

### **Metabolomics of Taste**

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Recent advances in understanding the molecular basis of taste physiology opens new opportunities to optimize in cellular agriculture. This is particularly relevant at a time when alternative ingredients and processing (e.g. 3D printing) are being increasingly used, potentially altering the digestibility and acceptability of alternative diets, even if they are nutritionally balanced. The molecular characterization of taste receptors reveals common taste discrimination mechanisms, common structures within taste groups leading to predictability of a taste profile from metabolite profiling.



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**Taste** is an important part of our perception of foods. Taste perception in humans is considered to consist of five canonical basic taste qualities: Sweet, Sour, Salty, Bitter, and Umami. These 5 basic taste qualities interact in almost every consumed food. The primary function of taste is to identify substances that lead to energy and/or electrolyte balance, while avoiding ingestion of toxic substances. Taste can also serve a metabolic function by preparing the body to assimilate ingested nutrients more effectively. Taste interactions can either be enhancing or suppressing, depending on both the taste quality, specific tastants (those metabolites that enduce a flavor response) and tastant concentrations. These interactions are complex and, even though the interactions between tastes have been extensively researched and reviewed, the mechanisms are still not well understood. However, we continue to learn more about tastants and how changes in a tastant profile lends to changes in food flavor.

Skeletal muscle metabolites found in beef, chicken and fish include amino acids and sugars that are precursors of volatile compounds associated with aroma. Muscle metabolites are useful indices to predict or evaluate meat flavor and overall palatability. Metabolic profile comparisons between meats of different animal breeds, feeding conditions, and cellular processes can indicate changes in taste profiles. Studies reveal that metabolomic information is expected to provide indices to predict sensory phenotypes of meat.





**Bitter, sweet, and umami receptors** are well understood. The receptors for each of these taste qualities are, by and large, restricted to a single cell types within the taste bud, allowing encoding of information by activation of unique populations of cells. One misconception is that taste receptors are only in the taste buds in the oral cavity (Figure 1). In fact, taste receptors are distributed throughout the body from the nasal cavity to the intestines.

Taste signals are mediated by distinct transduction pathways (Figure 2) expressed in subsets of taste receptor cells. Specifically, sweet and umami tastes are detected by the G proteincoupled receptor (GPCR), T1R family. Umami is detected by metabotropic glutamate receptors. Bitter taste, on the other hand, is detected by GPCR T2R family. Sour and salty tastes are modulated by specialized membrane channels. For sour taste, acid sensing ion channels and for salty taste, epithelial sodium channel facilitates its detection. The out puts of these taste receptors include ATP and neurotransmission through the gustatory nerves.







### Sweet, Bitter & Umami Tastants

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# SWEET



**Sweet taste** receptors (Figure 3) are composed of a heterodimer of taste 1 receptor member 2 (T1R2) and taste 1 receptor member 3 (T1R3). Accumulating evidence shows that sweet taste receptors are ubiquitous throughout the body, including the gastrointestinal tract and the hypothalamus. These sweet taste receptors are heavily involved in nutrient sensing, monitoring changes in energy stores, and triggering metabolic and behavioral responses to maintain energy balance. Not surprisingly, these pathways are heavily regulated. Dysfunction in one or more of these pathways may be important in the pathogenesis of common diseases, such as obesity and type 2 diabetes mellitus.



The receptor tastant pathway for sweetness has been extensively studied. Binding of a ligand to the sweet taste receptor leads to activation of the heterotrimeric G-protein  $\alpha$ -gustducin. Phospholipase C  $\beta_2$  is subsequently stimulated, leading to release of intracellular Ca<sub>2+</sub> and activation of the transient receptor potential cation channel M<sub>5</sub> (TRPM<sub>5</sub>). This sequence results in the release of ATP, which can then activate adjacent sensory afferent neurons that send signals to brain centers involved in taste perception.

Sweet tastants include simple sugars (glucose, fructose, sucrose, maltose and sucralose), artificial sweeteners (e.g., saccharin, aspartame, cyclamate), sweet amino acids (D-tryptophan, D-phenylalanine, D-serine), and sweet proteins (monellin, brazzein, thaumatin). The recognition thresholds for sweet substances are tightly linked with the circulating hormone leptin levels

Endocannabinoids also likely enhance taste cell responses to sweeteners. These findings suggest that endocannabinoids may enhance sweet taste response in sweet taste cells expressing T1R3.

A growing number of studies have demonstrated that sweet taste receptors are expressed throughout the body, including the nasal epithelium, respiratory system and pancreatic islet cells. The function of the sweet taste receptor system in the gastrointestinal tract is likely involved in nutrient sensing, glucose homeostasis, as well as secretion of GI peptides.

The sweet taste is appetitive – meaning sweetness can increase our appetites for calorie rich foods, like sugary carbohydrate containing fruit.







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### Umami Taste

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# UMAMI



**Umami** or savoriness taste is elicited by many small molecules, including the amino acid (L-glutamate) and nucleotides (inosine 5-monophosphate (IMP) and guanosine- 5-monophosphate (GMP)) through taste receptors (Figure 4). Umami tastants are widely present in meat broths and fermented products. Some amino acids are sweet or bitter, however, take on an umami flavor when IMP or GMP is present. The umami taste is often described as a meaty, broth-like, or savory taste, and is independent of the four other traditional basic tastes — sweet, sour, salty and bitter. Meaning high levels of umami flavors. As a tomato ripens, the natural content of L-glutamate increases and the tomato becomes more tasty. Similarly, as cheese matures, there is a significant increase in L-Glutamate which contributes to the taste. Kombu (Asian Kelp or brown seaweed) is also high Umami flavor. Kombu is source of L-glutamic acid, iodine and fiber. Umami is thought to evolve as an indicator of healthy food since many of the umami tastants come from protein and a diet high in protein is very desirable.



The taste receptors (Figure 4) responsible for the sense of umami include glutamate receptors mGluR4, mGluR1, and taste receptor type 1 (TAS1R1 + TAS1R3), all of which have been found in all regions of the tongue bearing taste buds. These receptors are also found in some regions of the duodenum.

Receptors mGluR1 and mGluR4 are specific to L-Glutamate whereas TAS1R1 + TAS1R3 are responsible for the synergistic responses. However, the specific role of each type of receptor in taste bud cells remains unclear. They are G protein-coupled receptors (GPCRs) with similar signaling molecules that include G proteins beta-gamma, PLCB2 and Pl3-mediated release of calcium (Ca2+) from intracellular stores. Calcium activates a so-called transient-receptor-potential cation channel that leads to membrane depolarization and the consequent release of ATP and secretion of neurotransmitters including serotonin. Cells responding to umami taste stimuli do not possess typical synapses, but ATP conveys taste signals to gustatory nerves and in turn to the brain that interprets and identifies the taste quality via the gut-brain axis.

In 2006, a Japanese research team found the glutamate receptor type 1 variant (mGluR1), in stomach tissue. As the umami taste sends signals to the brain through the taste nerves after activation of its receptors on the tongue, umami receptors in the stomach also send signals to the brain via the vagus nerve. The vagus nerve is the nerve that transfers sensory information of ingested foods from various alimentary organs, including the stomach, to the brain to regulate digestion of food. Upon receiving those signals, the brain responds by preparing the stomach for the digestion of food taken into the body via other nerve fibers of the vagus.

While L-Glutamate is associated with umami flavor, the optical isomer, D-Glutamate, is more associated with sour taste. L-Glutamate containing peptides have also been associated with umami flavor depending upon amino acid sequence. However, gamma-Glu dipeptides are associated with Kokumi flavor and para-glutamate peptides with sweet.

Umami is appetitive encouraging consumption of savory, protein rich meat sources.



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### **Bitter Taste**

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# BITTER



**Bitter taste** is thought to guide organisms to avoid harmful toxins, noxious substances, unsafe or unripe foods and thus is critical to human survival. Bitterness could suggest rotten meat. The T2R bitter receptors also play in processes as diverse as innate immunity, secretion, contraction, and reproduction. Like other unpleasant tastes (sour, salty), some bitter taste is acceptable and part of healthy diet flavor, however, high levels of bitterness would suggest unsafe or rotten food.

The sensors for bitter compounds (T2Rs or TAS2Rs), are a class of GPCRs originally identified in type II taste receptor cells in the taste bud (Figure 5). Humans possess 40 to 80 different types of bitter taste receptors.

The bitter receptor, T2R38, is also expressed in the cilia of human sinus epithelium. It is activated by microbe-derived quorumsensing molecules (e.g., acyl-homoserine lactones [AHLs]) generating nitric oxide, a potent bactericide and releases antimicrobial peptides. Hence bitterness warns of both rotten food, as well as, food with high amounts of bacteria.

Alkaloids, quinine, sulfamides, and caffeine are among the most of bitter substances with extremely low taste <u>thresholds</u> and are detectable in very low concentrations. The size of such molecules is one aspect to account for degree of bitterness. An increase in length of chains of carbon atoms in organic molecules tends to be associated with increased bitterness Due to the number and complexity of bitter related receptors, bitter chemicals cover a large range of chemical classes.

Because drugs are often bitter to the taste, quite a bit has been studied to understand bitterness. In fact, a bitter database exists (//bitterdb.agri.huji.ac.il) and a bitterness prediction tool (*Sci Rep* **7**, 12074 (2017). BitterPredict suggests that about 40% of random molecules, and a 66% of clinical and experimental drugs, and of 77% natural products have bitterness. The high percentage of predicted bitter compounds in this set suggests that bitter taste may be among the most abundant tastes encountered in nature. Food ingredients represented in the food data base, (<u>https://foodb.ca</u>) are predicted to include 38% bitter compounds suggesting bitterness as a critical factor in a healthy diet.

Aside from alkaloids and important bitter tastants, peptides represent a large and growing list of bitter tastants. Bitter peptides are a structurally diverse group of oligopeptides often generated in fermented, aged, and hydrolyzed food products that make them unfavorable for consumption. Knowledge of the structural features of bitter receptors and of the factors that stimulate bitter receptors will aid in understanding the mechanism responsible for bitter taste perception.









### **Bitter Genetics**

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Genetics of bitter taste detection (reference: 23AndMe).

The **TAS2R38 gene** codes for a protein within the bitter taste receptor, that can detect the bitter chemical called PTC. PTC isn't usually found in the human diet, but it is similar to chemicals present in vegetables like broccoli and brussels sprouts. People with the G variant have a taste receptor that can detect these PTC-like chemicals. This means people with the G variant may taste bitterness in these foods and avoid them all together.

Genetic predictions:

Genetic result "GG" or "GC" means individual is likely **able to** detect certain bitter tastes. Genetic result "CC" means individual is likely **unable** to detect certain bitter tastes.

Humans aren't the only ones with food preferences related to genetics.

**Giant pandas** cannot detect umami taste because their umami taste receptors don't work properly. This means they can't taste meatiness, and don't show a preference for meat. Scientists believe this explains their strict bamboo diet, despite being genetically a true bear.











### Salty & Sour Taste



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# SALTY



The **salty taste** is mediated through the epithelial sodium channel, ENaC, which serves as the salty receptor. ENaC is co-expressed with the voltage-activated ATP release channel CALHM1/3 in a subset of taste cells and that these cells mediate the salty taste. The degree of saltiness decreases in the following order: ammonium (most salty), potassium, calcium, sodium, lithium, and magnesium (least salty).

Na<sup>+</sup> Sodium Ion (Salty)

The degree of saltiness is evolved as either a good or unpleasant taste. Sodium is an essential nutrient, so some saltiness is necessary and sought in flavor. Our bodies use salt (largely as sodium chloride) to regulate fluids and to create nerve impulses. Yet unlike other vital minerals, such as calcium (which we store in our bones), we can't store salt for later use. However, too high saltiness is unpleasant and acts as a consumption warning. Too high salt is not healthy. Drinking sea water will kill you, and a diet with consistently too much salt has been linked to heart attacks, stroke, and high blood pressure. A high salt diet also puts heavy a burden on your kidneys and can lead to painful kidney stones.

**Sour taste** is considered the simplest of the basic tastes because it is elicited only by hydrogen ions. However, there is not a clear understanding of that relationship to allow sour taste intensity to be predicted and rationally modified in foods. The intensity of sour taste perception is related to the molar concentration of all organic acid species. Acids are detected by the type III taste receptor cells (TRCs). The first step in sour taste transduction is believed to be entry of protons into the taste bud cell, which leads to acidification and the generation of action potentials.



While sour receptors are yet to fully delineated, studies suggest that 4 carbon diacids (Fumarate, Succinate, Itaconate, D/L-Malate and Tartaric) have a higher sourness score than smaller or larger common acids (Citrate, lactate, Levulinate, Sorbate) and higher scores than D-Glutamate and N-AcetylGlutamate. The sugar (Galactouronate) has a higher sourness score than lactones Gluconolactone, D/L-Ascorbate, Ribonolactone and Galactononlactone.

Sourness has also evolved as a test of food value. Ripe fruit has just the right amount of sourness when ready for consumption. Sour taste is acceptable when mild, but becomes unpleasant when strong. It helps us to avoid unripe fruit and damage our tissue with acids. For example, too much lactic acid may suggest milk has gone bad or spoiled.



SOUR



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### **Other Candidates for Flavor Sensors**

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#### **OLEOGUSTUS, OILY OR FATTY TASTE**

Lipid sensors have been identified on the tongue which suggests that fat can be considered as the sixth taste. People can identify the distinct taste of fat as something totally separate from its texture. While the pure flavor of fat might sound delicious, it's not. Oleogustus is described as "unpalatable," "rancid" and "irritating." when it's tasted on its own. However, combined with other flavors, oleogustus can be delicious. Fatty taste itself is not pleasant. When concentrations of fatty acids are high in a food it is typically rejected, as would be the case when a food is rancid. Long chain nonesterified fatty acids (LC-NEFA) are proposed as stimuli for "fat taste". While shorter chain fatty acids (2 to 5 carbons) stimulate a sensation similar to sour and middle chain fats (6 to 12 carbons) to provide a more complex flavor. In general, as chain length increases to long chain (13 to 21 Carbons) this sensation changes to an oleogustus taste.



#### **KOKUMITASTE**



Kokumi is another putative taste quality gaining interest in the field of sensory sciences. Kokumi is a well-accepted taste sensation in Asian cuisine. It is described as a sensation of enhancement of sweet, salty and umamitastes when associated with specific compounds

The human Calcium Sensing Receptor (CaSR) has been designated as the putative kokumi taste receptor for humans. CaSR is a member of the same receptor class as the T1R receptors for umami and sweet taste, the class C of GPCRs. CaSR has been found to be expressed in most tissues involved in calcium homeostasis e.g. the parathyroid glands, kidneys, thyroid and the brain, as well as the gastrointestinal tract and taste papillae (Figure 1). It is also known to be involved in many physiological processes including, gastric acid secretion, insulin release from beta-cells in the pancreas and promoting glucose tolerance, as well as, pathophysiological processes such as vascular calcification and osteoporosis.

γ-glutamyl peptides have been identified as a primary tastant for Kokumi and for agonist activity against hCaSR. Like Umami, kokumi is an important taste modality for carnivores that enhances the palatability of meat-derived compounds such as peptides and amino acids.

#### STARCHINESS OR STARCHY TASTE

It is widely accepted that humans can taste mono- and disaccharides as sweet substances, but they cannot taste longer chain oligo- and polysaccharides. From the evolutionary standpoint, the ability to taste starch or its oligomeric hydrolysis products would be highly adaptive, given their high nutritional value. Glucose oligomer detection (7 to 14 glucose units) is found to be independent of the  $T_1R_2/T_1R_3$  sweet taste receptor. Because starch is one of the primary sources of energy that enables the body to perform its function, its gustatory detection would be highly beneficial. Large glucose oligomers and polymers (e.g. starch) can be detected through the gustatory system, independent of the sweet taste, when starch is broken down into smaller glucose oligomers by an enzyme in our saliva called alpha-amylase. These smaller glucose oligomers can be tasted by specific receptors. The taste of these glucose oligomers is cereal-like, bread-like or rice-like and generally referred to as "starchy".





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### **Tastomics of Meats**



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Skeletal muscle characteristics are designed by a functionally cooperative set of genes specific to the spatiotemporal requirement in each muscle. Gene expression is further modulated at levels of transcription, post-transcription, translation, and protein modification during development, growth, and maturation stages of the muscle or muscle cultivate. Accordingly, muscle metabolites determine the physiological muscle characteristics and meat quality traits as the major phenotypic components. Hence each type of meat muscle (e.g. Fish, chicken, beef) has its own metabolic, nutrient and tastant profile conditional to its source and generation. Although often meats are cooked and seasoned as food, the end product is heavily influenced by the raw muscle tastant combinations and metabolic profiles.



#### **TASTOMICS OF FISH**

Fish live in a totally foreign environment than beef and chicken. High levels of osmolytes are required to maintain cellular osmotic pressure which can bring a bitter taste. High levels of fats are required for thermal homeostasis bringing in a fishy or fatty taste. The taste active components of fish also include high amounts of amino acids like glutamate (umami), glycine (sweet), alanine, arginine and proline and nucleic acids like nucleotides inosine 5'-monophosphate (IMP), adenosine 5'monophosphate (AMP), guanosine 5'-monophosphate (GMP) are also in fish muscle. Acids (sour) such as lactate and succinate are important contributors to the taste of raw and processed fish products. L-Glutamate contributes to umami taste intensified by the co-existence of IMP, GMP and AMP. However, a large amount of alanine or glutamate can suppress the sweetness effect of glycine through antagonistic effects. Hence a balance of these amino acids, nucleotides and fats lends to the taste perception in fish products.



#### **TASTOMICS OF BEEF**

When you are craving meat, most likely what you're really craving is fat. The unique mixture of fat and umami, a savory taste, creates a particular texture of creaminess and juiciness within meat. Inosinate (a nucleoside found in meat and fish) and guanylate (like in dried mushrooms) contribute to that umami taste. When a number of these substances combine, the umami taste intensifies to what chefs are calling a "u-bomb." Beef muscle is also high in fat content, that can contribute a fatty taste or oleogustus flavor. Alanine, Glutamate and Ser are the major amino acids that can also contribute to flavor in beef products.



#### **TASTOMICS OF CHICKEN**

Chicken has a higher level of D-amino acids than beef and fish adding a higher sweet contribution from these amino acids than the more bitter amino acid levels found in beef and fish. Studies have suggested that chicken breast muscle taste differences are caused by the altered metabolism of carbohydrates, protein and amino acids, combined with fatty acid oxidation products. Discriminators in chicken meat flavors may include branched chain amino acids, histidine, creatine, beta-alanine, long chain fatty acids, carnitine, carnosine and anserine. Increases of alanine, serine, glutamate, taurine, and leucine are particularly notable for adding favorable taste through combination of sweet and umami flavors.









### Amino Acids & Taste Reference Chart



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Amino Acids	D Taste	L Taste	L form with IMP/GMP Enhancement
Arginine	Bitter	Bitter	
Isoleucine	Bitter	Bitter	
Lysine	Bitter	Bitter	
Ornithine	Bitter	Bitter	
Methionine	Bitter	Bitter	
Tyrosine	Bitter	Bitter	
Proline	Bitter	Sweet	
Hydroxy proline	Bitter	Sweet	
Glycine	Sweet	Sweet	Added Umami
Asparagine	Sweet	Bitter	
Histidine	Sweet	Bitter	
Leucine	Sweet	Bitter	
Phenylalanine	Sweet	Bitter	
Tryptophan	Sweet	Bitter	
Valine	Sweet	Bitter	
2-Aminobutyrate (abu)	Sweet	Sweet	
Alanine	Sweet	Sweet	Added Umami (Only L)
b-Alanine	Sweet	Sweet	
Glutamine	Sweet	Sweet	Added Umami
Serine	Sweet	Sweet-umami	Added Umami
Threonine	Sweet	Sweet	
Aspartic acid	Sour, Salty	Sour, Bitter	Added Umami
Cysteine	Sour, Bitter	Sulphurous	
Glutamic acid	Sour	Umami	Enhanced Umami
Succinyl-Arg		Umami	
Succinyl-Glu		Umami	
GABA		Bitter	
Carboxymethyllysine (CML)		Bitter	
Frucosyl-Val		Bitter	







### Peptides & Taste Reference Chart



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Peptides	Taste	Peptides	Taste
Glu-Trp	Bitter	Val-Asp	Bitter/Umami/Sour
Glu-Tyr	Bitter	Val-Glu	Bitter/Umami/Sour
Glu-Phe	Bitter	Glu-Glu	Umami
Glu-Gly	Bitter	Glu-Asp	Umami
Glu-Thr	Bitter	Glu-Ser	Umami
Glu-Val	Bitter	Glu-Asp-Glu	Umami
Gly-Val	Bitter	Glu-Gly-Ser	Umami
Gly-Gly-Val	Bitter	Asp-Glu-Ser	Umami
Gly-Val-Val	Bitter	Thr-Glu	Umami
Val-Val-Val	Bitter	Ala-Glu	Umami
Val-Leu	Bitter	Val-Gly	Umami
Val-Ile	Bitter	Val-Gly-Gly	Umami
Val-Phe	Bitter	Val-Val	Umami
Val-Ile-Phe	Bitter	Glu-Gln-Glu	Umami
Leu-Val	Bitter	Ser-Glu-Glu	Umami
lle-Val	Bitter	Fructosyl-Glu	Umami
Phe-Val	Bitter	Asp-Val	Sour
Phe-Ile-Val	Bitter	Gly-Val	Sour
Met-Ile	Bitter	γ-Glu-Gln	Sweet
	Bitter To Sour	γ-Glu-Gly	Sweet
Arg-Leu		Leu-Gln	Sweet
Phe-Thr	Bitter To Sour	lle-Gln	Sweet
Phe-Gln	Bitter To Sour	Thr-Phe	Sweet
Pro-Leu	Bitter	Pro-Lys	Sweet
Gly-Gly	Flat	lle-Glu	Sweet
Ala-Gly	Flat	Ala-Ala	Sweet
Gly-Ala	Flat	Ala-Gly-Gly	Sweet
Gly-Val-Gly	Flat	Val-Gly-Val	Sweet
Val-Val-Gly	Flat	γ-Glu-Glu	Kokumi
Glutathione	Bitter	γ-Glu-Phe	Kokumi
Anserine	Bitter	γ-Glu-Gly	Kokumi
Acyl-hSer-Lactones	Bitter	γ–Glu-Cys-Gly	Kokumi
Carnosine	Bitter	γ-Glu-Val-Gly	Kokumi



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### Common Acids and Others & Taste Reference Chart



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Others	Taste	
Vit C	Sour, Acidic	D/L-N
Vit D2	Tasteless	Fumaric
Vit E	Fatty Distasteful	Itaconic Aci
Vit K1	Tasteless, Mild Sweet	L-Tartaric Acid
Vit A	Stale, Weak	Succinic Acid
Vit B1	Sour, Bitter	Citric Acid
Vit B2	Strong Bitter	D/L-Ascorbic Acid
Vit B12	Tasteless Flat	Lactic Acid
Butanoic acid 4:0	Rancid, Sour	Levulinic Acid
Caproic Acid 6:0	Sour, Sweaty	Sorbic Acid
Caprylic acid 8:0	Sour, Yeasty	Cis-Aconitic Acid
Capric Acid 10:0	Sour Citrus	D-Glutamic Acid
Palmitic Acid C16:0	Flavor Enhancing	D-Gluconic Acid
_inolenic Acid C18:3) OMEGA 3	Flavor Enhancing	D-Glucuronic Acid
Linoleic Acid (C18:2) OMEGA 6	Flavor Enhancing	Gluconolactone
Oleic Acid (C18:1) OMEGA 9	Flavor Enhancing	L-Threonic Acid
Stearic Acid C18:0)	Flavor Enhancing	Glutaric Acid
Lutein	Bitter	N-Acetyl-L-Glutamic A
Zeaxanthin	Bitter	Ribonolactone
Plant alkaloids	Bitter	
lant carotenoids (xanthophylls)	Bitter	
Plant Flavanoids	Bitter	
Glycosides	Bitter	
Urea	Cooling Saline Metallic	
Glycerol	Sweet	
Galactosylglycerol	Sweet	
TMAO	Bitter	
	Umami Enhancing	
IMP GMP AMP		







### **Summary & References**



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Taste is a complex sense based on a combination of all of our senses. The 5 taste receptors (sour, salty, umami, sweet and bitter) have been identified, while others (Starchy, Oleogustus, Kokumi) are becoming more accepted as unique tastes in themselves. Each taste bud recognizes different tastants, while some tastants interact with others for a complex flavor response. Metabolomic profiling of raw meat muscle and muscle cell products can allow for fine tuning taste, cell line optimization and nutrient assessment.

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