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REVIEW ON PRAKRITI (HUMAN CONSTITUTION) IN THE VIEW POINT OF PHARMACOGENOMICS

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ABSTRACT

Pharmacogenomics is the science that analyses individual responses to therapeutic agents and their genetic inheritance. It is a re-definition of diseases on the molecular level so that diagnosis & therapeutics can be targeted to specific patient populations sub typed on the basis of genetic make-up & thereby offer the right treatment for right patient population. According to *Ayurveda*, every individual possesses a unique constitution referred as *prakrti* and this *prakrti* forms the basis of health and disease. *Prakrti* based medicine can play a vital role in this changing scenario of global health wisdom as *Ayurveda* offers its modalities by way of *ahara* (diet), *vihara* (lifestyle), and *aushadhi* (medication), which are the three pillars of *prakrti*-based medicine making. Information extracted from various Ayurvedic classics i.e. *Charaka, Sushruta, Ashtanga Hridaya* and *Ashtanga Sangraha,* other treatise and relevant articles are revised for correlation. The benefits of knowing your *Prakṛti*, its role in health care and wellness, factors influencing the formation of *Prakṛti* and its relationship with epigenetic factors as understood in Traditional Indian medicine (Ayurveda) are explained. *Prakrti* of a person is unique as a genome sequence. Correlation of prakrti with genomics is done with the above principle. Selection of appropriate medicine for a person Prakrti type is the most practical and time tested method followed in *Ayurveda* since ages. It is inexpensive and the methods are easy to remember and can be practiced easily by physicians and individuals for their health benefits. It is comprehensive in scope, spanning both physical and mental aspect. It is not merely a diagnostic tool but also a guide to action for good health.

KEYWORDS: *Ayurveda***,** Pharmacogenomics, *Prakrti.*

INTRODUCTION

Pharmacogenomics, the science that examines the heritable variations in genes that dictates the drug response of humans, microbes (anti-microbial) and tumours (anti-cancer drugs); and explores the ways these variations can be used to predict the patients response, either good or poor, to the drug. This may help in the development of more target specific and safer drugs. It deals with the systematic identification of all the human genes, their products, inter-individual and intra-individual variation in expression and function.[1]

Ayurveda is an Indian system of predictive, preventive, personalized and promotive medicine documented and practised since 1500 B.C. It accentuates the treatment of disease in highly individualized manner as it believes that every individual being unique has a different constitution. Based on the theory of *tridosha*, it classifies all individuals into different '*prakriti*' types with each type having varying degree of predisposition to different ailments. *Prakriti* being fixed at the time of birth remains invariant throughout the lifespan. This is independent of geographical, racial or ethnic considerations and may provide adequate means of classifying phenotypes to be considered collectively for genotyping. Similarly it categorizes the drugs based on *rasapanchaka* (*Ayurvedic* pharmacology), which states that the action of drug is ascribed to certain attributes present in the drug namely *Rasa* (taste), *Guna* (property), *Virya* (potency), *Vipaka* (post digestive taste), and *Prabhava* (effect), while in modern pharmacology the action of the drug is attributed to the chemical structure of a molecule.[2] The *rasapanchaka* modality provides treatment by taking into consideration the *prakriti* of the person as well as the pharmacodynamics and pharmacokinetic properties of a drug unlike a modern treatment that elicits varied response from person to person.

In present study, review of ayurvedic and modern pharmacy literatures, journals and articles was carried out for *prakriti* with pharmacogenomics. Collected references are further critically discussed which will gives knowledge regarding the concept of *prakriti* & importance in towards modern concept of pharmacogenomics. Study will help the researchers who are focusing the classical review of *prakriti* and also the relation with pharmacogenomics.

MATERIALS AND METHODS

The materials were collected from the classical Ayurvedic and modern pharmacy literatures and research journals.

Prakriti: In Ayurveda, predisposition to a disease as well as selection of a preventive & curative regime is primarily based on phenotypic assessment of a person which includes one's body constitution termed as "*Prakriti*". *Prakriti* is a consequence of the relative proportion of three entities - *Vata*, *Pitta* & *kapha* which are generally genetically determined (*Sukra-Sonita*).It is also influenced by environment, maternal diet & lifestyle.[3-7]

"*Pra*" refers to before, beginning, commencement or source of origin, in different contexts. Similarly "*kriti*" means creation or to do. Therefore, *Prakrti* on the whole means 'the first formed nature' or 'the original form of the being'.[8] *Prakritis* are discreet phenotypes and they are determined on the basis of physical, psychological, physiological and behavioural traits, and independent of social, ethnic and geographical variables.[9-11]

The etymology of these Sanskrit terms suggests that Vata originates from movement, Pitta from digestion and *Kapha* from accumulation. Since *Prakritis* underlie an individual's predisposition to disease as well as response to treatment, it is imperative in *Ayurvedic* practice to identify the *Prakriti* of a patient before treatment.[12]

Ayurvedists have used the term *prakrti* in the sense of personality. *Sushruta* has also used the term *KAYA PRAKRTI* and *MAHA PRAKRTI* in the same sense. (S.S. III. 4/99). The following definitions regarding *Prakrti* are available in classics.

1. Sukra Sonita Samyoge yo Bhaveddosa utkatah! Prakrtirjayate tena……. (S.S.III/4/63)
2. Dosanusayita hyesah Dehaprakrti ucyate!! (C.S.I./7/48)
3. Prakrtirnam Janmamarnantaral bhavini Garbhavakranti kale Svakarnodrekajanita Nirvikarkarani Sthitih! (Narasimhabhasya on Rasavaisesika)

Pharmacogenomics: Pharmacogenomics is the study of the role of the genome in drug response. Its name (pharmaco + genomics) reflects it's combining of pharmacology and genomics. Pharmacogenomics analyses how the genetic makeup of an individual affects his/her response to drugs. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single-nucleotide_polymorphisms with pharmacokinetics (drug absorption,

distribution, metabolism, and elimination) and pharmacodynamics (effects mediated through a drug's biological targets). The term pharmacogenomics is often used interchangeably with pharmacogenetics. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.

Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficiency with minimal adverse effects. Through the utilization of pharmacogenomics, it is hoped that pharmaceutical drug treatments can deviate from what is dubbed as the "one-dose-fits-all" approach. Pharmacogenomics also attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes, and how this may affect the efficacy of the patient's current or future treatments (and where applicable, provide an explanation for the failure of past treatments). Such approaches promise the advent of precision medicine and even personalized medicine, in which drugs and drug combinations are optimized for narrow subsets of patients or even for each individual's unique genetic makeup. Whether used to explain a patient's response or lack thereof to a treatment, or act as a predictive tool, it hopes to achieve better treatment outcomes, greater efficacy, minimization of the occurrence of drug toxicities and adverse drug reactions (ADRs). For patients who have lack of therapeutic response to a treatment, alternative therapies can be prescribed that would best suit their requirements. In order to provide pharmacogenomic recommendations for a given drug, two possible types of input can be used: genotyping or exome or whole genome sequencing. Sequencing provides many more data points, including detection of mutations that prematurely terminate the synthesized protein (early stop codon).[13]

Pharmacogenomics & Its Relationship with Prakrti: Concept of *Prakriti* in *Ayurveda* and the relationship of *prakrti* with genomics were hypothesized over a decade ago. Subsequent studies have attempted to correlate *Prakriti* classification with genetic information and association of single nucleotide polymorphisms (SNPs) in *HLA-DRB1*[14], *CYP2C19*.[15], *EGLN1*[16], inflammatory and oxidative stress related genes[17], CD markers for various blood cells.[18,19], DNA methylation alterations.[20] and risk factors of cardiovascular or inflammatory diseases have been reported.[21]

The Human Genome Project (HGP) was an international scientific research project with the goal of determining the sequence of chemical base pairs which make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and functional standpoint.[22] It was completed in the year 2003 and technological advancement in the field of DNA testing is so commendable that it has become a part of the medical field for diagnosis and treatment of various ailments.

A study on DNA methylation and *Prakriti* was also carried out. DNA methylation is a process by which methyl groups are added to DNA. Methylation modifies the function of the DNA, typically acting to suppress gene transcription. DNA methylation is essential for normal development and is associated with a number of key processes including genomic imprinting, X-chromosome inactivation, suppression of repetitive elements, and carcinogenesis.[23]

It recommended that the phenotyping or the *prakriti* analysis alone is not sufficient to comprehend Pharmacogenomics approach of Indian traditional Medicine. The physician has to closely examine the following 10 factors.

1) *Dusya* factor: Body Tissue functions & selection of medicine,
2) *Desa* factor: Habitat in which patient lives & selection of medicine, Patients,
3) *Bala* factor: Strength & immune factors in selection of medicine,
4) *Kala* factor: Chronobiology and selection of medicine,
5) *Agni* factor: Metabolic stage, digestive capacity &selection of medicine,
6) *Prakriti* factor : Phenotype -Systemic functions& selection of medicine,
7) *Vaya* factor: Age of the person& selection of medicine,
8) *Satva* factor: Mental faculties & selection of medicine.
9) *Satmya* factor: Homologation or wholesomeness & selection of medicine,
10) *Ahara* factor: Food habit & selection of medicine.

In Ayurveda Health and disease are described in terms of imbalance in the three functional principles (tri-*doshas*).viz. all the Neurological functions (*Vata*), All metabolic functions (*Pitta*) and all anabolic functions (*Kapha*) in their different combinations.

Factors Influencing Prakrti Formation – (acc. To ayurveda acharyas)

Maha-bhutha-vikaara-Prakr̥timiha-Naraanaam-Bhowthikeem-KechithAahu

Ayurveda states that life is a combination of *'PanchaMaha-Bhutha'* or the five universal elements, viz. *Aakasa* (space, as the absence of resistance), *Vayu* (principles of movement, vibration), *Agni* (principles of change), *Jala* (principles of fluidity, cohesion) and *Prithvi* (principles of solidity or mass) in its gross form or as the five states of matter. When referenced to life, these five elements are represented as the basis of all neurological functions (*Vata*), all metabolically functions (*Pita*) and all anabolic functions (*kapha*). Of these five, the predominant element of the sperm and ovum at the time of fertilization determines the *Prakrti* of a person. There is a detailed explanation of the subtle 24 principles transformed as *purusha* / self-based on this theory of evolution of a living organism.[24]

Aathmaja bhavas or soul or *purusha* origin: Factors transmitted from the "*purusha*" result in sensory perceptions, knowledge about self, qualities associated with mind, life force, etc. at a subtle level.

*Prakr̥*i is determined by the predominant features of the *'Tridoshas'* (*vata, pitta, kapha*) of *Sukra* (sperm) and *Sonitha* (ovum).[25] The major influences on the *Prakr̥*i are explained in terms of: *'Kaala-garbhasaya'* - the time and season of conception and the condition of the uterus; *'Aahaara-vihaara'* -food habits and behaviour of the mother during pregnancy; *'Prathyathma'* - the life styles of the parents, their thoughts and even occupation which in turn influence the *Sukra* and *Sonitha*; *'Jaathi-prasaktha'* the unique features of the parents' race; *'Kula prasaktha'* - the unique features of the community to which the parents belong; *'Desa-anupathini'* - the unique features his/her country or region of birth and *'Kalanupathini - anupathini'* - age of the parents.

Pithruja bhavas or paternal origin: Genetic factors transmitted from father for development of foetus includes factors related to male sexual organs, formation of head and hair on body parts, nail, teeth, bones, blood vessels, nerves and predominantly stable elements in the body.

Mathruja bhavas or maternal origin: Genetic factors transmitted from mother for development of foetus includes factors related female sexual organs, blood, muscles, adipose, nervous tissues, skin, lymphatic's, heart, liver, spleen, kidney, gastrointestinal system and predominantly soft tissues and elements in the body.

Satvaja bhaavas or mental origin: Genetic factors transmitted predominantly from parents for development mental attributes of the foetus results in predominance of the qualities of *satwa*, *raja* and *thamo guna* which is predominant. This results in happiness, sorrow, greed, anger etc and memory and intelligence of the child.

Saatmyaja and *Rasaja* or acquired qualities: These qualities are acquired after birth by virtue or influence of environmental changes, food habits, and growth conditions that influence the behaviour.

Prakrti and the Concept of Pharmacogenomics

Ayurveda has mentioned genetic concept in context of *Prakriti* thousands of years ago. *Ayurveda Acharyas* have explained that part of sperm and ovum (*Beejabhaga*) is responsible for formation of organ. If the part of seed (sperm or ovum) vitiated, it will result in the vitiation of the respective organ. Therefore, both possibilities are there (i.e. respective organs of progeny may or may not be vitiated depending upon the vitiation or otherwise of the part of seed responsible for formation of such organs).[26] Because of the defects in seeds (sperm or ovum), actions associated with soul, uterus, time and food as well as results in impairment of the shape, colour and sensory as well as motor organs of the offspring.[27] For example, a polyuric disease, biomedical approximation to diabetes (*Prameha*) is also incurable when there is genetic defect.[38,29]

Hence it is clearly seen that according to *Ayurveda*, the paternal germ cell and their basic constituents (*Bija*, *Bijabhaga* and *Bijabhagavayava*) play a definite hereditary role in determination of individual. The researches that were done in the field of genes and temperament have now shown that ancestry of individual gives the clue to this temperament. Now it is possible to demonstrate that attributes owe much to heredity, although it is impossible to specify what particular genes are involved in it. The whole matter is very complex and has to wait for further more investigations and researches than have been done.

Study of *Prakriti* and its association with diseases has been defined since Vedic period. According to Ayurveda, pharmacogenomics is nothing but *Prakriti* based medicine.[30] In addition, personalized medicine approach (*Purusham Purusham Vikshya Siddhant*) is well employed by *Ayurvedic* physicians in diagnosis and treatment.[31] Genetic polymorphism is due to the difference in DNA sequence among individuals, groups, or populations. It may be the result of chance processes, or may have been induced by external agents (such as viruses

or radiation). If a difference in DNA sequence among individuals has been shown to be associated with disease, it will usually be called a genetic mutation.[32] This concept may be related genetic concept of *Prakriti*. *Acharya* explained that part of sperm or ovum (*Beejabhaga*) is responsible for formation of organ.[33] If the part of seed (sperm or ovum) vitiated it will result in the vitiation of the respective organ.

Genetic polymorphism within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors. Inter-individual differences in response to drug therapy due to differences in acetylation of drugs are well-studied example of genetic polymorphism. These demographic and ethnic differences affecting genotype may be related to *ayurvedic* concept of factors responsible for *Prakriti* which include cast specific (*Jati Prasakta*), race specific *(Kula Prasakta)* and location specificity (*Deshanupatini)* types of *Prakriti*.[34]

A thorough enquiry of *Ayurvedic* literature reflects that mother and father chiefly exert their influence in makeup of personality through *Shukra* and *Shonita* (reproducing fundamental factors of mother and father), the respective productive factors of both of them. While describing the investigation of constitutional types of the human being, *Charaka* regards the nature of germoplasm (*Shukra* and *Shonita*) as one of the factor for determination of *Prakriti* of the foetus. It seems that *Charaka* went very deep in morphological description of *Shukra* and *Shonita* as he successfully describes three micro fine constituents of these germ cells, viz *Bija, Bijabhaga* and *Bijabhagavayava*. These names suggest that they are in descending serial sub constituents of former and latter is finer than former. It can be inferred in terms of nucleus, chromosomes and genes. *Charaka* has also given an indication that the sex determination of the child also depends upon *Sukra Shonita* predominance of germoplasm. *Sushruta* also holds that predominance of *Sukra* or *Artava* is responsible for the sex determination of the foetus. This concept of *Ayurveda* resembles in essence the modern theory of genes or X-Y chromosomes. A systemic integration of *Ayurveda* with modern science by adopting an interdisciplinary approach is needed to enlighten the approach toward personalized medicine and offer remedies.[36]

Purificatory Treatment Procedures and Prakriti Wise Treatment Potentials

As a result of improper metabolism, toxins (*Aama*) get accumulated in the cells and cause acute and chronic ailments. These toxins (also understood as free radicals causing inflammations and metabolic disorders) needs to be eliminated from the body though

methods of *Pancakarma* which include five purificatory measures Emesis (*vaman*), Purgation (*virechan*), medicated enema (*vasti*), Nasal medication (*nasya*), and bloodletting (*rakta moksana*). It is advised to undergo seasonal purificatory process to increase strength and immunity of a person. For example, a *Vata Prakriti* person should not undergo severe purificatory measures of emesis due to fear of disturbances in the neurological system. Similarly a *Vata prakriti* person should selected treatment protocols and medicines by selecting more medicated oil preparations for enema (*vasti*) in their purificatory (*Panchakarma*) treatment.

Based on the type of one's *Prakrti*, one can have a fair idea as to what kinds of disorders one is more prone to. In Ayurveda *Vata* type individuals are said to be prone to 80 specific disorders, *Pitta prakrti* individuals to 40 specific disorders and *Kapha prakrti* individuals to 20 sets of diseases entities. It is possible to extend the onset of such diseases or delay its pathogenesis if one is able to identify his/her *Prakrti* type.

Prakriti-based medicine can play a vital role in this changing scenario of global health wisdom as *Ayurveda* offers its modalities by way of *ahara* (diet), *vihara* (lifestyle) and *aushadhi* (medication), which are the three pillars of *prakriti*-based medicine. The potentials of *prakriti*-based medicine lie in:

1. Promotion of health and quality of life and thereby longevity.
2. Prevention of disease.
3. Understanding patient needs and risk factors for various chronic conditions.
4. Personalizing health care by monitoring *ahara*, *vihara*, and *aushadhi* on individual basis.
5. Disease management.
6. Reduction in morbidity and mortality.
7. Provision of new approaches for diagnosis and drug development.
8. Reducing the trial and error approach of health care system.
9. Minimizing adverse drug reactions.
10. Making healthcare affordable for people of various economic strata.
11. To utilize appropriate technologies for development of single and polyherbal products to make it globally acceptable.
12. To promote integrated research by AYUSH with modern medicine/modern science institutions and Indian systems of Medicine.[36]

CONCLUSION

With the advancement of human genome science now it will be easy for the clinicians to tailor the drug treatment through the specific prescription to the individual patient that target the drug to maximize its therapeutic efficacy and minimize the damage to surrounding healthy cells. Western allopathic medicine is excellent in handling acute medical crises, whereas *Ayurveda* has successfully demonstrated an ability to manage chronic disorders that Western medicine has been unable to.

*Ayurveda a*nd other traditional health practices can form the basis for a new, improved approach to public health, including health promotion, and affordable primary care functions, especially for communicable and chronic diseases. *Ayurveda's* holistic approach and its emphasis on prevention have the potential to improve the health status of the world's population. The promotion of health & prevention of diseases are stressed by both *Prakriti* based medicine & Personalized medicine. Fields of genomics study, the contribution of genes, proteins, metabolic pathways & non-genetic factors to human physiology & variations in pathways that has a vital role in disease susceptibility of an individual. It is there that Ayurgenomics can play its role in explaining how current drugs can be used more effectively by targeting them on patients of particular *prakrti*. The scientific studies carried out by various experts reconfirm the importance of *Prakrti* analysis and its role in innovative research programs in pharmacogenomics.

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