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"A CRITICAL STUDY OF AMA IN BRIHATRAYEE WITH SPECIAL REFERENCE TO AMA-INDUCED ONCOGENESIS: A CLASSICAL AYURVEDIC FRAMEWORK FOR CANCER UNDERSTANDING"

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ABSTRACT

Ama is a key pathological concept outlined in the Brihatrayee (Charaka, Sushruta, and Ashtanga Hridaya), signifying poorly digested or metabolized substances that become harmful elements within the body. Traditional Ayurvedic literature connects the development of several ailments to Agnimandya (poor digestion and metabolic function), resulting in the creation of Ama. In contemporary biomedical science, cancer is mainly linked to changes in cellular structure, oxidative damage, ongoing inflammation, and immune system imbalances—processes that conceptually echo the harmful nature of Ama. One of Ayurveda's six main treatments, langhana, utilizes fasting or lightening methods to reduce excess doshas, ama, or waste products, thereby restoring the body's balance. Using techniques like exercise and fasting, it works well, especially for conditions brought on by overeating, often without the use of medication. Langhana in Ayurveda is similar to autophagy because both processes encourage detoxification and rejuvenation by removing built-up toxins or impaired parts to restore balance.

KEYWORDS: Ama, Agnimandya, Cancer, Langhan, Autophagy.

INTRODUCTION

It is essential to understand the Ayurvedic perspective to comprehend illness. But because of its a vital role in the development of nearly all diseases. *Acharyas* have made it abundantly clear in our Ayurvedic texts, such as *Acharya Arundutta's* statement that "किलाम समुत्थः सर्वे व्याधयः,"

Which translates to that *Ama* causes all diseases. The term "*Amaya"* is also used by *Acharyas* as a synonym for disease when they provide the synonym for diseases, demonstrating *Ama's* importance in disease development. In common usage, the word *Ama* refers to something raw, unripe, and material that is immature and undigested. However, in the context of medicine, this word describes the circumstances that follow and the elements that come up as a result, as well as the events that occur after that. result of the compromised operation of *Agni*.

The overall processing of consumed food relies on the condition of *Agni*. When *Agni* is not functioning properly, the eaten food turns into fully raw, unripe, undigested, or partially digested substances. This inadequately digested food will be unsuitable for the body's tissues. In this scenario, there will be two clear outcomes.

1. The body's material will not receive proper nutrition since it will lack renewal due to the unsuitable way in which it is presented to them.
2. Secondly, since the body's substance cannot work with such materials, what is basically excess material in the body will build up. Therefore, the substances that are not beneficial to the body in their altered state will undergo decay and fermentation because of the accumulation and storage.

This incorrectly changed food item and any substance that cannot be attacked is referred to as *āma* in *Āyurveda*. It is also known as a toxic substance, and it is the origin of numerous illnesses.

In traditional literature, the characteristics of *ama* are not discussed separately. *Vijayraksita* has included the qualities of *ama* in his commentary on the chapter of *amavata*, which are as follows:[1]

"अविपक्वमसंयुक्तं दुर्गन्धं बहु पिच्छिलम्"|…..Ma.Ni.25-*Madhukosha*

AMA-FREE RADICAL THEORY

The concept of free radicals and their contribution to harming the human body is regarded as one of the most significant developments since Louis Pasteur discovered that germs are the cause of human illness. Free radicals are currently understood to be "Under the current scientific understanding, the excessive generation of free radicals in the body, along with the imbalance between these and the anti---" is involved in the pathophysiology of cancer, heart disease, arthritis, and potentially as many as eighty diseases that are not caused by infectious agents. oxidant defenses may be connected to processes like aging and many illnesses, including cancer, ischemic processes, senile dementia, diabetes, pulmonary and pancreatic disorders, lupus erythematosus, cirrhosis, intestinal inflammatory disorders, multiple sclerosis, arthritis, arteriosclerosis, cardiovascular diseases, and diseases of the central nervous system and the brain"[2] (Bermejo Vicedo T, Antioxidant the therapy of the future).

A. Definition and Properties

1. A free radical is an atom or molecule with one or more unpaired electrons that needs to be neutralized by free radical scavengers. As a result, it is in an incomplete metabolic state, which is also how *Ama* is described as *"Avipakvam*" (incompletely digested/metabolised).

2. Free radicals are generated in a free state and are incompatible with bodily parts. The situation with *Ama* is similar; when it is generated, it remains in an assimilable condition, which is why it is called *'Asamyuktam*.'

3. Free radicals damage the cell membrane, leading to cell death. This devastation could result in putrefaction and a foul odor, which is reminiscent of one of the properties of *Ama*, which is described as "*Durgandham."*

4. Although *Ama* remains in the body as *Asamyuktam*, it adheres rapidly to normal healthy body tissues because of its characteristics, such as *Bahupicchhilam*. The same may be said about free radicals. They rapidly assault the body's healthy molecules to establish stability in their structure, triggering a chain reaction in this way.

5. These harmful molecules constantly encounter cells all over the body. *Ama* is similarly referred to as *'Sadanamsarvagatranam*.' One may see from the above that the characteristics of free radicals are akin to those of *Ama* as described in the classics.

B. Line of Treatment[3]

For *Ama*, there are essentially three different procedures needed. The first involves utilizing *Langhana*, which aids in reducing the burden on *Agni* and lowers the creation of *Ama*. The second procedure is the application of *Dipana Dravya*, which works to boost the condition of *Agni* and improve its functions. Finally, there is *Pachana*, which assists in breaking down the *Ama* that has already been produced.

1. To protect the body against harm from free radicals, antioxidant therapy is employed, functioning in three primary ways, as previously discussed. One method is by preventing the production of reactive oxygen species. This can be done by eliminating the triggers and can be considered as *Langhana Karma*.

2. Secondly, this can be achieved by boosting the activity of antioxidant enzymes such as superoxide dismutase or catalase. This enhancement is facilitated by specific medications that promote the functions of these enzymes. In simpler terms, this might be viewed as *Dipana Karma*.

3. The third method involves the use of specific chemicals that aid in neutralizing free radicals by either accepting or donating electrons from free radicals. Due to such characteristics, many vitamins, including vitamins C and E, are able to participate in electron transfer processes and neutralize free radicals. This exercise is similar to Pachana. As a result, the two concepts are treated similarly.

The Ayurvedic Concept of "Ama" and Intestinal Autointoxication

“Ama” refers to a harmful, thick, greasy, and adhesive fluid that forms as a byproduct of the body's digestion and metabolic processes. The term “Ama” can be interpreted as signifying “underdeveloped” or “not fully processed. “Ama” accumulates in people who have either poor digestive capacity or consume inappropriate foods in excess.[4] Since a person's digestive abilities (Agni) are partly influenced by their Prakriti (genotype), people who have robust digestive abilities (a trait linked to Pitta Prakriti) can consume greater amounts and more indulgent foods without developing “Ama.” On the other hand, those with weaker Agni possess poor digestive capabilities (a characteristic related to Kapha Prakriti) and are more prone to creating “Ama” easily.

The Ayurvedic concept of “Ama” shares similarities with the Egyptian concept of “Ukedu” and the historical theory of auto-intoxication in the intestines, as introduced by Metchnikoff. He suggested that certain bacteria in the gut that break down proteins could produce harmful substances (such as phenols, indoles, and ammonia). Over time, these harmful substances from digestion built up and led to illness.[5] Notably, recent research confirms Metchnikoff’s views, as certain bacteria that break down dietary carcinogens (like heterocyclic amines found in cooked meats and fish) are linked to a higher likelihood of developing tumors.[6] The connection between intestinal auto-intoxication and illness aligns with Ayurvedic beliefs regarding “Ama” and its potential to cause disease (refer to the subsequent two sections).

Experimental Approaches for Investigating “Ama”: It's crucial to research cancer and inflammation in their respective contexts. "Ama" since it is thought to possess antigenic and pro-inflammatory characteristics. To determine if "Ama" can be used as a reliable, early indicator of chronic inflammation, preclinical tests can be conducted. Since the majority of "Ama" is found in the body's microchannels, isolating it in its pure form can be challenging.

Excessive "Ama" can be discovered in urine and on the tongue, according to Ayurveda. Thus, after the "clinical" characterization and confirmation of the "Ama" stages of the disease as described in Ayurveda, it is crucial to collect and identify samples of urine and tongue secretions carefully. One should use samples from the same person before the illness ("Nirama" stage), if possible, as controls. The paired samples can then be analyzed for possible toxicity, immunogenicity, and pro-inflammatory effects in vitro and using suitable animal models. It is possible to accomplish this by including varying amounts of "Ama" containing it, comparing samples to "Nirama" controls, and to cell lines taken from different kinds of tissue. The next step is to figure out if "Ama" is MTT, and other cell viability tests are performed to determine cytotoxicity and tests for cell death (apoptosis and necrosis).[7] Additionally, the majority of cell lines are immortalized or converted. It is crucial to evaluate the possible toxicity of "Ama" on the main cultures produced from healthy tissues. These toxicity studies ought to be reproduced in animal models as well if "Ama" is cytotoxic in vitro.

To find out if "Ama" can trigger inflammation, various amounts of "Ama" samples, along with "Nirama" controls, can be introduced to different types of cells. This allows for the measurement of different pro-inflammatory substances such as cytokines, adipokines, eicosanoids, NF-κB, and STAT-3. If the findings indicate that "Ama" possesses pro-

inflammatory characteristics, different doses of "Ama" samples, as opposed to "Nirama" controls, can be injected into distinct groups of mice. Subsequently, the same pro-inflammatory substances and inflammation indicators, including CRP and the ratio of omega-6 to omega-3 fatty acids, can be assessed in the test subjects compared to the control group. Should this data reveal that the samples containing "Ama" lead to inflammation when contrasted with the "Nirama" controls, it would confirm the notion of "Ama" being a pro-inflammatory agent.

Candidate Molecules for "Ama": If the previous studies indicate that samples containing "Ama" can lead to long-lasting inflammation, it is possible to conduct a comparative analysis of the biochemical makeup of "Ama" and "Nirama" samples. Additionally, one should be able to examine how the biochemical structures of "Ama" relate to various internal, pro-inflammatory substances produced during processes such as digestion, metabolism, and energy generation. There are at least five categories of internal pro-inflammatory substances that could symbolize "Ama." To start, poorly digested food in individuals with obesity serves as a strong candidate for "Ama," as it correlates with a changed gut microflora composition, which can subsequently trigger chronic inflammation by activating the lipopolysaccharide toll-like receptor-4 pathway.[8] The association between diets rich in fat, higher production of bile acids (like deoxycholic acid), and a greater risk of colon cancer is recognized. Nevertheless, a direct connection involving bile reflux, inflammation, and cancer has been established through research indicating that unconjugated bile acids strongly enhance the expression of cyclooxygenase-2 (COX-2), a key pro-inflammatory enzyme found in cells derived from oesophageal adenocarcinoma.[9]

Therefore, certain bile acids can exhibit pro-inflammatory properties, making them a second potential molecular factor for "Ama." The pro-inflammatory characteristics of abnormal bile acids are implied by the observation that altering the bile acid receptor (FXR) leads to anti-inflammatory outcomes. The third molecular factor linked to "Ama" includes advanced glycation end products (AGE), which build up in conditions such as diabetes, aging, and cancer. AGE may be indicative of "Ama" because its interaction with the receptor (RAGE) can initiate chronic inflammation. The fourth molecular factor linked to "Ama" involves protein-lipid peroxide (P-LPO) adducts, as LPO, which accumulates due to oxidative stress, can bond with lysine residues on specific proteins, leading to the production of the pro-inflammatory cytokine, TNF-α.[10] Lipid peroxides may interact with DNA, leading to the

formation of promutagenic compounds like etheno-deoxyadenosine. Elevated amounts of these etheno-DNA adducts found in human blood and urine might act as indicators of long-lasting inflammation in those at risk for cancer from previous carcinogen exposure.[11]

Therefore, these etheno-DNA adducts might symbolize a fifth molecular option for "Ama."

The experiments mentioned earlier might indicate that "Ama" contains an abundance of one of these five potential molecules. Conversely, "Ama" might be made up of a diverse blend of these five candidate pro-inflammatory molecules, which include partially digested food fragments, certain bile acids, advanced glycation end products, peptide-linked oxidized lipid compounds, and etheno-DNA adducts, all resulting from irregular digestion and metabolism in tissues and cells.

Langhana in Ama promotes "Autophagy"

The term 'langhana' signifies healing through fasting, the experience of hunger, or the practice of deliberate deprivation of food.[12] In a broader perspective, it includes the therapies intended for reducing or depleting, or lightening the body components. This is one of the six basic treatment protocols in Ayurveda. (Ch.Su. 22/4). This treatment is used to lower any abnormally high body component and return it to its normal level to maintain balance. It is evident in the unusual accumulation of dosha (pitta/kapha/rakta), any waste product, the state of dosha linked to ama, and indigestion. With or without any medicine, Langhana therapy can be prescribed. (Chakrapani on Cha.Su. 22/12-13). Langhana therapy has proven to be very effective and is gaining popularity in treating illnesses caused by excessive nutrition. The most common methods of langhana therapy include fasting and physical exercise.

Autophagy - The term "autophagy" comes from the Greek words "auto," which means "self," and "phage," meaning "to eat." This process is a natural function in the body that focuses on breaking down cells. It helps maintain homeostasis or regular function through the degradation of proteins or fats. Autophagy primarily ensures a balance between creating cellular parts and breaking down damaged or unneeded organelles and other cellular elements. Additionally, autophagy helps in removing and cleaning up damaged organelles from cells. It serves as a natural and regulated process that dismantles unnecessary or malfunctioning components. Overall, it facilitates the systematic breakdown and recycling of cellular elements.[13]

Issues with autophagy have been associated with multiple human illnesses, such as neurodegenerative disorders and cancer, leading to an increased interest in altering autophagy as a possible remedy for these conditions.[14-15]

Four forms of autophagy have been identified: macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), and crinophagy.[16-17-18] In macroautophagy, which is the most well-studied type of autophagy, parts of the cytoplasm, such as mitochondria, are identified and separated from the rest of the cell inside a double-membraned sac called an autophagosome.[19-20] which eventually merges with a lysosome that is accessible, introducing its unique waste management and elimination process; ultimately, the materials within the vesicle (now referred to as an autolysosome) are broken down and reused. In crinophagy (the least recognized and studied type of autophagy), surplus secretory granules are broken down and repurposed.

In the context of illness, autophagy is viewed as a way for cells to adapt to stress, aiding their survival. However, in certain situations, it seems to lead to cell death and worsening health. During severe starvation, the disassembly of cell parts supports survival by sustaining energy within the cells.

Fasting and cancer- Fasting could be useful in both preventing and treating cancer. While there is currently no research involving humans on the impact of intermittent fasting or prolonged fasting in cancer prevention, their ability to lower IGF-1, insulin, and glucose levels, along with raising IGFBP1 and ketone levels, may create a safer environment that minimizes DNA damage and the development of cancer. At the same time, these factors could make conditions unfavorable for tumor and precancerous cells (Longo VD et al, 2010). Additionally, the blood serum from individuals lacking IGF-1 protected human epithelial cells against DNA damage from oxidative stress. Moreover, once the DNA sustained damage, those cells had a higher chance of undergoing programmed cell death (Guevara-Aguirre J et al. 2011). Therefore, fasting could offer cancer protection by minimizing damage to cells and DNA, along with promoting the elimination of precancerous cells.

Autophagy plays an important role in cancer, both in protecting against cancer as well as potentially contributing to the growth of cancer.[21] Autophagy may assist cancer progression by helping tumor cells endure starvation or by breaking down apoptotic elements via autophagy. In these situations, employing substances that inhibit the later phases of

autophagy, like chloroquine, in cells that depend on autophagy for survival raises the count of cancer cells eliminated by anticancer medications.[22]

Researchers have discovered that abstaining from food for a period of 12 to over 24 hours activates autophagy, which is believed to be one factor linking fasting to a longer lifespan.

Ohsumi, a Nobel Prize laureate, pioneered a new scientific field through his studies on autophagy in yeast. He found that the genes responsible for autophagy are utilized by more complex beings, including humans, and that mutations in these genes may lead to diseases. Organisms such as animals, plants, and single-cell life forms depend on autophagy to survive during periods of scarcity.

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