Gut: a key mediating centre for the ageing process

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Survival was the main issue in the initial stage of evolution for humans. Now the priorities have shifted to immortality or graceful ageing[1]. There is always a quest to understand the cognitive ageing process, which could be associated to a source of nectar or an organ that might be holding the key to ageing[2]. Different doctrines evolved in different times or in parallel; they all explored and tried to understand in their own way the process of ageing. In Ayurveda ageing is defined as *jara*; and there are reports about manageing the ageing process, suggesting how to decelerate the *jara* process. To understand this issue and its inherent complexity, we have mined the Ayurvedic literature and the associated as well as parallel concepts in the context of emerging scenario of gut microbiome. Further, we look into the prevailing doctrines and ask whether at any point, the modern way of understanding human physiology and the Ayurvedic concept – two independent ways of thinking processes – agree or overlap for a typical idea. We attempt to understand the key modulators associated with the ageing process. There are different options like adjusting the nutrition, lifestyle and/or using herbal preparations, which have helped in slowing down the ageing process[3–5]. Here, we discuss the ageing process in the light of gut microbiota (GM) interactions and its relevance to different organs.

Ayurvedic concept believes that the ageing process can be slowed down; in some cases, its reversal is also possible and this has been supported experimentally[6]. In Ayurvedic biology, *agni* includes all physiological processes that govern the vital body functions, including the maintenance of body temperature. *Pitta* is used as a synonym of *Agni*. Charaka has mentioned that *agni* in the body is implicit in *pitta*[7]. Sushrutra also has considered *pitta* of the body and *agni* as identical[8]. According to *Charak Samhita*, the physiological and clinically relevant functions are influenced by *pitta*. The balanced nature of *pitta* is responsible for a typical and characteristic behaviour of a person; it includes courage, cheerfulness, and lucidity of mind; according to Vagbhata, it also governs cognitive functions of the brain[9].

The question arises: where are the coordinates of *pitta*/*agni* located in the body, and what are the physiological parameters that collectively provide a typical condition of *pitta*/*agni*? The Ayurveda texts state that *pitta* is situated in the organ called *grahani*, which is situated below the stomach and above the large intestine. This means *grahani* is/could be small intestine. According to the Ayurvedic viewpoint, another important organ for metabolism is *yakrit*, that is, liver, which governs the three vital functions, viz. the *ranjak pitta*, *raktvaha srotas* and *raktadhara kala*. The *raktadhara kala* of the liver maintains the *rakta dhatu*, i.e. blood. This function empowers the blood for its proper functioning in different places of the body[10].

We propose that the *grahani* (small intestine) decides optimum physiology and plays as a key node of the ageing network, supported by the detoxification function of the liver. This nexus with other organs collectively modulates the ageing process.

The functioning of *grahani* involves the collective physiology or total gut ecosystem with specific microbiome that provides the additional extended genomic information which supports the overall metabolomics in humans. This association of genetic information gets disturbed in a scenario such as different diseases that could be of bacterial origin or due to clinical conditions such as hypertension, asthma or cardiovascular risks and others, including the physiological imbalances observed in older individuals[11–13]. This host and microbiome interaction leads to the generation of different types of metabolites, which are/can be used as disease-specific markers in diagnosis[14]. For different scenarios, the aberration or shift in microbiome could be studied; however, the issue remains – how do we define microbiome for healthy individuals with wide variations in genetic characteristics of the host? In the gut lumen, the microbiome, with the help of enzymes and juices released by the host, converts complex materials to secondary metabolites. The process also neutralizes any toxins which are ingested. However, sometimes the toxins are left as such, or compounds that could be deleterious are also produced as by-products of undesired physiology. Ayurveda defines that the partial hydrolysis/unregulated degradation of complex materials under a defined scenario leads to accumulation of deleterious compounds. This mixture of undesired intermediates results in the *ama*. These deleterious materials cannot be digested further or they are toxic in nature. This is also supported by Vagbhata that due to lower levels of *agni* the first *dhatu* namely *ras* is not properly formed; instead, the *anna ras* undergoes fermentation or putrefaction and is retained in the stomach. This state of *ras* is called *ama*. It has been suggested in the Ayurveda that the factors contributing to the ageing process could be directly proportional to the maintenance of *agni*, which is considered to be a vital biochemical process. The aberrations in *agni* lead to different *ama* compositions. The processed feed with variation due to *ama* affects the intestine that finally controls the downstream processes of *ras* generation.

The interspecies microbial interactions generate a series of signalling molecules, and in controlled experimental conditions, they have been shown to modulate the ageing process[15]. If we consider only the signalling molecule or bacteria influencing this signalling only, we may be ignoring the metabolic plasticity provided by the available metagenome associated with the gut. To understand the dynamics of change in interactions requires how the *ama* at different stages or different clinical scenarios changes the biochemical environment of the gut. Diet, lifestyle, and ageing have been shown to have a correlation. Experimental evidence supports the idea that controlled diet plans could delay the ageing process by a change in microbiota[16,17]. This can be extended further by understanding the microbiome in time series for an individual or different disease conditions, that provides insights regarding how to restore the healthy microbial population. Ayurveda believes that diet and environment influence the overall health status for an individual; and for any physiological corrections, it considers different perturbations that might

have taken place to generate *ama*. Similarly, it has been reported that the endotoxins generated by dead or live bacteria can trigger dysfunctions of the mucosal barrier, which can lead to translocation of undesired metabolites, toxins or even viable bacterial cells. This influences the local immune system in intestine and shift in microbiome structure with added clinical conditions[18–20]. This deleterious scenario could be defined as a part of *ama*. The change in the small intestine environment with ageing is an issue, which gets further complicated with different clinical conditions. Hence, to correct these situations, the concept of molecules as part of food supplement which supports 'good bacteria' in the gut, or directly using 'good bacteria' as part of the food supplement is emerging[21,22]. The question arises: are there only few 'good bacteria' that can decide the overall functional physiology of the gut that changes with age[23]. This diverse bacteria population provides the overall intelligence of the ageing physiology. It can be noted that this diverse bacterial population provides the overall intelligence required for the ageing physiology or it may be just adjusting to the changes made in the host physiological system. So, whether it is the few 'good bacteria' which can influences the overall proportion of different bacterial species residing in a specific host? So what could be the frequency of such supplements? Do such supplements protect a host against all sort of dis-regularized lifestyle scenarios? Thus this finally suggests us how to regulate or if possibly compromise with *ama* conditions, so that, what resides in the gut remains active are 'good microbiota'.

The liver has been shown to actively participate in the detoxification mechanism via cytochrome 450 systems[24]. The recent development shows that the gut microbiota and liver functions are related[25,26]. It has been reported that intestinal inflammation has a direct correlation with inflammatory liver disease[27]. By modulating the gut-associated immune system, which is highly influenced by gut microbiota, we can control both gut and liver inflammatory issues. This typically involves the down-regulation of expression of the NF-κB and pro-inflammatory cytokines[28]. Similarly, brain is the controlling organ which coordinates the expression of various functions for different physiological scenarios. For example, the brain serotonergic system can directly influence the expression of the cytochrome P450 system; an activation of this system represses the detoxification function[29]. The same system has also been shown to have a direct relationship with the brain–gut axis, where gut microbiome has a crucial role in the functioning of these interactions[30]. The brain–gut microbiome axis has now been postulated as controlling the metabolism of various signalling molecules and at the same time bidirectional modulating activity. This creates a coordinate linkage, which can modulate together functions of brain, liver and gut under the control of gut microbiome functional capacities.

We can summarize that gut microbiome plays a major role in the modulation of only the host gut physiology. Ayurveda considers that depending upon lifestyle every host feeds this population of diverse microbes with different levels and types of deleterious material, i.e. *ama* that influences the composition of the microbial population. Interestingly, it further believes that the *ama* condition could affect different parts of the intestine in different ways. At the same, it has been considered that different diseases have linkages with a different part of alimentary canal[31]. This raises a question whether there are different localized environments in the intestinal tract, which are created by differential biochemical properties. In such a scenario, the response of specific biochemical environment and its relation to differential localization of microbial community could be addressed. The intestinal organization, based on recent reports, does not directly suggest that there are different regions in the intestine, but it does suggest that there are three different pockets, which are defined with different microbial densities. These pockets with different densities and probably different community compositions could be the cause of varied biochemical environment and its involvement in synergistic activities with the host. These diverse activities are collectively responsible for the expression of intestinal cells, which includes immunomodulation to the generation of hormones to bridge the brain–gut axis.

The above discussion suggests that the intestine with its biochemical properties creates an environment for colonization of microbes. The collective intelligence of host–microbiome generates the biochemical signal, which is situation-specific. Any perturbation to this knowledge-sharing between host and microbes leads to a clinical scenario that sometimes is not acceptable to the host, this leads to a clinical condition with a shift in physiological activity. One of the simpler situations is time-dependent subtle stress to this synergistic association, which could be related to the ageing process. Ayurveda suggests *rasayan chikitsa* for reducing the rate of ageing. This rasayana treatment targets the *ojas* that is vitality of a person. There are many methods described in Ayurvedic texts which are person-specific, but each approach is through detoxification of gut which leads to re-establishment of *agni*. *Agni* is directly associated with a physiological status which can provide *ojas* to a person. At the same time, *agni* is also closely related to host–microbiome interaction. This suggests that host–microbiome interaction plays a significant role in deciding the *ojas*, which is directly linked to the ageing process.

In conclusion, there is a need to understand the stress or lifestyle-specific scenarios to define *ama* and *agni*. For the digestive system as a bioreactor, the feed quality varies with *ama* and influences microbial community dynamics. The additional variable parameter attributed to this reactor is the condition-specific secretions from the host and host genotype[32]. Therefore, to achieve the optimum steady-state conditions for this bioreactor, the *ama* generated should not influence the microbial community dynamics. This means that by regulating the *ama* at least through the feed, the ageing process can be influenced and maintain the *agni* for a person. Thus we propose that the modulation of ageing is through *grahani*, the intestine. The collective knowledge of host and microbiome plays a key role in the ageing process for defining the state of *agni*. Therefore, the dominating microbial community associated with different pockets of the intestine needs further exploration[33]. The *agni* which is associated with all the organs gets *ama*-free *ras* from *amasaya* and *grahani*. This nourishes subsequent *dhatus* which is finally responsible for the creation of *ojas* which is directly linked with longevity[34].

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