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Review Article

AN ANALYTICAL AYURVEDIC PERSPECTIVE ON MICROBIOTA AND ITS UNDERSTANDING IN ARTAVAVAHA SROTO VIKARA WITH SPECIAL REFERENCE TO POLYCYSTIC OVARIAN SYNDROME (PCOS)

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ABSTRACT

The causes of polycystic ovarian syndrome (PCOS) include diet, host genes, environmental factors, stress and hormonal changes; however, research have shown its association with variations in the gut microbiome which has a direct influence on microbiota of reproductive system. The global prevalence of PCOS is estimated between 4% and 20%. Acharya Cakrapani classifies Udbhavasthana of Vyadhi as two-Amashaya and Pakwashaya. Based on the type of diet and regimen of an individual, the Amashaya gets affected causing Agni Dusthi in turn influences the formation of Rasa Dhatu and its Upadhatu Artava causing diseases like Artava Kshaya. There are Ayurvedic references related to microorganisms which reside in different sites of human body including gut and reproductive system capable of producing disease which are known as Krimi and these are capable of producing gynecological disorders. The aim of this study is to explore the Ayurvedic concepts that may provide to generate ideas related to association between gut microbiota on the function of reproductive system and role of reproductive system microbiota in causation of PCOS and to analyse the benefits of Ayurvedic principles in the management of PCOS. Methods: This review aims to utilise existing literature on the relationship between the microbiome and PCOS and put forth the related Ayurvedic concepts. Results: The main focus is on identifying novel therapeutic and preventive strategies where Ayurveda proves beneficial. Discussion: The microbiota interacts with estrogen, androgens, insulin, and other hormones and influences to cause metabolic disorders like PCOS. Disturbance in menstrual cycle can be due to various causes and Krimi could be one of the causes. Conclusion: Artava kshava mentioned by Acharya Sushruta presents with similar menstrual abnormalities that of PCOS which can be treated with an effective Ayurvedic management protocol.

INTRODUCTION

Irregular menstrual cycle, metabolic disorder, insulin resistance and hyperandrogenism are the symptoms which are associated with PCOS and studies have shown that all these factors are associated with altered gut microbiota. Microbiota present in the gastrointestinal system plays an important role in digestion regulation, but its importance goes much

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beyond that. In PCOS, there is variation in hormonal levels. Microbiota especially related to gut exerts various effects on the intestinal milieu which influences distant organs and pathways, it is considered to be a full-fledged endocrine organ². Reports claim that estrogen affects the gut microbiota and function of the body depends on the type of microbiota influenced by estrogen (Vieira et al., 2017). When women have sufficient estrogen in their bodies, their intestinal microbiota exhibits species diversity, with beneficial bacteria dominating and the growth of harmful bacteria being inhibited³.

In 2012, the Dysbiosis of gut microbiota (DOGMA) hypothesis suggested that, following imbalance of intestinal flora, an increase of intestinal

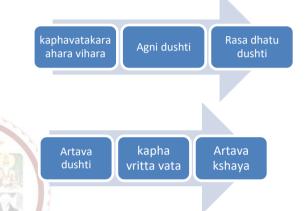
permeability could cause leakage of lipopolysaccharide (LPS) into the systemic circulation. The result is the activation of the immune system and inflammatory response that leads to insulin resistance⁴. LPS is a type of lipid molecule that makes up the outer membrane of gram-negative bacteria which is an endotoxin. Krimi is the term used in Avurvedic literature that depicts growth of such microorganisms which causes diseases. Krimi are said to be abording at various sites like Amashaya, Pureesha, Raktaja etc. There is a direct reference of use of the term Jantu or Krimi of reproductive tract according to Acharva Charaka and Acharva Vaabhata that causes Yonivvapad namely *Acharana* and *Vipluta* respectively^{5,6}. This suggests that Ayurvedic scholars were well aware of the fact about the presence of microorganisms that can cause diseases not only in the gut but also in the reproductive system. Studies have shown that presence of altered microbiota in the gut can influence the microbiota of the reproductive system further causing inflammatory changes in the tissues leading to disorders in females and affecting the menstrual cycle.

Acharva Sushruta have explained Artava Kshaya as a condition where the amount of menstrual blood is reduced and either the menstrual cycle is delayed or menstruation does not occur on time7. Vamana as Shodhana and use of Agneya Dravyas⁸ orally helps restoring the menstrual pattern and improving the quantity of blood flow. However, Acharya Cakrapani comments that in Artava Kshaya, Virechana as a Shodhana procedure can also be administered9. Virechana expels the vitiated Pitta and corrects Vayu by its Vatanulomana property. Studies showed that in PCOS women there is marked inflammatory response of the reproductive tract by altered microbiomes and in such cases Ayurvedic management can be administered to achieve maximum benefits. The aim is to improve the immune response of the host against these harmful microbiomes. Hence procedures such as Shodhana, Basti, Uttara Basti and Sthanika chikitsa administered reduces the inflammatory potential of microbiota thereby eliminating the toxins and aggravated doshas out of the gut as well as from the reproductive tract. Shamana Aushadhi provides Dosha Shamana chikitsa and brings back the dosha, dhatu and mala in their normal state.

Nidana and samprapti

Ayurveda put forth various theories to explain the cause of diseases. Kapha and Vata Vriddhi Kara Ahara and Vihara are the Vishishta Nidana for Artava Kshaya. Similar Nidana for PCOS can be considered; although there is no direct reference of PCOS in the Ayurvedic literature, considering the Nidana and Samprapti of Artavakshaya, the following points can be postulated.

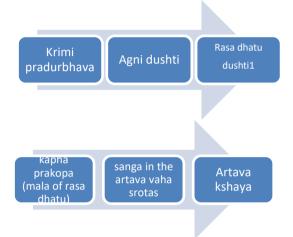
1.Acharya Charaka have mentioned Mithyachara, Pradushta Artava, Beeja Dosha and Daiva¹⁰ as the factors that causes Yoni Vyapad and similar Nidana influences the Artava Chakra. Faulty diet and regimen cause Agni Dushti that disturbs further Dhatugata metabolism. Rasa is the first affected dhatu that undergoes *Dushti* in the process of pathogenesis. As a result of Rasa Dushti. Artava dushti occurs as Artava being the upadhatu of rasa; thereby irregular menstruation sets in the affected females leading to Artava kshaya. Acharya Sushruta have explained Kaphavrita Vata causing Sanga in the Artavavaha Srotas, Kapha is the Mala of Rasa dhatu which vitiates the *Artavaha srotas*. The female reproductive tract is considered to be in *Apana sthana* and in *Artavakshya*, Apana vayu dushti is also evident.



2. Ayurvedic literature have explained that diseases originate from Vaikrika krimi which are pathogenic in nature. Acharva Charaka explains about Sahaja and Avaikarika krimi that live in human body from birth till death and which is not harmful. The term Krimi derived from dhatu "Kunja himsayam" which literary means either to produce fatal effects or that which destroys or that which creates diseases11. In Atharva Veda, Krimi is divided into Drishta and Adrishta type meaning visible and invisible¹². There is mention of Durnama and Sunama Krimi as well which may be considered as pathogenic and non-pathogenic. There is mention of etiological factors for both Bahya and Abhvantara Krimi in Samhitas. The Bahva or external Krimi are produced due to "Mrija barjana" means unhygienic and dirty habits13.

Krimi or jantu has been included as one of the causative factors that occurs following unhygienic practices among women which is mentioned in the context of Acharana yonivyapad according to Acharya Charaka and Vipluta yonivyapad according to Acharya Vagbhata respectively. This gives a direct reference of presence of *krimi* or microorganisms of reproductive tract females that causes gynaecological problems including irregular menstruation. The term Krimi can be understood in

different forms and the disease arising has different signs and symptoms. Microbiomes out of millions that harbours in the human body can be considered as certain form of *Krimi* that are capable of producing diseases resulting in *Agni Dushti* and *Dosha Prakopa*. *Agni Dushti* due to the presence of pathological *Krimi* in *Amashaya* results in defective metabolism that further affects the *Dhatu* formation leading to *Rasa Dhatu Dushti*. *Artava* as *Upadhatu* and *Kapha* as the *Mala* of *Rasa Dhatu* gets vitiated causing *Sanga* in the *Artavavaha Srotas* leading to *Artava Kshaya*.



Regarding *Abhyantara Krimi* some general and some specific etiological factors are mentioned. The general cause includes *Ajeernabhojana*, regular intake of *Madhura* and *Amla rasa*, consumption of *Drava*, *Guda*, *Virudha bhojana*, *Divaswapna* and *Avyayama*¹⁴.

Based on the types of *Krimi, Vishista* nidanas are separately explained for Kaphaja, Purisaja and Raktaja Krimi; whereas, the Krimi that manifest in the *Amashaya* can spread in various directions upwards or downwards explained by Acharya Charaka. Hence the term *Krimi* whether it is pathogenic or non-pathogenic points toward microbiome in gut or reproductive tract that may spread to various directions through the cellto-cell contact or may leak through the tight junction of the intestinal cells as per the concept of the contemporary science. The microbiome is present in many parts of the body but the largest collection of over 30 trillion bacteria is in the gut15. The gut microbiome participates in vital processes including digestion, energy homeostasis and metabolism, the synthesis of vitamins and other nutrients, and the development and regulation of immune function. It also contributes to the production of numerous compounds that enter the blood and affect various tissues and organs of the body^{16,17}. The microbiota plays a major role in the reproductive endocrine system throughout a woman's lifetime18. PCOS is a proinflammatory state, and emerging data suggests that chronic low-grade inflammation underpins the

development of metabolic aberration and ovarian dysfunction in the disorder. Novel data presented suggests that in PCOS. diet-induced inflammation may directly invoke hyperandrogenism¹⁹. Women with PCOS (hyperandrogenic) show a markedly altered microbiota, as it changes from first to third trimester of pregnancy, with an overall increase in Proteobacteria and Actinobacteria and reduced richness²⁰. Presence of *Krimi* during pregnancy causes early and mid-trimester abortions namely Garbhasrava and Garbhapata (Krimi vata abhighataistu tadaiva upadrutam phalam. Patati akale api yatha tatha syad Garbha vichyuti) 21. Hence the potential effects of microbiomes either in gut or in the reproductive tract can be a threat for a woman in causing diseases like PCOS.

Microbiota and its influence on hormones:

In humans, the gut microbiota is influenced by changes in estrogen and androgen levels due to factors such as pregnancy, puberty, menopause, or conditions like PCOS. Due to the presence of sex hormone receptors in the digestive tract, many healthy women suffer changes in gastrointestinal symptoms during the menstrual cycle (Bharadwaj et al., 2015; Mohib et al., instance. early menstruation characterized by lower stool consistency than midmenstruation; visceral somatic impulses may be perceived more strongly, resulting in pain, bloating, and nausea, particularly on the first day of the menstrual cycle. In addition, hormonal changes during menstruation can lead to alterations in the function and activity of the body's microbiota. This is due to the microbiota's control over steroid hormone levels, including estrogen (Parida and Sharma, 2019), microbiota can metabolize sex hormones through numerous enzymes. such as hvdroxysteroid dehydrogenase, which controls the balance of active and inactive steroids²².

Role of Bile acids

Sex bias of the gut microbiota may depend on bile acids after being synthesized in the liver from cholesterol. They are metabolized by the gut microbiota into secondary bile acids, which in turn can modify the structure of the microbiota and lead to various pathologies. Since testosterone is synthesized from bile acids²³ and as described above, bile acid levels are altered by the microbiota, it is tenable that the microbiota might indirectly influence the level of testosterone as observed in PCOS leading to hirsutism, acne, albicans nigrum and male pattern of baldness.

Role of microbiota on enzymatic action

The action of microbial community in the host also depends upon the biochemical changes that is

carried out by the enzymes that balances the gut environment. As indispensable catalysts within biological systems, they are involved in the metabolic processes of both the host and the microbes. The role of enzymes in modulating the gut microbiota is multifaceted and significant, including digestive support, competitive interactions, microbial crossfeeding, toxin degradation, immune modulation, microbial metabolism regulation and reshaping microbial communities²⁴.

The commensal microbial community can affect sex hormone levels through the activity of its enzymes. In this way, the term "strobolome" has been coined to define as the set of genes in the gut microbiota capable of activating estrogens from their inactive glucuronides; the enzymes β-glucuronidases, deconjugate estrogens into their active forms^{25,26,27}. These active estrogens pass into the bloodstream and act on estrogen receptors alpha (ER α) and beta (ER β)²⁸. Similarly, a recent study has concluded that the gut microbiota is involved in the metabolism and intestinal deglucuronidation of dihydrotestosterone (DHT) and testosterone, resulting in extremely high levels of the most potent androgen, DHT. Enzymes provide a range of therapeutic benefits, including disease treatment, a reduction in oxidative stress, and the regulation of immune responses.

Role of gut microbiota in causing metabolic disease like PCOS

The microbiota plays a major role in the reproductive endocrine system by interacting with estrogens, androgens, insulin, and other hormones. Imbalances in the gut microbiota composition can lead to pregnancy complications, adverse pregnancy outcomes, and conditions like polycystic ovary syndrome (PCOS). PCOS is said to be a metabolic disorder associated with obesity and insulin resistance. Gut microbiota has been linked to such diseases due to presence of chronic low-level inflammation which is mainly influenced Lipopolysaccharide (LPS), the intestinal barrier, and several metabolites derived from metabolism. The LPS is involved in chronic low-grade inflammation by inducing the secretion of potentially diabetogenic pro-inflammatory cytokines and key components of the innate immune response in adipose tissue²⁹. The disturbance in the immune cells due to altered microbial activities lead to the development of metabolic syndrome and further influence the hormones.

The Vaginal Microbiota

Normal menstruation with regular changes in estrogen and progesterone balances microenvironment (including the balanced microbiota

community) in the reproductive system. On the contrary, the irregular menstruation in PCOS women would lead to the alternation about the composition of lower genital tract microbiomes. Some studies investigated the lower genital tract microbiome composition of PCOS women and healthy women. Studies demonstrated in PCOS women significant decrease in composition of Lactobacillus. On the other hand, some other microbiomes such as Gardnerella vaginalis, Chlamydia trachomatis and Prevotella increased at the same time. Moreover, these increased microbiomes are regarded as potential pathogenic taxa in the vagina and cervical canal. Alternations in the composition of microbiota might be linked to the fact that PCOS women are often disturbed by infertility, abortion, and several other adverse reproductive outcomes³⁰.

Role of Endotoxin

Endotoxin (LPS) are lipopolysaccharides is a immunomodulator. Endotoxin phospholipid that forms the outer membrane of most Gram-negative bacteria. Circulating endotoxin binds lipopolysaccharide-binding protein, forming a complex that leads to the production of inflammatory cytokines. Endotoxin gains access to the blood when there is a severe localized infection. The gut epithelium is an efficient barrier that prevents the absorption of liposaccharide (LPS). Structural changes to the intestinal epithelium in response to dietary alterations allow LPS to enter the bloodstream, resulting in an increase in the plasma levels of LPS (termed metabolic endotoxemia). LPS activates Toll-like receptor-4 (TLR4) leading to the production of numerous proinflammatory cytokines and, hence, low-grade systemic inflammation. Thus, metabolic endotoxemia can lead to several chronic inflammatory conditions. Obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) can also cause an increase in gut permeability. PCOS can be considered to be induced due to such inflammatory reactions caused due to faulty diet and production of endotoxins³¹. In women with PCOS serum levels of lipopolysaccharides (LPS), the LPS to high-density lipoprotein (HDL) ratio and LPS-binding protein (LBP) are significantly greater than those of normal control subjects³².

Concept of Agni and Artava

Amashaya is the seat of Pachakagni that transforms Rasa Dhatu to Uttarotara Dhatus. While considering the function of reproductive system or Artavavaha Srotas, the basic formation of Artava is dependent on the quality of rasa dhatu as Artava is the Upadhatu of rasa. Due to Mithyachara and Asatmya Ahara and Vihara, Agni Vaishamya occurs further leading to Dosha vitiation and Rasa Dhatu Dushti

affecting the formation of Artava that causes menstrual irregularities. As per *Acharva Sushruta, Artavakshaya* is caused due to Kaphavritta Vata, the woman experiences Yathochita Kala Adarshana (absence of mensruation), or *Alpata* (less/ scanty) menstrual flow associated with symptoms like Yonivedana. PCOS closely resembles the description of Artava Kshava where Agni Dushti can be taken as cause of the disease. Based on the modern concept, the digestion is affected by the gut microbiota that controls the metabolism. Most bacteria in intestine form complex networks which include beneficial bacteria and harmful bacteria. Under normal circumstances, they exist optimally and are beneficial to the health of the host, but when an imbalanced occurs, the risk of disease increases. The secretion of bacterial biofilm is also one of the factors that leads to the development of human diseases. Ancient scholars have postulated the theory of agni dushti and ama formation as the cause of most of the diseases. Due to advancement in technology, now scientists are able evaluate that presence of type of microbiomes whether good or harmful microorganism in the alimentary tract decides the quality of digestion, processes, homeostasis, metabolism and immunity of an individual. A balanced and diverse microbiome is critical for maintaining health and immunological balance^{33,34}.

Management strategies:

Diet profoundly shapes the gut microbiota composition; a diverse diet rich in fiber, fruits, vegetables, and fermented foods promotes microbial diversity and health, while diets high in processed foods and sugars can lead to dysbiosis, characterized by an imbalance in microbial communities³⁵. Lifestyle factors such as eating junk food, sleep patterns, stress levels, less physical activity, and medication use also influence the gut microbiome. Chronic stress and inadequate sleep can disrupt microbial balance and compromise gut health. Dysbiosis has been linked to various health conditions, including gastrointestinal disorders, metabolic diseases like obesity and diabetes. autoimmune disorders, allergies, and mental health issues such as depression and anxiety³⁶. PCOS is a lifestyle disorder that affects the endocrinal systemand in such condition, the Ayurvedic principle of controlling a disease can be considered. Hence, the following management strategies can be planned

"Tatra samshodhanameva ca agneyanaam dravayanaam vidhiyat upayogah" (Sushruta Samhita Sutrasthana. 15/12)

out domain. 10/12)	
Pathya (beneficial)	Apathya (avoid the following)
Pittavardhaka and Vata Kapha Shamak, Ushna, Tikshna, Dipana, Pachana, Dravyas are used and these Dravyas can remove Srotoavarodha of Artavaha Srotas	Kaphavatakara Ahara and Abhishyandi Ahara Diet rich in fat, slimy, and heavy to digest
Tila, Karvi, Guda Kashaya	Anshan, Adhyashana, Virudha Ahara
Krishna Tila Kwath with Guda, Mishreya Methika, Muli, Gajara, Shatpushpa kashsya	Use of pastries, cake, chips, chocolates
Masha, Matsya, Jyotishmati Patra	Cold drinks especially carbonated drinks
Amla Rasa Pradhana Dravyas Dadhi, Saktu, Sura, Madya, Kanji, Takra	Bread, sweets, bakery products
Use of fruits like papaya, pineapple and fruits rich in essential nutrients and minerals	Canned items, stale food, processed food
Use of dry seeds like flax seeds, pumpkin seeds, sunflower seeds	Vega Dharana
Sadvritta, meditation, prayer, chanting Shlokas	Asat Mana, Manastaapa, stress and anxiety
Appropriate <i>Vyayam</i>	Ati or Alpa Vyayama
Following appropriate <i>Dinacharya, Ritucharya</i> and <i>Rajaswala Charya</i>	Ratri Jagarana and Diwaswapna
Vamana, Virechana	Atisamshodhana, Atisamshamana

Samshodhanamih vamanam na virekah etyapare". Sushruta Samhita Sutrasthana 15/12

Ayurvedic procedures: Udwartana, Amapachana, Snehapana, Vamana, Virechana, Basti, Uttara Basti, Sthanika Chikitsa.

-Shamana Aushadhi- Ayurvedic formulations mentioned in the classical texts to be administered in such conditions.

Ayurveda emphasizes on specific diet and regimen to be followed during menstruation so as to maintain the

balance of *Agni*, *Dosha* and *Dhatus* through *Rajaswala Paricharya*. This ensures the reproductive health of a woman that can be maintained through optimum gut health. Thus, it can be interpreted that *Rajaswala Paricharya* should be followed appropriately in order to maintain the gut health and in turn maintaining the hormones which are under the influence of *Agni*. This shows that a rhythmic menstrual cycle in a woman is optimized through diet and gut health.

DISCUSSION

Obesity. insulin resistance. hormonal imbalance, menstrual irregularities and metabolic dysfunction are the features of PCOS. Hence the treatment comprises of dietary management, lifestyle adjustments, and Shodhana therapies like Vamana, Virechana, and Basti and using certain Avurvedic formulations as Shamana Aushadhi³⁷. Modern research has highlighted a potential link between gut microbiota and obesity. Studies have shown that obese individuals tend to have a higher ratio of Firmicutes to Bacteroidetes bacteria in their gut. While certain microbial communities may contribute to increased energy harvest and weight gain, the exact role of gut microbiota in obesity remains multifactorial and complex. Such conditions are said to be in Bahu Dosha Awastha where Agnidushti, Dhatugata Dushti and Sanga of the Artavavaha Srotas should be corrected. An appropriate Ama Pachana followed by Shodhana should be adopted which comprises the initial line of treatment³⁸. Shodhana Karma cures the disease from the root cause³⁹. Acharva Susruta mentions that Vamana in Artava Kshaya expels the vitiated Kapha out of the gut. Dalhana explains that for purification, only Vamana Karma should be done and Virechana should not be done as Virechana is Pittahara and it will decrease the Agneya Tatwa of the tissues. Whereas Chakrapani comments that Virechana is equally beneficial when administered in such individuals as this procedure will do Vatanulomana and correct the function of Apana Vayu by removing the Sanga of the Srotas. Both Vamana and Virechana act at microcellular level and help to maintain the normal physiology of tissues⁴⁰.

Basti including Niruha Basti, Anuvasana Basti and Uttara Basti comprises the main treatment for vitiated Vayu. In Artava Kshaya, Apana Vayu Dushti is observed. Pakwashaya and Artavavaha Srotas are the Sthana for Apana Vayu. Therefore those treatment which treats the Apana Vayu Dushti targets to cure both gut as well as the reproductive system and Basti is said to be best treatment modality for this. Basti is administered by anal route and the medicines which are used in this procedure are having Vatahara property. Basti is a detoxifying therapy which can help to maintain the favourable medium & habitat for

beneficial gut microbiota thereby maintain the physiology of the systems. *Basti* expels the harmful toxins and harmful microbiota out of the large intestine and maintains the normal pathway of the hormones so that the menstrual irregularities are corrected⁴¹.

In Ayurveda, it has been emphasized that consuming Satmya Ahara (diet), maintaining adequate Nidra (sleep), and following Brahmacharya (regulated conduct) maintain the health of an individual and balances the Doshas, Agni, and Dhatus to function normally. In conditions like PCOS along with following an appropriate diet, sleep patterns and good conduct, the administration of Shamana Dravyas can give beneficial results. Acharya Susruta mentions to take Agneya Dravya Pradhana Aushadhi that improves the Agni and corrects the Rasa Dhatu Dushti. Thereby, Artava which is Agneya Guna Pradhana improves in its quantity through the concept of Samanya Vriddhi Karana. Hence a judicious use of Ahara and Aushadhi can improve the function of gut and control the microbiomes by reducing the inflammatory responses.

CONCLUSION

The management strategies followed according to *Ayurveda* have shown beneficial results in curing diseases arising out of altered gut mechanism (*Amashayagata* or *Pakwashayagata Vyadies*) especially in PCOS individuals with metabolic and endocrinal disorder. The association between the gut microbiota and reproductive system microbiota is well established. Hence, the recent theory of gut microbiota influence in causation of disease like PCOS which can be dealt effectively through *Ayurveda*.

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