetic mechanisms relating to the CVD risk.[7] Homocysteine induced alteration in DNA methylation of vascular smooth muscle cells are involved in atherogenesis.[7]

**Role of diet and lifestyle modification in epigenetic dysregulation**

Polyphenols present in plants have been shown to modify activity of DNA methyltransferases, histone acetylases & histone deacetylases that induces reversibility of epigenetic dysregulation.[8] Consumption of *Amalaki*, which is considered to be one among the *Nithya sevaneeya Ahara dravyas* contains 10 phenolic compounds including gallic acid, five gallic acid derivatives, ellagic acid and 3 ellagic acid derivatives in it.

Studies have supported the role of oxidative stress in the development and pathogenesis of cardiovascular diseases, where the principal contributor to oxidative stress in the body is the generation of excess reactive oxygen species. In the case of cardiovascular disorders, oxidative stress and reactive oxygen species (ROS) have been implicated in endothelial damage, progression to atherosclerosis and injury in sustained myocardial infarction. The polyphenol, Curcumin is the active component of *Haridra* which is one among the *Ahara upayogi dravya.* Curcumin possesses antioxidant properties that protect against the oxidative stress shown upon the proteins and lipids. The dietary polyphenol in turmeric demonstrates preventive actions over cardiovascular disorders as well as act as attenuating factors involved in the pathophysiology of cardiovascular disease.

A study on patients on coronary artery disease showed that a lifestyle modification program that included stress management, exercise & vegetarian diet resulted in sustained modulation of gene expression that ameliorated cardiovascular risk.[9] Thus it clearly shows the evidence of the followance of *Ahara- Vihara* (diet and regimen) as well as its role in reversal of epigenetic dysregulation. *Vyayama* (exercise) or involvement in any kind of physical activity has been associated with higher methylation in peripheral blood lymphocytes of long interspersed nucleotide element -1 (LINE-1) elements, which are considered to be a class of repeated sequences that are observed to be highly repeated in the human genome. The presence of low methylation in these elements is associated with various inflammatory responses and chromosomal instability.

Acharya Charaka in *Shareera Sthana* have quoted that nourishment of *Garbha* (fetus) are mainly used for 3 processes mainly, formation of *rasa*, for maternal nourishment and foetal nourishment as well as formation of *sthanya.* It is further stated in classics that due to abnormalities of *bija, atma – karma, ashaya, kala* and *ahara* along with *Vihara* of mother, the vitiated *dosas* produce abnormalities of fetus, affecting its appearance, complexion and *indriyas.* The contemporary literature also agrees to it by quoting nutrition abnormalities, environmental toxicants can promote epigenetic alteration in a gestating mother thus affecting the fetus & influences 3$^{rd}$ generation's phenotype.

In a study examining epigenetic effects of intrauterine protein restriction, epigenetic changes were localized to specific genes that may contribute to CVD risk.[10] In this study, prenatal protein restriction was demonstrated to alter DNA methylation patterns in 204 genes in fetal liver, including liver X receptor α [LXRA, also known as NR1H3], a nuclear receptor that targets downstream genetic regulators of lipid and fatty acid metabolism. Hypermethylation of LXRA promoter was associated with reduced expression of LXR-α together with reduced expression of genes encoding the established lipid regulators ABCG5, ABCG8 and ABCA1.

*Masanumasika Garbhini Paricharya* and usage of *Garbhasthapaka dravyas* can play a key role in preventing the epigenetic modifications that can occur in the foetus. *Acharya Charaka* in *Shareera Sthana* advices of giving up non congenial diet and mode of life and protect herself by practicing good conduct and switching onto congenial mode of dietetics and activities. *Acharya Vagbhata* had adviced the use of internal and external usage of *Jivaniya* group of drugs. *Acharya Kashyapa* had explained the use of *ushna jala, dugda* and *mamsa* for *garbhini paricharya.* Milk provides nourishment and stability to the foetus due to its

*svadu – sheeta- mrudu- snigda gunas* as well as its *jivaniya* and *Rasayana properties. Mamsa* helps in providing fetal nourishment, suppresses *vata* in pregnant woman.

In addition to the epigenetic changes in newborn as a result of maternal smoking, studies have demonstrated a direct effect of smoking on gene specific methylation in adults, where researchers hypothesized that serotonin released from activated platelets could be involved in vascular modifications induced by smoking.[7]

Avoidance of *Garbhopaghatakara Bhavas* is equally important when it comes to the prevention of congenital anomalies in the fetus and other aspects of preventive cardiology. *Acharya Charaka* has enlisted the list of contraindications during the *Garbha kala* as – coitus, exercise, emaciation, trauma, mode of conveyance causing excessive jerks, night awakening, day sleeping, suppression of natural urges, indigestion, prolonged exposure to heat, anger, grief, fear, fasting, squatting etc.

**HAT Inhibition by Dietary Compounds**

The therapeutic goal of avoiding harmful effects while reducing risk, combined with research supporting chemo preventive role for some of the plant based food have stimulated the investigation of epigenetics properties of selected dietary compounds.

Curcumin (diferuloylmethane), the abundant Polyphenols in turmeric inhibits HAT activity. In an animal model of heart failure, consumption of Curcumin at a dose of 50mg/kg/day inhibited p300 HAT activity preventing the ventricular hypertrophy and preserved systolic function.[11] Consumption of *Haridra* one among the *Ahara upayogi dravya*, can be inculcated into our daily diet regimen which can be considered as a part of primordial prevention.

*Vrikshamla* (Garcinia Indica) which is presented as a potent drug for the treatment of metabolic syndrome and obesity is observed to show some significant changes in the epigenetic variations. Garcinol – a polyisoprenylated benzophenone derived from the Garcinia Indica, strongly inhibits p300 HAT and reduces global gene expression.[12] it was used to investigate the role of histone modification in the regulation of EGR – 1 gene, which encodes the zinc finger transcription factor early growth response 1 protein. EGR – 1 has been implicated in cardiovascular processes, including thrombus formation, endothelial cell migration and proliferation.

**Ayurnutrigenomics – An Emerging Concept**

Nutrigenomics assures its relevance in the public health and nutritional interference by human genomic variation. It is a systematic integration of nutritional practices according to Ayurveda in relation to the prakruthi of an individual which amalgamates the knowledge from genomics, proteomics and metabolomics which is projected to provide evidence based science for the advancement of personalized nutrigenomic dietetics. Development of ayurceuticals to augment the healing processes is a crucial area of nutritional research to cure fully developed diseases. Genetic (*prakrithi*) and environmental factors (*mahabhuta vikara*) together with *Ahara* and *Dinacharya* particularly over nutrition and sedentary behavior are interrelated with promoting progression and pathogenesis of these polygenic diet related disease. This Ayurveda inspired concept of personalized nutrition is a novel concept in the realm of nutrigenomic research that develops personalized functional foods and nutriceuticals which is suitable to one's own genetic makeup.

## CONCLUSION

This correlation and understanding of the process of healing and health maintenance will improvise the understanding and communication between Ayurveda and the contemporary system and lead to better integration of both sciences in the management of optimal health. A Shift from generalized approach of dietetics to a nutriepigenetic paradigm where personalized nutritional advice according to genetic variability is necessary. Central government can put efforts in encouraging scientific, political & public awareness by acknowledging role of genetics in public health policy. Establishment of further research facilities, promoting consciousness of genetic predisposition and making screening facilities accessible through government subsidies should be promoted.

Only an informed individual, fully aware of his dispositions & risk can make lifestyle choices suitable for his health. Healthy population is the greatest contribution to the nation, which lies solely in our hands.

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