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## Review Article

## Evolution of dietary preferences and the innate urge to heal: Drug discovery lessons from Ayurveda

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## ABSTRACT

Highly specialized and functionally integrated cognitive systems facilitate hedonistic and healthy food preferences. Guided by survival needs, flavor preferences not only select safe, nutritious dietary components, but also those with negligible calorific value but significant health benefits, for example, spices. Feeding behavior, both innate and acquired, is guided not only by taste receptors on the tongue but also visceral organs. The gustatory cortex receives information from all senses, not just taste, suggesting multiple checkpoints in predicting and evaluating healthy foods. Ayurvedic interpretation of 'rasa' as chemistry is compatible with medicinal value of diets because, taste and odor are chemosensory perceptions. As flavor and taste are linked to the chemical structure of compounds, taste might offer clues about pharmacological activity. Ayurvedic idea of *vipaka*, or post digestive perception of taste, recognizes the extended role of taste receptors beyond the tongue and stretching into the viscera. Ayurvedic wisdom is consistent with evolutionary guideposts that suggest three successive stages of nutritional appraisal: before, during, and after ingesting food. While olfaction induces affinity or revulsion even before ingestion, gustatory receptors on the tongue evaluates nutritional value upon contact, and the chemoreceptors in the deeper metabolic systems probably pronounce the final verdict on the nutritive and health benefits of ingested substances. Alliesthesia, neophobia, and the extreme variation in human T2R genes (coding for bitterness receptors) illustrate the importance of adaptive learning of dietary preferences. These evolutionary clues are compatible with the Ayurvedic principle of 'rasa', in facilitating the process of drug discovery.

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## 1. Introduction

Despite human diets being richly diverse and sometimes mutually irreconcilable, (one man's meat is another man's poison!) cuisines all over the world are united in their purposes of nourishment and palatability. Humans have evolved highly specialized, functionally integrated cognitive systems that facilitate hedonistic food choices that nourish and endow health. Despite astounding cultural and geographical diversity, food preferences do share many universals. For instance, all humans crave for sweets and find toxins

bitter and offensive [1]. Natural selection favored the survival of those who derived pleasure and developed craving for the sweetness that characterize energy rich sugars. Similarly, those endowed with an instinctive aversion to bitterness were saved from poisons that are typically bitter. Basic instincts for food preferences partly explain the evolutionary mismatch that results in the high prevalence of contemporary illnesses like diabetes and obesity. Likewise, this article will try to explain how instinctive flavor preferences are in harmony with the Ayurvedic wisdom that produced a repertory of time-tested remedies.

## 2. How does the urge to heal shape nutritional choices?

Flavor preferences are not only directed towards selecting safe and nutritious food, but also employ the instinctive preference for dietary constituents with potential therapeutic value. Human cognitive skills evolved to identify and discriminate between molecules that can heal or harm. The urge to heal, intrinsic to all

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living creatures, manifests right from the molecular level; even the DNA is endowed with the devices for self-repair. Chimpanzees not only seek out and nibble on specific plants (e.g. *Vernonia amygdalina*) when they fall sick [2] but also learn the protective effect of alkaloids against parasitic infections. Chimps also eat clay, which adsorbs tannins that cause gastrointestinal problems by binding to proteins. In short, dietary phytochemicals and minerals can elicit a wide variety of perceptual, cognitive and behavioral responses in both human and non-human primates [3].

Although food preferences evolved primarily to select for safe and nutritious high calorie foods, several natural products with negligible calorific value (e.g. spices) have been selectively and judiciously incorporated into diets. There is no exaggerating the importance of spices; wars have been fought to control its trade. Most spices are rich in plant secondary metabolites that possess anti-microbial, anti-oxidant, gastro protective, anti-inflammatory and anti-hypertensive effects that promote survival [4,5]. A study by Lv et al. demonstrated that increased consumption of spicy food reduces mortality due to cancer, cardiac and respiratory diseases [6]. The lower prevalence of Alzheimer's disease in India may be due to the high consumption of dietary turmeric [7]. Interestingly, many such dietary phytochemicals are unpalatable at high concentrations that could be toxic. All dietary preferences are guided by safety, which is why dietary salt is indispensable at optimum concentrations but extremely offensive in excess. Likewise, the minimal taste threshold of spices prevents us from consuming toxic doses. Spices are effective against common food-borne microbes like *Escherichia coli*, *Shigella*, *Salmonella*, and *Clostridium* etc. When used in combination, spices exhibit synergism in their antimicrobial property [8]. The antimicrobial property of spices must have played a protective role, particularly in tropical diets, because the latitudinal gradient corresponds well with the spiciness of cuisines [9].

Many plant secondary metabolites are perceived as bitter because bitter principles primarily evolved to serve as a defense against herbivores [10]. However, during the evolutionary course of cognitive sophistication, humans evolved taste preferences which help identify the therapeutic value of molecules with a bitter taste. Detection and perception of tastes involve multiple sensory and behavioral systems in which the taste receptor on the tongue is only a part. One important principle in the evolution of hedonistic taste preferences is the ability of the brain to connect and remember the chemical properties of the ingested material with its value to health.

### 3. Detection and perception of taste

Distinct G-protein coupled receptors identify different tastes such as sweet, umami, sour, salt and bitter. T1R1/T1R2 receptors recognize sweetness and T1R1/T1R3 identify L-amino acids, L-glutamate in particular. Another group of receptors named Epithelial Sodium Channel (ENaC) detect salt. The group of T2Rs is linked to bitter taste. Acid sensitive Ion channels (ASICs) respond to sour taste. Taste perception in the tongue prepares the body metabolism to receive and digest food [11]. Taste receptors are not restricted to the tongue but are also present throughout the body, e.g., stomach, intestine, pancreas, respiratory tract and sperm [12]. T2Rs, present in the human airway smooth muscles, react to potentially harmful inhalants, and respond by eliciting a protective reflex by constriction of airway smooth muscles [13]. T1R1/T1R3 umami receptors are present in human spermatozoa and have been found to play an important role in acrosome reaction [14]. Taste receptors in the gut (expressed by entero-endocrine cells in intestinal epithelium) regulate feeding behavior via neuro-endocrine pathways and enhance nutrient absorption [11]. T1R2/T1R3 and GPR92 receptors in the stomach detect sugar and peptides and

regulate secretion of gastric hormones such as ghrelin, somatostatin, and gastrin. In duodenal L-cells T1R2/T1R3 and  $\alpha$ -gustducin receptors help regulating glucose level and satiety via GLP-1 secretion [15]. The distribution of various taste receptors in the gut and their role has been reviewed by Ref. [16]. Apart from this, taste receptors are also present in brush cells of gall bladder and bile duct, though their function is still unknown [17].

Taste receptors on the tongue inform the brain about the chemical composition of food, preparing the body to select nutrients by both learned and instinctive responses. Unlike the taste receptors on the tongue, visceral taste receptors in the gut can transduce nutrient signals to the brain (through neuro-peptides and vagus activation) and modulate appetite and metabolism [18]. A study in rats showed that non-nutritious but highly palatable food was acceptable only for a limited period of time, after which rats began to reject it. On the other hand, rats acquired learned preferences towards distasteful but nutritious food. While nutritional value nurtures the development of learned food preferences, faking a favorable taste for non-nutritious food does not endure the test of time. In other words, visceral appraisal (subconscious) of dietary principles can overwhelm gustatory preferences (conscious). Studies show that sucrose elicits a reward pathway in the brain, inducing satiety and suppressing feeding behavior. On the other hand, artificial sweeteners alter the reward pathways, promoting feeding and obesity [19,20].

Taste receptors in the gut also regulate nutrient transporter expression and nutrient uptake, thereby playing an important role in energy and glucose homeostasis. A better understanding of the interplay between the multiple signaling pathways of gustatory and visceral taste receptors would not only throw light on complex pathological conditions such as diabetes and obesity but also aid drug discovery [16]. For instance, bariatric surgery – but not gastric banding – has been found to decrease the preference for sweet foods, probably because of the surgical removal of visceral taste receptors [21].

### 4. Development of flavor preference

Human food preferences are both innate and acquired. Functional developments of olfactory and gustatory perception begin in the first trimester of pregnancy. During late gestation, fetus shows specific responses to tastes in the amniotic fluid. Even newborns show different responses to different tastes. After birth, food preferences are altered by factors such as age, health status, socioeconomic condition and culture. Neurobiology of taste receptors and the development of flavor memory also contribute to acquired food preferences [22]. Gustatory preferences are guided by two important factors namely nutritional value and safety. Flavor memory plays an important role in the fixation of gustatory preferences from early life. Aversion is as crucial to the shaping of food preferences as craving. Aversion towards spoiled or contaminated food is called '*Sauce-Bearnaise effect*' or '*Gracia effect*'. Innate and learned gustatory preferences also play a role in avoiding unfamiliar and inappropriate foods [22]. Humans, irrespective of culture, avoid unfamiliar foods (neophobia). This phenomenon is also observed in rodents and is called *bait shyness* [23]. Neophobia must have augmented survival by preventing the ingestion of potentially harmful substances that are relatively uncommon in a given environment. If a preferred flavor is followed by an illness, we tend to develop an aversion towards it. On the other hand, we tend to develop an affinity towards flavors that are associated with the recovery from illness. This phenomenon is termed as 'alliesthesia' [24]. Food aversion can develop if nausea is induced after ingestion. There is a visceral basis to alliesthesia; ingested food moving past the duodenal chemoreceptors can affect the perception of taste.

The receptor T2R, associated with the perception of bitterness, influences the selection and incorporation of plant secondary metabolites in the diet. Studies have shown that primates are less sensitive to bitter taste than other mammals. The increased amino acid substitution in T2R genes of primates is probably guided by the natural selection of dietary preferences. Human populations differ more with respect to T2R genes than other regions of the genome. Prevalence of malaria in African populations is inversely correlated to their sensitivity to bitter taste. Diminished perception of bitterness towards anti-malarial phytochemicals has probably encouraged these populations to ingest plants that protect them from malaria [25]. Humans have a quinine taste threshold of 8  $\mu\text{M/L}$  while non human primates have quinine threshold values ranging from 0.8 to 800  $\mu\text{M/L}$ , reflecting the diversity of adaptation to different nutritional environments [26].

Taste perception has also been causally linked to nutritional choices that spur adaptation and eventually lead to speciation. For instance, adaptive changes in taste receptor functions are believed to have transformed insectivorous ancestors into nectar-feeding humming bird species [27].

## 5. Diet and the epigenome

Nutritional impact goes deeper, even up to the level of gene expression through heritable epigenetic modifications. Diet during pregnancy being critical in controlling fetal gene expression, food preferences are altered during pregnancy. The extreme vomiting in pregnant women helps avoid dietary teratogens. Craving for non-food substances like earth, clay, chalk, etc. arise during conditions like pregnancy. Geophagia and pagophagia, commonly observed during pregnancy, are attributed to iron deficiency anemia [28,29]. Geophagia is encouraged among women in Nigeria owing to the anti-diarrheal property of clay [30].

Diet is one of the most important environmental factors affecting the epigenome. Dietary constituents such as folic acid, Vitamin B, methionine etc., are involved in the direct transfer of methyl group to the epigenome. Many modern diseases such as cancer, metabolic syndrome, auto immune disorders, and neurodegenerative diseases are also associated with epigenetic changes. Epigenetic implications in cancer are well known. Many enzymes involved in the epigenetic modifications are important drug targets [31] (e.g. HDAC inhibitors, DNMT inhibitors etc). Several dietary phytochemicals are known to be effective in treating cancer. The pleiotropy of dietary phytochemicals such as curcumin, epigallocatechin, resveratrol could be partly due to their epigenetic effects [32].

Innate food preferences, combined with the extended phenotype, in the form culture, assist adaptive learning of healthy dietary preferences. This is called Baldwin effect. As healthier diets promote greater reproductive success, this pseudo Lamarckian inheritance pattern underscores the importance of culture in culinary preferences. Baldwin effect implies that phenotypic plasticity, endowed by adaptive learning of dietary preferences, can be passed on to the next generation. Learned behavior being more flexible than instinctive behavior, organisms can adapt easily to the changing environments, thereby accelerating the rate of evolution. Baldwin effect also takes into account the costs and benefits of learning. The heritability of learned behaviors can also be attributed to epigenetic modifications that can be passed on to the next generation. The French paradox is an illustrative case of how acquired food preference and its inheritance through culture can promote health and survival [33].

## 6. Lessons from Ayurveda

In Ayurveda, taste or *rasa* of a given medicine is associated with its curative potential. '*Rasa*' also means chemistry. *Rasa* is not

limited to the taste experienced by the tongue. It is the wholesome feeling generated by a combination of individual perceptions that include sensations by the taste buds, in addition to what is picked up by the chemesthetic receptors of retronasal, olfactory and visceral body compartments. While *Rasa* is described as the experience when a substance comes into contact with the tongue, *anurasa* represents the perceptions that occur afterwards [34].

It is therefore unlikely that the Ayurveda missed the connection between the chemistry of the substance and its taste. The idea of *vipaka*, or post digestive perception of taste, at least in principle, recognizes the extended role of taste receptors beyond the tongue and stretching into the visceral domain. How Ayurveda interpreted this principle, based on personal experiences of the *acharyas*, is a matter of conjecture. However, Ayurvedic descriptions of *rasa* and *anurasa* in the context of *vipaka* appear to have predicted an extended role for gustatory and olfactory senses in shaping dietary preferences [35]. The same principles were probably extrapolated in the selection of appropriate herbs for a spectrum of illnesses. In the absence of analytical techniques, the chemo receptors of smell and taste should be considered the most appropriate indicators of a compound's biological value to health. The elaborate sensory systems for the appraisal of taste and flavor, engineered by the overwhelming urge to survive and procreate, must have played a role in the instinctive choice of medicinal herbs in native medical systems like Ayurveda.

As the biological perception of flavor/taste/*rasa* is linked to the structure and reactivity of a molecule, taste is a plausible predictor of enzymatic interactions and pharmacological activity [36]. In Ayurveda, *Gurvadi gunas/Guna* describe the physical properties and pharmacological aspects of the drugs and facilitate prediction of drug activity [37]. Therefore, understanding the Ayurvedic principles such as *rasa* (taste), *viryā* (potency), *vipaka* (bio transformation) and *guna* (drug activity) could play a supportive role in predicting the pharmacodynamic and pharmacokinetic properties of drugs [34,37].

## 7. Discussion and conclusion

As nutritional prudence is the *sine qua non* for survival, it is not surprising that the gustatory cortex receives information from all senses, not just tongue, suggesting multiple checkpoints in predicting and evaluating nutritive/health value of foods [38]. It is possible that three successive stages of appraisal, namely, before, during, and after ingesting food, should have shaped evolutionary fitness during natural selection. Starting with prokaryotes and culminating in humans, this cognitive sophistication is primeval, instinctive, elaborate and precedes sexual selection. While the gustatory and olfactory senses offer a preliminary conscious assessment, visceral responses from internal chemoreceptors supervened whenever metabolic exigencies imposed a moderating role. Olfaction helped generate affinity or revulsion even before ingestion. Gustatory receptors on the tongue assess nutritional value upon contact, and the chemoreceptors deeper down in the metabolic systems probably pronounce the final verdict on the nutritive and health benefits of whatever is ingested and processed. Thus olfactory, gustatory and the visceral chemoreceptors probably operated (with considerable flexibility) at three successive checkpoints, perfecting feeding behavior for maximizing survival in a constantly changing environment, both internal and external. The Ayurvedic wisdom, consistent with evolutionary guideposts, possibly exploited the most sophisticated and maximally individualized analytical chemistry methods available by borrowing from life experiences.

The current paradigm of allopathic drug discovery is based on xenobiotic small molecules addressing individual targets in

isolation. Although high potency and extreme target specificity are considered foremost requirements of a successful novel drug molecule, we often find drugs being withdrawn from the market. Quite by contrast, very old drugs like metformin and aspirin, with very low potency and considerable pleiotropy, have stood the test of time. The shift towards biologicals, though more recent, still continues to treat the body as a machine consisting of many parts. This idea mostly ignores the passage of evolutionary history behind our present form. Not all parts/systems of the body are equal in their phylogenetic maturity. Some are more recent than the other in evolutionary timescale. For instance, cellular processes such as metabolism and energetics are robust, precise, efficient and time tested. Such systems are the result of many hundreds of millions of years of natural selection [39]. Hence, these systems are difficult to manipulate without disturbing homeostatic equilibrium. Health and disease need to be understood in the context of evolution, which is not yet the case in modern medicine [39,40]. Moreover, Ayurveda is more personalized in its approach while allopathic medicines mostly ignore individual variations. Differences in ethnicity, genes and diet can lead to differences in pharmacodynamics, pharmacokinetics, and drug-resistance.

Ayurvedic drugs depend less on xenobiotics and draws more from nature and the principles that are fundamental to nature. Ayurveda, by deciphering chemistry through '*rasa*', is closer to a human interpretation of therapeutic worth. Being empirical, allopathy gives excessive importance to the mechanism of action, only to learn much later that there could be dangers that have escaped attention. Therefore, it might be a good idea to borrow from Ayurvedic principles during the process of modern drug discovery. It is also important for modern science to work closer with Ayurvedic practitioners for greater application of the principle of *rasa* in therapeutics. The evolutionarily robust taste perception and food selection can give valuable clues in the search for new drugs. In Ayurveda, taste (*rasa*) and physical properties (*guna*) can predict the drug activity and help in drug discovery from natural products.

In retrospect, it is therefore not surprising that 50% of the drugs approved by the FDA over the past three decades are derived directly or indirectly from natural products and native systems of medicine. Moreover, nearly 75% of drugs for cancer approved between 1940s and 2010 are derived from natural products [41]. On the other hand, combinatorial chemistry and high throughput screening systems have yielded next to nothing [42]. Evolutionarily privileged molecular scaffolds of natural products bind multiple protein targets and exhibit extensive pleiotropy. Molecules from nature bear much greater resemblance to endogenous metabolites/intermediates/receptors/modulators than synthetic molecules [43]. The recent Nobel Prize for artemisinin reiterates the value of learning from nature.

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### Conflicts of interest

None.

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