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Agni Revisited: A Contemporary Review Correlating Jatharagni, Dhatvagni, and Bhutagni with Digestion, Metabolism, Mitochondrial Function, and Endocrine Regulation

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Abstract

Agni is an ayurvedic term that can be defined as digestion, transformation, assimilation, nourishment of tissues and maintenance of metabolic balance. A contemporary biomedical perspective of the review of *Agni* and its possible functional relationship with gastrointestinal physiology, tissue-specific metabolism, biochemical transformation, mitochondrial bioenergetics and endocrine regulation is focused on this review, specifically on *Jatharagni*, *Dhatvagni* and *Bhutagni*. *Jatharagni* is taken into consideration as a digestive process, absorption of nutrients, signalling by hormones from the gut, communication between the gut and the brain, and the metabolism of microbes. The examination of *Dhatvagni* is done in conjunction with the use of nutrients at the tissue level, handling of substrates, the communication between one organ to another and metabolic regulation, while *Bhutagni* is examined through the post-digestive biochemical transformation, nutrient sensing and metabolic regulation. The review also takes into account important aspects of regulated energy transformation, such as mitochondrial substrate oxidation, ATP generation, redox balance, organelle quality control and cellular signaling. The role of endocrine and temporal regulators such as thyroid hormones, glucagon, circadian rhythms and meal timing in systemic metabolic coordination are discussed. Artificial intelligence and machine-learning approaches may further support this integrative perspective by analysing multidimensional physiological, metabolic, endocrine, microbiome, and temporal data to identify complex regulatory patterns. Explainable AI may be particularly useful for exploring interpretable relationships between traditional functional classifications and measurable biomedical parameters without assuming direct biological equivalence. Altogether these mechanisms can all help to interpret *Agni* as a systems-level physiological construct, rather than as a one-to-one match of any single molecular pathway. *Agni* should not be confused with any particular enzyme, hormone, mitochondria or receptor. A functional and integrative approach will offer more scientific bases for comparison of the physiology of Ayurveda with the modern science of metabolism. Standardization of assessment, quantifiable physiological endpoints and well-designed mechanistic and clinical studies should be the focus of future research.

1. Introduction

Agni is a basic principle in Ayurvedic physiology, and is traditionally considered as the engine which powers the digestion, metabolism, assimilation and transformation processes in the body. It is not just about the digestion of food in the gastrointestinal tract, but also about the transformation of nutrients into compounds that are suitable for the nourishment of tissues, production of energy, maintenance of physiological stability and overall homeostasis. According to Ayurveda, there are various functional levels of *Agni* which are of particular importance for the present discussion including *Jatharagni*, *Dhatvagni* and *Bhutagni*. *Jatharagni* is mainly related to the process of digestion in the

gastrointestinal tract, *Dhatvagni* to metabolic transformation of the tissues and *Bhutagni* to later stage of elemental processing of food components. These concepts can be integrated and used at multiple levels to understand metabolism as a coordinated process starting with digestion and leading to cellular and systemic transformation.

It is believed that *Jatharagni* is the most important digestive element in this framework as it is directly related to the digestion of the food consumed. Traditionally, Balanced *Jatharagni* is connected to good digestion, assimilation, nourishment to tissues and keeping health and if it is not balanced then it is connected to incomplete digestion, *Ama* formation. Ayurvedic understanding of *Ama* is an incompletely digested food or drink which can disrupt the normal physiology. Modern debates have focused on *Jatharagni*, digestion and *Amotpatti*, the latter of which is considered as root of all imbalance in body metabolism, which further supports the concept of importance of digestive efficiency in the context of other metabolic balance (Usharani et al., 2021).

The significance of *Jatharagni* has also been talked about with regard to quality of food changing and the effects of poor digestion. Incomplete metabolism and accumulation of improperly processed substances are the symptoms of disturbance in *Agni*, which indicates that *Agni* is understood as an organised, functional and meaningful process of transformation and utilization, rather than just digestive heat (Ambulgekar et al., 2021). The wider interpretation offers a valuable framework for rooting the concepts of Ayurvedic descriptions within the modern concept of digestion and metabolism without forsaking the notion of a difference between traditional and modern concept.

Recent research has started to explore the possibility of measuring the traditional ayurvedic physiological concepts in order to study them. The use of structured observation approaches to investigate *Jatharagni* among the young adults was shown to be an exploration of the concepts. Such effort is worthwhile as it provides a pathway to bring together traditional classification with current methods of research but does not imply that the two are of a biological basis (Kuttikrishnan et al., 2022). Likewise, the potential link between *Jatharagni* and basal metabolic rate has been examined in healthy adults and some of the indicators of traditional metabolic capacity could be explored using measurable indicators of energy expenditure and physiological function (Ojha, 2022).

Modern digestive science also knows that the gastrointestinal process is rather dynamic and can be modulated by both biological and food factors. Digestion requires enzymes and digestions as well as the physical structure, composition and matrix of food. These properties determine the nutrient release rate and extent during the gastric processing and subsequently their availability for absorption and subsequent metabolism (Somaratne et al., 2020).

In addition to this, the concept of “nutrient sensing” has been advanced by modern physiology, leading to a greater understanding of digestion. The gastrointestinal tract is an active organ that senses nutrients, and triggers neural, cellular, endocrine and metabolic changes that affect appetite, glucose control, digestive function, and overall energy balance. The nutrient sensing system thus connects the gastrointestinal environment with the wider regulation of the system and offers a modern perspective of some of the condition of *Agni* (Venugopal & Bishu, 2021) that are traditionally associated with it.

The term '*Agni*' is not limited to *Jatharagni*. *Dhatvagni* is the metabolic transformation that takes place at tissue level, whereas *Bhutagni* is related to processing of the elements of foods. These ideas imply that

Ayurvedic medicine considered metabolism to be a continuous, partially distributed physiological process; not a single event occurring in the digestive organs. In a modern ayurvedic perspective, *Agni* is considered a more complex biological transformer that is responsible for the conversion, assimilation and metabolic processes at various physiological levels (Halgekar et al., 2024).

The implications of *Agni* are also wider as discussed pertaining to the relationship between poor metabolism and digestive and systemic ailments. In recent literature, there is growing interest in the role of *Agni* dysfunction in metabolism beyond just gastrointestinal functions (Lal et al., 2024). In the present background, the present review takes a contemporary integrative view of the concept of *Agni*. It discusses the potential role of *Jatharagni*, *Dhatvagni* and *Bhutagni* in gastrointestinal digestion, transformation of nutrients, tissue metabolism, mitochondrial bioenergetics and endocrine regulation. There is no intention to make direct comparisons or connections between the Ayurvedic constructs and certain enzymes, organelles, hormones or molecular pathways. Instead, the review is intended to uncover the points of conceptual convergence, physiologic similarity and possible scientific relevance. In this review, the study of *Agni* as multilevel model of digestion and metabolism aims to create a balanced approach that will be respectful to the integrity of Ayurveda, but also a critical approach to the contemporary biomedical knowledge. The increasing use of artificial intelligence in healthcare provides an additional opportunity for investigating such complex physiological frameworks. Machine-learning approaches can integrate heterogeneous variables related to digestion, metabolic rate, hormonal activity, microbiome composition, mitochondrial function, nutrient utilization and circadian patterns to identify multidimensional associations that may not be evident through conventional analysis alone. In this context, explainable artificial intelligence could be particularly valuable because it can provide interpretable relationships among physiological variables while avoiding reduction of traditional Ayurvedic constructs to individual biomarkers or molecular pathways. Such computational approaches may therefore complement future attempts to operationalize and quantitatively investigate systems-level concepts such as *Agni*.

2. Classical Framework and Physiological Dimensions of *Agni* in Ayurveda

Agni is one of the basic building blocks of the the physiology of Ayurveda and helps to understand the digestion, assimilation, transformation, and nourishment of the tissues. The term “digestive fire” is often used to describe the physiological process, which is much more extensive than digestion. *Agni* means the capacity to transform, adapt and make available to the body, makes everything functional. It is thus linked not only to digestion in the gastrointestinal tract, but to the following metabolic activities that provide energy for the maintenance of tissues and internal physiological homeostasis. Modern ayurvedic explanations also view *Agni* as a regulatory mechanism that functions in digestion, absorption, assimilation and metabolism and not as a single anatomical structure or biochemical component (Kumar et al., 2024).

According to classical viewpoints, there are thirteen main forms of *Agni* categorized on three levels of functioning; one *Jatharagni*, five *Bhutagni* and seven *Dhatvagni*. It is a sequential classification in which the nutrients in the food are transformed in the gastrointestinal tract, then processed based on their elemental properties, and then used at the tissue level. The arrangement of these various types of *Agni* indicates that Ayurveda considered metabolism as a scattered and related process as opposed to the one confined

to the digestive system of the gut. The transformations of nutrients that occur at each stage contribute to the progressive transformation and hence the continuity of the food intake, assimilation, tissue formation and maintenance of physiological functions.

Jatharagni is the topmost of all these. It is part of the digestion system and, in fact, it takes care of the first digestion and transformation of the food being eaten. In the process the ingested material is differentiated into nutritive and non-nutritive fractions which form a substrate for the subsequent physiological processing. *Jatharagni*, therefore, is the first of the stages at which the food gets assimilated. It has traditionally been considered as being balanced (*Sama*), reduced (*Manda*), excessive (*Tikshna*) or irregular (*Vishama*). These differences in the functioning of the system highlight an Ayurvedic understanding that digestion is different in each person and the efficiency of digestion can also vary depending on other internal and external factors.

The second level of this hierarchy of metabolism is called *Bhutagni*. According to Ayurveda, there are five *Bhutagni* which are allied with the five *Mahabhutas – Prithvi*, Ap, *Tejas*, *Vayu*, *Akasha*. After the main action of *Jatharagni* these are known to function on related elements in the processed food. The function of this stage is to make the constituents within the diet suitable for further use by elements with similar properties in tissues. While the theoretical elements of *Panchamahabhuta* can be directly linked to the current biochemical elements, or the nutrient classes, the concept of *Bhutagni* indicates a crucial difference in theory between digestion in the gut and digestion of absorbed material.

Dhatvagni is the third major functional level which is related to the seven *Dhatus Rasa*, *Rakta*, *Mamsa*, *Meda*, *Asthi*, *Majja* and *Shukra*. Every *dhatu* is believed to have its own *Dhatvagni* that enables its transformation and utilization of nutrients according to the *dhatu*. This process helps in the maintenance, regeneration and nourishment of *Dhatus* and also provides matter for the higher level of organization of tissues. Fire (*Agni*) translates accordingly as the *Dhatvagni* which relates to metabolic activity in the tissues. Recent debates on *Agni* and metabolism have also highlighted the poly-level character of the process, pointing towards its digestive-assimilative-metabolic transformations, rather than treating the process of digestion and assimilation as separate physiological processes (Preeti et al., 2025).

There is coordination between the functioning of *Jatharagni*, *Bhutagni* and *Dhatvagni* which plays a central role in physiological balance. If the disturbance happens in an earlier stage, it could in theory have an effect on later stages as everything relies on well-processed information from the previous stage. In this context the *Agni* framework offers a view of digestion and metabolism as a continuum of function. Gastrointestinal transformation is required to allow proper processing and/or metabolism and tissue-level transformation is essential for proper assimilation and utilization of nutrients.

Other factors such as *Dosha* predominance, *Prakriti*, food pattern, food quantity, food quality, age, season, activity, mind state and food timing also have an influence on *Agni*. As a result, it is considered to be dynamic or changing. More recently, this concept has been extended by analyzing the relationship of *Agni* with the metabolic cycles of the day and season, which are conceptually similar to the current understanding of how meal timing, circadian control and environmental cycles can affect metabolic efficiency (Gaikwad & Bhojani, 2025). These remarks help to reinforce the view of *Agni* as a controlling mechanism which adapts to individual constitution and physiological changes.

The best modern reading of this classical schema is in its functional sense, however, rather than its literal one. The three *Vagni* (digestive fires) *Jatharagni*, *Bhutagni*, *Dhatvagni* should not be equated with digestive enzymes, metabolic pathways, organelle or specific biochemical reactions. Rather they are different degrees of transformation of an integrated physiological model. In recent reviews the hierarchical nature of these forms of *Agni* and their overall role in digestion, metabolism, nourishment of the tissues and maintenance of homeostasis has been pointed out (Patel et al, 2025). This classical model can serve as the basis for exploring, in later sections, the role that selected aspects of the physiology, tissue metabolism, mitochondrial bioenergetics, and endocrine regulation of the gastrointestinal system could have as functional counterparts in the modern understanding of the concept of *Agni*.

3. *Jatharagni* and Gastrointestinal Physiology: Digestion, Absorption, and Metabolic Signaling

Jatharagni, the main digestive fire of Ayurveda, is mainly linked with the initial stage of the digestion of food in the gastrointestinal tract. It is associated with correct digestion, digestion and separation of nutritive and non-nutritive substances and in preparation of nutrients for next metabolisms. This wide spectrum of roles can be explored in the light of modern physiological knowledge, as part of gastrointestinal digestion, intestinal absorption, nutrient sensing, enteroendocrine activity, gastrointestinal–brain interactions, and microbial metabolism. Comparing them is most useful at the level of functional similarity and not direct biochemical equivalence. *Jatharagni* is an Ayurvedic construct at a systems-level, whereas the modern gastrointestinal physiology is described by specific molecular and cellular pathways.

The gastrointestinal tract is now recognized as a dynamic metabolic and signalling organ rather than a place where food is broken down with increasing biomedical understanding. The gut is constantly engaged in a dialogue with the central nervous system via neural, hormonal, immune and metabolic routes, all of which affect energy intake, energy control of glucose, feeding behavior and whole body energy balance. This gut–brain communication is important for postprandial physiology as it can be influenced by the exposure to nutrients in the intestine, which can impact metabolic responses in the central and peripheral nervous systems. The coupling of intestinal signals to central regulation thus indicates that intestinal digestion has systemic effects that go far beyond the gastrointestinal lumen (Wachsmuth et al., 2022). The interrelationships of *Jatharagni* with modern gastrointestinal and metabolic physiology have been summarized in Table 1.

Table 1. Functional Mapping of Jatharagni to Contemporary Gastrointestinal and Metabolic Physiology

Ayurvedic Functional Domain	Contemporary Physiological Correlate	Principal Mechanistic Process	Functional Relevance to Metabolic Homeostasis

Food transformation	Gastrointestinal digestion	Enzymatic and luminal processing	Converts food into absorbable nutrients
Digestive coordination	Gut–brain axis	Neural and hormonal signaling	Regulates appetite and energy balance
Nutrient response	Enteroendocrine signaling	Gut hormone secretion	Coordinates insulin release and satiety
Metabolic integration	Gut microbiome	Microbial metabolite production	Influences glucose and lipid metabolism
Nutrient sensing	Incretin signaling	Detection of luminal nutrients	Supports postprandial glucose control
Appetite regulation	Gut hormonal pathways	Hunger and satiety signaling	Modulates food intake
Substrate transformation	Microbial metabolism	Biochemical modification of nutrients	Generates bioactive metabolites
Metabolic balance	Diet–microbiome interaction	Host–microbial metabolic interaction	Supports systemic metabolic homeostasis

One of the key elements of this regulation is endocrine activity of the intestine. The enteric endocrine system contains a group of cells located throughout the gastrointestinal tract that are responsive to the chemical composition of the contents of the gut and regulate gastric emptying, pancreatic secretion, appetite, insulin secretion and nutrient utilization. A coordinated action of multiple hormones, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY), cholecystokinin (CCK) and ghrelin, is responsible for the regulation of the transition from nutrient intake to metabolic response. The intestine is a known endocrine organ, highlighting the close relationship between digestion, nutrient availability and systemic metabolic regulation (Bany Bakar et al., 2023).

The intestine is also closely associated with gut microbiome to form a highly interactive metabolome. Intestinal microbial communities convert dietary substrates into metabolites which can affect intestinal integrity, glucose regulation, lipid metabolism and hormone levels. These microbial products can exert local effects in the gut or have systemic effects and influence distant organs, thus playing a role in whole body metabolic homeostasis. Endocrine and metabolic functions are thus tightly linked to the activities of the intestinal microbial ecosystem, which is gaining in importance to understand obesity, diabetes and other metabolic disorders (Meyer & Duca, 2023).

Incretin hormones are one of the best examples of nutrient-sensing by the intestine and the subsequent systemic metabolic response. Specific enteroendocrine cells are equipped with receptors, transporters and

intracellular signaling pathways to identify nutrients and nutrient-derived signals (carbohydrate, fat, protein, and others). This detection triggers the release of incretins hormones which promote insulin release in a glucose-dependent manner, have an effect on gastric emptying and appetite. These mechanisms illustrate the intricate relationship between digestion and absorption and endocrine regulation, and the involvement of the gut in regulating nutrient metabolism in response to nutritional needs (Santos-Hernández et al., 2024).

This integrated regulation is also partially mediated by a large family of gut hormones. These hormones regulate digestive motility, digestion, pancreatic endocrine activity, sensation of satiety, appetite and energy expenditure. They influence physiological processes so that food consumption is related to the required digestive and metabolic function. Several aspects of gastrointestinal-endocrine communications are essential for maintaining energy balance and the development of metabolic dysfunction, including the regulation of energy balance and the coordination of digestive processes (Cho & Lim, 2024).

The other major physiological process that is regulated is appetite (Satiety). Endocrine and neural signals from the gut regulate appetite via central circuits that are involved in the regulation of meal size, nutrient composition and energy availability. Hypothalamic and vagal pathways are involved in the interaction between satiety and hunger signals and food intake, which in turn affects nutrient exposure. This relationship shows that digestion is not only a process that regulates and controls the intake of nutrients, but also the process that regulates the timing and quantity of food intake, as the gastrointestinal tract helps to regulate the entire process. (Hong & Choi, 2024)

The gut microbiome is another layer of complexity in gastrointestinal metabolism because the microbes generate biologically active compounds from both the dietary and endogenous substrates. Short-chain fatty acids, bile acid metabolites and amino-acid derived metabolites have the capacity to modulate host signaling pathways that regulate glucose homeostasis, lipid metabolism, immune regulation and expenditure of energy. Current research has moved away from correlations of the host's microbiome and disease to elucidation of how microbial products influence the host's metabolism (Koh & Bäckhed, 2020).

The functional aspect becomes crucial in metabolic health where alterations in the composition and activity of the microbiota have been linked with obesity, insulin resistance and type 2 diabetes. The metabolic effects of the gut microbiota are however also determined by the type of microorganisms present, as well as the interaction of microbiome with diet, physiology and microbiome metabolites. The gut is thus a complex ecosystem and metabolic process with digestion, microbial transformation, host signaling and endocrine responses happening concurrently (Fan & Pedersen, 2021).

4. *Dhatvagni* and Tissue-Level Metabolism: Nutrient Utilization and Metabolic Homeostasis

Dhatvagni represents the tissue-level dimension of metabolic transformation in Ayurvedic physiology and extends the concept of *Agni* beyond gastrointestinal digestion into the domain of selective nutrient utilization and tissue maintenance. Ayurveda describes seven *Dhatvagni* corresponding to the seven *Dhatus*, implying that each tissue possesses a distinct capacity to transform, assimilate, and utilize nutritive material according to its own functional requirements. This framework is notable because it conceptualizes metabolism as a distributed and differentiated process rather than as a uniform biochemical event. From a contemporary perspective, *Dhatvagni* may

therefore be examined in relation to tissue-specific substrate handling, nutrient partitioning, metabolic signaling, cellular turnover, and coordinated inter-organ regulation.

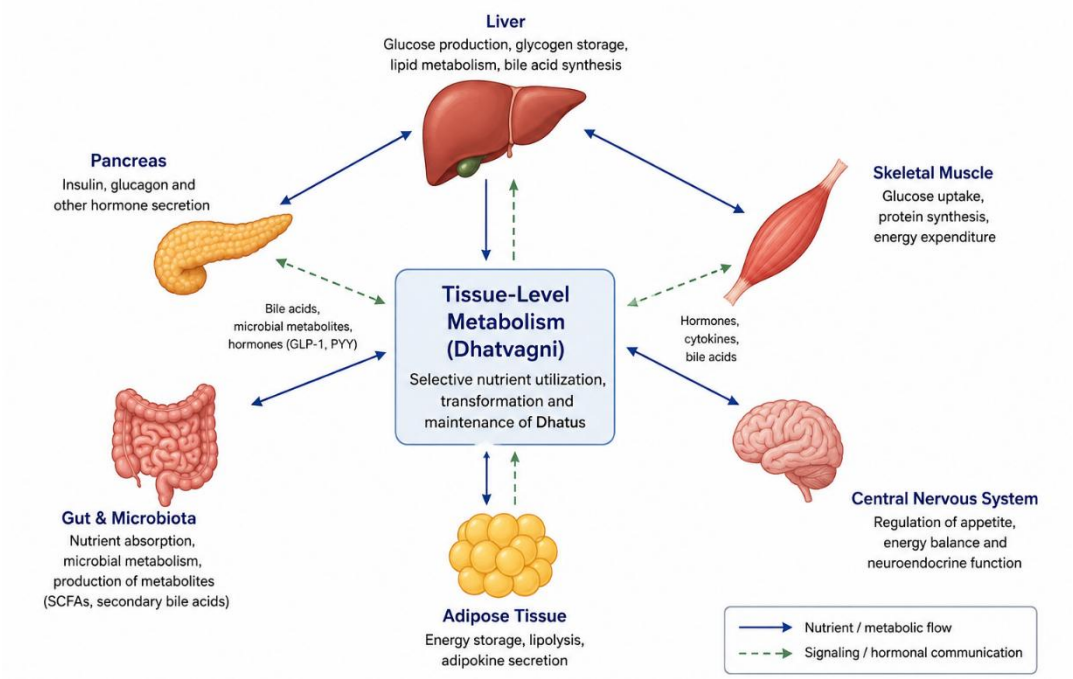


Figure 1. *Dhatvagni* and Inter-Organ Metabolic Regulation

In modern physiology, it's also shown that the metabolism of a given tissue is different depending on its metabolic needs. Glucose production, storage of glycogen, synthesis of lipids, metabolism of cholesterol and distribution of circulating substrates are controlled by the liver. Skeletal muscle is a significant source for glucose uptake and energy expenditure, adipose tissue stores excess energy and releases fatty acids when needed. Other tissues change their metabolism in response to energy state, hormonal environment and substrate availability, and the pancreas uses endocrine signaling to control nutrient utilization. These different metabolic functions act as a functional parallel with the concept of Ayurveda that each *Dhatu* has its own transformative capacity and does not work in a similar way in the metabolism.

Circulating signaling molecules (Xie et al., 2021) are a key aspect of tissue level metabolism, with local activity constantly modified by these circulating molecules. Bile acids are an example of the regulatory integration. They are classically known to participate in lipid digestion but are now known to be signaling molecules that can influence glucose metabolism, lipid homeostasis, energy expenditure and inflammatory pathways in various organs. Their activities throughout the liver, intestine, adipose tissue and other metabolic tissues illustrate that what is associated with digestion can gain general regulatory functions at the tissue level.

The gut microbiota also is involved in another level of regulation by producing metabolites that impact peripheral tissues. The effects of microbial products on glucose

handling, lipid metabolism, insulin sensitivity, inflammatory responses and energy balance have been described (Moser et al., 2022). Their actions are not limited to the GI system, but can also affect the microbiota–gut–brain axis and the liver, adipose tissue, and skeletal muscle by circulating metabolites that can affect the central nervous system. The concept of distributed metabolic communication is particularly important to the *Dhatvagni* model as it is an example of how the metabolic state of a tissue can be influenced by signals from other tissues in the body. Such distributed metabolic communication also represents a potential application area for machine learning and network-based artificial intelligence. Computational models can integrate biochemical, hormonal, microbial and organ-specific metabolic variables to identify patterns of inter-organ interaction and predict changes in metabolic homeostasis. Explainable AI approaches may be especially relevant because they can indicate which physiological variables contribute most strongly to a predicted metabolic state, thereby supporting biologically interpretable systems-level analysis.

The bile acids are also metabolic signals whose actions are influenced by their molecular constituents, activation of receptors and enterohepatic dynamics. They also can modulate glucose production, lipid oxidation, thermogenesis, and energy expenditure, highlighting that tissue metabolism is controlled in addition to substrate availability by signaling activity. These results confirm the modern concept of coordinated communication between metabolic organs in nutrient handling, besides biochemical conversions (Li & Chiang, 2023).

Bile acid metabolism is also more complex, sequentially transformed into a variety of metabolites. Given that the intestine is populated by microorganisms, they can convert primary bile acids into secondary and structurally modified bile acids that have different biological activities. These are derivatives that have the potential to affect a variety of metabolic and immune pathways, which is a possible effect on the function of tissue other than gastrointestinal. The ability of molecules to develop new physiological roles at different steps of the transformation is conceptually similar to the Ayurvedic notion of progressive tissue-level metabolic transformation (Mohanty et al., 2024).

The bile-acid signaling has systemic effects on glucose homeostasis, lipid balance, immune function, and energy metabolism. The communication between bile acids and the receptors in various tissues establishes a pathway of communication between intestine, liver, adipose tissue and other metabolic pathways. This coordination is crucial for internal stability and demonstrates that metabolic homeostasis requires the functioning of several tissues and pathways to occur rather than a single pathway or organ (Jia et al., 2024).

5. *Bhutagni* and Biochemical Transformation of Nutrients

Bhutagni lies between the digestion of food in the gut and its utilization at the level of tissues and is a concept connecting the primary digestion of food with the secondary digestion at the tissue level. After the activity of *Jatharagni*, digested food is believed to get transformed further with the action of five *Bhutagnis* related to the five *Mahabhutas*—*Prithvi*, Ap, *Tejas*, *Vayu* and *Akasha*. The categories are not to be understood as equivalent to the contemporary nutrients, chemical substances and molecular processes. Instead, their contemporary significance comes from their broader physiological significance that digested substances require further biochemical manipulation before they can be readily used by tissues. Modern metabolism also suggests that the handling of nutrients does not end at intestinal absorption, but extends into the enzymatic conversion, microbially

mediated modification, sensory detection, selection and transport of nutrients to other organ systems, and metabolic signaling.

A useful example of such a sequential transformation today is the metabolism of bile acids. Cholesterol is converted to bile acids in the liver, excreted in the intestine, modified in the enterohepatic circulation and modified by intestinal microorganisms. These modifications also modify their chemical characteristics as well as their signaling and metabolic functions. Bile-acid imbalance is now linked to various aspects of glucose metabolism, lipid metabolism and immunity and to the wider metabolic disease. It is a representation of the physiological significance of a molecule being altered at each step of biochemical processing and regulation. (Wang et al., 2024) Table 2 shows the main functional similarities between *Bhutagni* and current mechanisms of nutrient transformation and metabolic regulation.

Table 2. Functional Correlates of *Bhutagni* in Nutrient Transformation

***Bhutagni* Domain**	**Modern Correlate**	**Key Mechanism**	**Metabolic Role**
Post-digestive transformation	Bile-acid metabolism	Synthesis and microbial modification	Generates bioactive metabolites
Substrate modification	Gut microbial metabolism	Biotransformation of dietary substrates	Produces signaling metabolites
Adaptive utilization	Metabolic flexibility	Switching between fuel substrates	Matches energy supply with demand
Nutrient sensing	mTORC1 signaling	Detection of nutrient availability	Regulates anabolic metabolism
Energy sensing	AMPK signaling	Detection of cellular energy status	Promotes energy-generating pathways
Nutrient allocation	Incretin and pancreatic hormones	Insulin–glucagon regulation	Coordinates storage and mobilization
Metabolic adaptation	AMPK-dependent control	Regulation of glucose and lipid metabolism	Supports metabolic homeostasis

The gut microbiota plays an additional layer to this conversion. The microbial communities produce a wide array of metabolites from dietary and host-derived metabolites which can impact the physiology or processes of both the local intestine and the distant systems. There has therefore been a recent change in the microbiome research from simply identifying microbial species to investigating community-level metabolic activity, substrate utilization and metabolite production. Functional perspective highlights metabolism as the outcome of processing available food by microbial ecosystems, and the interaction between microbial ecosystems and host physiology (Noecker & Turnbaugh, 2024). In this regard, the term *Bhutagni* can be tentatively understood as a generalisation of the concept that the nutrients need additional change in their structure after their initial digestion, before they reach their physiological significance.

The metabolism of these modified substrates also depends on the adaptability of the cells. Under different nutritional, energy demand and physiological conditions, the proportion of carbohydrate and lipid oxidation constantly needs to be adjusted. Therefore, it is crucial to have efficient utilization of substrates

by the mitochondria which is called mitochondrial adaptation and metabolic flexibility. A decrease in metabolic flexibility has been associated with insulin resistance, obesity, and impaired metabolic homeostasis, and thus, the availability of nutrients is not enough unless they are used by cells to make the right choice and process the available substrates (Tsilingiris et al., 2021). The biochemical shift is an important contemporary example of the biochemical transformations that are coupled with cellular energy demands.

The use of transformed substrates is also regulated by sensory mechanisms of nutrients. Mechanistic target of rapamycin complex 1 is one of the important regulators of this process and integrates information on amino acids, growth factors, energy status of the cells and the environment. In this signaling pathway, cells are able to decide whether or not nutrients should be used for protein synthesis, production of lipids, growth, storage, or other anabolic processes. The mTORC1 pathway thus shows that metabolism of nutrients isn't simply a chemical reaction, but that the cell actively interprets the availability of the nutrients.

AMP-activated protein kinase, one of the major sensors of the energy balance in cells, also plays a complementary role. If there is insufficient energy (ATP), AMPK turns on energy-generating systems and blocks systems that require a significant energy input. This in turn impacts on glucose uptake, fatty-acid oxidation, mitochondrial function and cellular adaptation to metabolic stress. AMPK mediated regulation demonstrates that biochemical transformation is constantly regulated with the energetic requirement of the cells and metabolic balance requires the proper response to the varying nutrient and energy requirements (Sharma et al., 2023).

Endocrine mechanisms also at the systemic level influence the metabolic destinations of absorbed nutrients. Glucose disposal, nutrient storage, substrate mobilization and metabolism after a meal are regulated by incretins and other pancreatic hormones (insulin and glucagon). The hormones serve to coordinate the entry of nutrients in the intestine with metabolic activity in the liver, skeletal muscle, adipose tissue and other organs. Thus, nutrient transformation needs to be considered within a dynamic matrix that involves biochemical substrates, cellular sensors, and endocrine signals in their interplay to decide on the fate of the nutrients either stored, oxidized, redistributed, or used for biosynthesis (Reed et al., 2024).

This regulatory integration is especially prominent in diseases of metabolism. Abnormal AMPK signaling may be associated with glucose and lipid homeostasis, that can lead to diabetes related metabolic complications, and that can also impact insulin sensitivity. This confirms the idea that the metabolic health is not just based on nutrient availability but also on the capacity of cells to sense, convert and use substrates as required by the physiological needs (Kakoti et al., 2024).

6. *Agni*, Mitochondrial Bioenergetics, and Cellular Metabolic Regulation

Agni, in its context outside of its gastrointestinal meaning, is a more general concept of transformation, of using energy and regulating the physiology in Ayurvedic philosophy. Mitochondrial bioenergetics is one of the most relevant and current fields in which this broader metabolic aspect can be studied at the cellular level. Mitochondria play a key role in the regulation of substrate oxidation, ATP production, redox control, metabolic signalling and adaptation to altered energy requirements. But any comparison between *Agni* and mitochondrial function should be conceptual and not literal. While *Agni* is a classical system-level construct, mitochondrial metabolism is defined by specific organelles, enzymes, substrates, signaling networks and biochemical reactions. Their shared focus is on regulated

transformation and maintenance of functional balance, as that is the value of comparison.

The generation of energy is constantly regulated by endocrine and cellular signaling, reflecting its dynamic aspect. Estrogen is a single example of a hormone with the ability to influence mitochondrial biogenesis, oxidative phosphorylation, generation of reactive oxygen species, and metabolic efficiency in a variety of tissues. This points towards the fact that cellular energy production is linked to a larger hormonal regulation and physiological state (Klinge, 2020). This type of regulation serves as a useful functional frame of reference for thinking about *Agni* as a metabolically responsive principle, as opposed to a hard coded digestive capacity.

The ability of mitochondria to function at the molecular level relies on an intricate network of proteins that are highly coordinated. These proteins control entry of substrates, activity of the respiratory chain, transport of metabolites, organization of membranes, protein import and several quality control processes. The study of mitochondrial function through systems-biochemistry approaches has revealed that the function emerges from interaction between numerous molecular components instead of a single biochemical pathway (Sung et al., 2020). Artificial intelligence can extend such systems-level approaches by analysing high-dimensional metabolic and molecular datasets in which numerous variables interact simultaneously. Supervised and unsupervised machine-learning techniques may assist in identifying metabolic phenotypes, detecting patterns of mitochondrial dysfunction, and relating bioenergetic variables to endocrine and physiological outcomes. When combined with explainability methods, these models can help identify influential metabolic features rather than functioning solely as black-box predictors, which is particularly important when computational findings are interpreted in a physiological or clinical context. The following network-based organisation is important in the interpretation of *Agni* as it illustrates the importance of co-ordinated action on several levels of regulation in the process of biological transformation. A summary of the functional interpretation of *Agni* in terms of mitochondrial bioenergetics, cellular signalling and metabolic homeostasis is presented in Table 3.

Table 3. Functional Interpretation of *Agni* in Mitochondrial Bioenergetics and Cellular Metabolic Regulation

Ayurvedic Functional Dimension	**Contemporary Mitochondrial Process**	**Principal Regulatory Mechanism**	**Bioenergetic Significance**
Energy transformation	Oxidative metabolism	Substrate oxidation and ATP generation	Supports cellular energy demands
Hormonal responsiveness	Estrogen–mitochondrial signaling	Regulation of biogenesis and oxidative phosphorylation	Modulates metabolic efficiency
Metabolic integration	Mitochondrial protein networks	Coordinated enzymatic and transport functions	Maintains bioenergetic organization
Functional maintenance	Mitochondrial quality control	Mitophagy, dynamics, and proteostasis	Preserves metabolic competence
Cellular signaling	Mitochondrial signal transduction	Redox, calcium, and metabolite signaling	Coordinates adaptive responses

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Endocrine coupling	Beta-cell mitochondrial metabolism	Metabolic signaling for insulin secretion	Links nutrient status with glucose control
Metabolic resilience	Mitochondrial adaptation	Substrate switching and stress response	Supports metabolic homeostasis
Bioenergetic regulation	Mitochondrial membrane dynamics	Control of respiratory-chain organization and flux	Optimizes oxidative phosphorylation

Mitochondrial efficiency also depends on continuous quality-control mechanisms. Damaged proteins, membranes, and organelles must be identified, repaired, recycled, or removed to preserve cellular function. Mitochondrial dynamics, mitophagy, proteostasis, and organelle turnover are therefore essential for sustaining metabolic competence. Impairment of these processes can lead to accumulation of dysfunctional mitochondria, disturbed energy production, oxidative stress, and disease progression (Eldeeb et al., 2022). This illustrates that effective cellular metabolism depends not only on energy generation but also on preservation of the biological machinery responsible for metabolic transformation.

Mitochondria additionally function as signaling platforms that communicate metabolic status to the rest of the cell. Alterations in membrane potential, calcium flux, redox state, metabolite concentrations, and energetic balance can influence nuclear gene expression and cellular responses. Through these pathways, mitochondrial activity participates in the regulation of stress adaptation, growth, immunity, differentiation, and metabolic homeostasis (Picard & Shirihai, 2022). This expanded role is particularly important because it demonstrates that mitochondria integrate energy production with cellular decision-making rather than functioning simply as ATP-producing structures.

The connection between mitochondrial metabolism and endocrine regulation is especially evident in pancreatic beta cells. Glucose metabolism generates mitochondrial signals that participate in the coupling of nutrient availability with insulin secretion. Metabolic cycling and mitochondrial substrate oxidation contribute to the generation of signaling intermediates that regulate beta-cell function and postprandial glucose control (Merrins et al., 2022). This relationship illustrates how cellular energy transformation can directly influence systemic endocrine responses and thereby contribute to whole-body metabolic homeostasis.

The clinical importance of mitochondrial regulation becomes clearer in metabolic disease. In metabolic dysfunction-associated steatotic liver disease, mitochondrial abnormalities may include altered substrate oxidation, increased oxidative stress, impaired mitophagy, disturbed dynamics, and reduced metabolic adaptability. These changes can contribute to hepatocellular injury and progressive metabolic dysfunction, demonstrating that failure of mitochondrial quality control can have consequences at both cellular and organ levels (Shin et al., 2023). This reinforces the broader principle that metabolic health depends on maintaining a balance between substrate availability, energy production, and adaptive capacity.

Contemporary mitochondrial biology increasingly places mitochondria at the center of communication among metabolism, stress responses, and disease processes. These

organelles interact with the nucleus, endoplasmic reticulum, lysosomes, and other cellular compartments and respond to changes in nutrient availability, environmental stress, and physiological demand. Their dysfunction can therefore disturb multiple cellular systems simultaneously and contribute to a wide spectrum of metabolic and degenerative conditions (Suomalainen & Nunnari, 2024). Such interconnectivity provides an important systems-level perspective for interpreting the broader physiological dimensions associated with *Agni*.

Mitochondrial membrane composition also plays a critical role in regulating bioenergetic performance. Membrane lipids influence respiratory-chain organization, metabolite transport, membrane curvature, and the efficiency of oxidative phosphorylation. Changes in lipid composition can alter bioenergetic flux and modify the capacity of mitochondria to respond to fluctuations in nutrient supply and energy demand (Decker & Funai, 2024). This demonstrates that cellular energy transformation depends not only on metabolic substrates and enzymes but also on the structural environment in which bioenergetic reactions occur.

7. Endocrine Regulation of *Agni* and Systemic Metabolic Homeostasis

The general physiological meaning of *Agni* is not just the breakdown and change of the food in the stomach but includes the harmonious modulation of energy balance, nutrient utilization, hormonal activity and time management of metabolism. In modern physiology, metabolic homeostasis in the body is achieved through the constant interplay of endocrine signals, circadian clocks, cellular metabolic processes and organ-specific metabolic reactions. All these processes contribute to define the way nutrients are absorbed, stored, mobilized and used under different physiological situations.

Circadian regulation is a key factor in the regulation of metabolic function. Endogenous “biological clocks” mediate the daily (circadian) rhythms of glucose metabolism, lipid handling, hormone release, energy expenditure and feeding behavior. These rhythms are mediated by the synchronized functioning of central and peripheral clocks which allow tissues to prepare for periodic transitions between feeding, fasting, activity and rest. Loss of circadian organization leads to reduced coordination of metabolic responses, thereby contributing to a higher risk of dysregulated glucose metabolism, lipid metabolism and metabolic dysfunction (Guan & Lazar, 2021). This temporal organization is especially relevant in the context of *Agni* since the physiology, too, is similar with Ayurveda, in that the digestive and metabolic functions fluctuate with respect to time, routine and physiology.

There is also a robust transcriptional control of circadian timing/metabolism. Molecular clock systems control the expression of genes that mediate nutrient handling, substrate oxidation, synthesis of lipids, glucose production and responsiveness to hormones. Peripheral tissues like liver, adipose tissue, skeletal muscle and pancreas contain their own clocks, which modulate their metabolic response in relation to time of the day. The connection of circadian transcription to metabolic pathways highlights the circadian regulation of physiology, but also in predictable temporal rhythms, across tissues (Kim & Lazar, 2020). This offers a modern explanation as to why some individuals may be more efficient at metabolizing the provided food than others.

Meal timing is another example of "temporal metabolic regulation. Eating at inappropriate times could disrupt glucose tolerance, metabolic rate, hormonal levels and energy balance, while regular meals in synchrony with internal circadian rhythm could facilitate a more effective metabolic use. The

time of nutrient consumption, then, could be an important determinant of metabolic outcomes, in addition to overall energy intake, as suggested by the current evidence (McHill & Butler, 2024). There is a significant physiological correlation in this relationship with what is taught in Ayurveda with reference to proper timing of eating with digestional capacity and balancing the body system.

Another aspect of metabolic homeostasis is the endocrine regulation. Thyroid hormones have broad actions on BMR, thermogenesis, carbohydrate turnover, lipid turnover, mitochondrial function and tissue-specific energy expenditure. Their actions are coordinated, and rely on synthesis, transport to the site, local activation, receptor signaling and tissue response. Modern studies on the physiology of the thyroid have established that metabolic rate is controlled by very integrated endocrine mechanisms which act in many organs instead of in a single central process (Galton & Hernandez, 2023).

The gastrointestinal system itself is also involved with thyroid hormone metabolism, further reflecting the close connection between the digestive system and thyroid hormone. The ability of thyroid hormones to be transformed and bioavailable in the intestine, their enterohepatic circulation, nutrient availability and gastrointestinal physiology may affect thyroid hormones. These interactions illustrate how endocrine control is not just a part of the gastrointestinal system, but is part of a broader metabolic network that connects gastrointestinal, liver, circulatory and peripheral tissues (Fenneman et al., 2023). This interdependence comes into force particularly when we talk about the system level concept of *Agni* and its relationship with digestive transformation and all the other physiological regulations.

Thyroid hormones are also cellular metabolic messengers. Their effects are tissue specific, depending on the hormone status at the given tissue, and affect mitochondrial biogenesis, substrate oxidation, thermogenesis, lipid metabolism and energy expenditure. The tissue specificity of their responsiveness underscores the intimate connection between endocrine signals and bioenergetics, and provides a functional link between the regulatory aspects of *Agni* and *Dhatvagni* mediated tissue metabolism with the transformation of energy in mitochondria (Sinha & Yen, 2024).

Another example of systemic endocrine coordination is that of glucagon. Glucagon is frequently described as a hormone which antagonizes insulin, but is known to exert a variety of other physiological actions, including stimulation of glucose production from the liver, stimulation of amino acid metabolism, stimulation of lipid mobilization, stimulation of energy expenditure and adaptation to fasting. Normal expression of glucagon signaling is important for metabolism and metabolic diseases, such as type 2 diabetes, because of its role in maintaining disturbed metabolic homeostasis implies disturbed energy regulation in these conditions relies on proper and context-dependent glucagon responses (Hædersdal et al., 2023).

The ability of cells to respond metabolically is also an essential requirement for endocrine signals to have a proper physiologic effect. Mitochondrial quality-control mechanisms maintain organelle integrity, control turnover, maintain redox balance and promote adaptation to altered nutrient and energy requirements. Mitochondrial dysfunctions of energy metabolism and cellular signaling can lead to a further increase in systemic metabolic dysfunction when the quality control of the mitochondria is disturbed (Liu et al., 2024).

The multidimensional nature of digestion and metabolic regulation also creates opportunities for artificial intelligence to support future investigation of the

physiological interpretation of *Agni*. Metabolic function is determined by interactions among gastrointestinal processes, circulating hormones, microbiome-derived metabolites, mitochondrial bioenergetics, tissue-specific substrate utilization, lifestyle factors and circadian rhythms. Machine-learning approaches are particularly suited to analysing such heterogeneous and nonlinear biological data and may help identify recurring physiological patterns or metabolic phenotypes across individuals. Supervised learning could potentially examine whether combinations of measurable physiological variables are associated with predefined digestive or metabolic phenotypes, whereas unsupervised learning may identify naturally occurring patterns without imposing predefined categories.

Multimodal computational approaches could further integrate biochemical, microbiome, endocrine and physiological measurements. Explainable artificial intelligence may be especially useful in this context because it can identify the variables contributing most strongly to computational classifications or predictions and thereby improve physiological interpretation. However, computational associations should not be considered evidence that traditional Ayurvedic categories are directly equivalent to specific molecular mechanisms. Future investigations could combine standardized *Agni* assessment with objective metabolic measurements and interpretable machine-learning models to determine whether reproducible physiological patterns are associated with traditionally described functional states.

8. Conclusion

Agni refers to several aspects of Ayurveda, including digestion, transformation, nourishment of tissues, regulation of energy and preserving physiologic balance. If viewed in the light of modern biomedical understanding, its three main parts – *Jatharagni*, *Dhatvagni* and *Bhutagni* are in significant functional parallel with gastrointestinal processing, tissue-specific metabolism, biochemical transformation, mitochondrial bioenergetics and endocrine regulation. *Jatharagni* relates to co-ordinated digestive and absorptive activities, *Dhatvagni* to the utilization of nutrients on the tissue level, and *Bhutagni* to the gradual biochemical conversion of nutrients for use. Recent studies also show integrated networks between nutrient sensing, gut-derived signals, metabolic activity of mitochondria, hormonal regulation, and circadian regulation, all of which are involved in the regulation of metabolism. These mechanisms are reflective of the integrated nature of digestion and metabolism at cellular, tissue, organ and systemic levels. In this context, the model of metabolic regulation presented by *Agni* is helpful. However these correlations need to be interpreted – not reductive. Do not equate *Agni* directly to mitochondria, enzymes, hormones, receptors or individual metabolic pathways. It is of current interest because it offers a conceptual model focusing on coordinated transformation, adaptability and metabolic balance. Artificial intelligence and machine-learning approaches may provide additional tools for integrating multidimensional physiological data and identifying interpretable patterns related to metabolic regulation. Explainable AI may further support future investigations by clarifying the relative contribution of metabolic, endocrine, mitochondrial and temporal variables without implying direct equivalence between Ayurvedic constructs and specific biomedical mechanisms. Future studies should focus beyond a mere descriptive comparative approach and utilize well-defined physiological parameters, standardized evaluation techniques, and clinically relevant study designs to better explore and validate these links and to support the integration of

Ayurvedic physiology with mainstream metabolic science on the basis of evidence.

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