# IMINOSUGARS: highly functional but elusive natural ingredients

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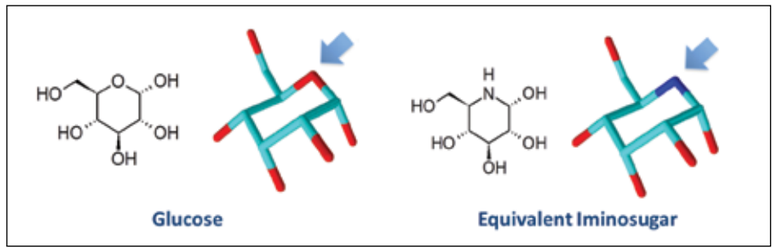
Plants produce sugars by photosynthesis and also produce a wide range of iminosugars to prevent herbivores and pathogens using those sugars efficiently. Iminosugars in their simplest forms can be monosaccharide analogues with a nitrogen atom replacing the oxygen in the ring of the sugar (Figure 1). Like sugars, iminosugars are colourless, very water-soluble and stable in solution, but, unlike most sugars, iminosugars are tasteless and appear not metabolised by mammals (1). The iminosugars show great diversity in biological activity and are arousing interest as treatments for a wide range of diseases including diabetes, viral infections, cancer, lysosomal storage disorders, inflammation and for weight control (2). The iminosugars show great stereoselectivity in biological activity which is not surprising when one considers just glucose which has $2x10^5$ forms in the pyranose and furanose forms; each form is recognised by biological systems and highlights that sugars far surpass the structural and biological information shown by amino acids of equivalent molecular weight. Sugars and their control are crucial to good health. Every type of cell in our bodies has a unique sugar coating and aberrations in these coatings and messaging occurs in many if not all diseases (3). There is also good evidence that imbalances in glycosidases (enzymes that breakdown complex sugars) are associated with many diseases including Alzheimer's, depression, and cancers and indeed these imbalances are often used as markers of disease.

Figure 1. Iminosugars



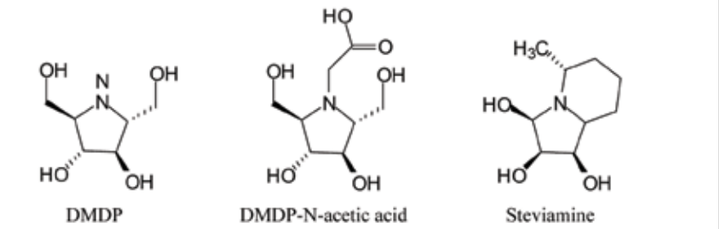

The sugar-based language is very difficult to understand and control but iminosugars offer great potential to specifically correct defects. Most important of their activities seem to be inhibiting or stabilising glycosidases or interacting with sugar receptors. It is remarkable that there are many iminosugars in our foods and medicinal plants but they are rarely seen or identified because they are hidden by common sugars and amino acids which are usually present in higher quantities and have similar analytical properties. The affinity of these sugar analogues for the glycosidases and receptors can be very potent, coupled with good oral availability, distribution and stability in vivo, it makes their presence in many fruits and vegetables of potentially great significance in the diet of people and other animals. Other types of natural products are more easily seen such as the coloured flavonoids and so tend be focused on despite many of them having low relative activity or showing non-specific binding activity. The iminosugars may be the elusive active compounds of many herbal medicines.

Perhaps the best examples of major foods containing iminosugars are potatoes and rice. We were the first to find the iminosugars in potatoes in 1993 and they are in all of them (4). The iminosugars in rice were only recently discovered and are not in all types of rice (5). The nor-tropane calystegines of potatoes are potent glucosidase and galactosidase inhibitors while the iminosugars of rice (e.g. fagomine) can inhibit a wider range of enzymes. It is notable that selection of food plants for shelf-life or other commercial attributes seems to have altered their sugar analogue content without anyone knowing and, for example, each potato variety has a distinctive iminosugar profile with wide variation in amounts and which ones are present. Since the iminosugars of potatoes inhibit glucosidases the different amounts present means that they will differently slow the release of glucose from the potato in the diet and from other foods eaten at the same time. It is also notable that iminosugars such as those in potato and rice are stable on cooking and our research shows that they go through the body of humans and dogs unchanged and are excreted eventually in urine (1).

A group looking into the basis of the anti-diabetic activity of mulberry in TCM identified the first plant iminosugar, DNJ (1-deoxynojirimycin) in 1976 (2). As a potent inhibitor of various glucosidases it has formed the basis of the diabetes drug Glyset™. Quality controlled mulberry leaf products (e.g. Reducose™) are being developed by the UK company Phynova. DNJ is probably the most commonly naturally-occuring and studied iminosugar and it and a derivative Zavesca have been shown to also inhibit infection by viruses such as HIV and SARS-CoV-2 by altering surface glycans (6). In May 2019, a team of Chinese researchers found that the compound could also ameliorate symptoms associated with angina pectoris, such as chest pain, in patients with coronary heart disease (7).

Maintaining a balance of sugars is crucial to good health and losing good control seems involved in the ageing process. Perhaps due to their main presumed evolutionary purpose to protect sugars such as glucose, the iminosugars of plants and microbes that resemble glucose appear able to help to maintain this balance. While some such as DNJ are potent intestinal glucosidase inhibitors and can cause gastrointestinal problems at high concentrations, there are others that appear able to control blood sugars without being enzyme inhibitors. One such example occurs in the Indian Ayurvedic medicinal plant Gymnema sylvestre. It contains one very major iminosugar (BR1) that controls blood sugar in mouse studies by itself (8). This plant has some clinical evidence that over time it can have restorative effects on insulin responses and beta cell health. Probably mistakenly, most Gymnema products concentrate a group of saponins to the total exclusion of the BR1.

Figure 2. Stevia Iminosugars

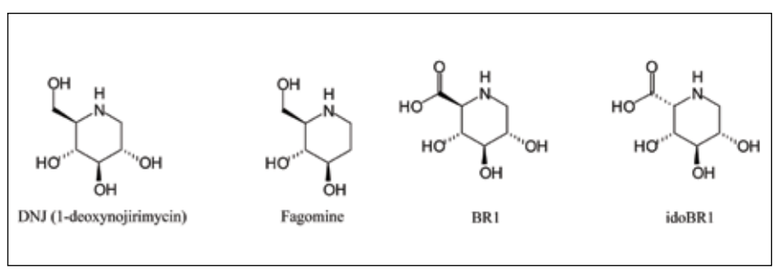



If the body regulates sugar levels well there are many benefits in terms of energy balance and preventing tiredness and craving for sweet foods; many natural iminosugars seem to have evolved with this beneficial effect even if unintended by the plants. For the roughly 422 million people worldwide who have diabetes, sugar is dangerous. Too much glucose in the blood and the risks of long-term health problems are heightened. Reducing sugar intake is one way of alleviating diabetes but selecting foods that have sugar analogues such as iminosugars is another potential way of slowing glucose release into the blood and also probably removing glucose more quickly from the blood stream. The body seems to have many ways of controlling glucose in the body and even advanced glycation end products (AGEs) (produced by too much sugar in the body), when given orally can surprisingly control blood sugar and lipids (9).

Artificial sweeteners or highly purified sweet compounds like Steviosides (from Stevia rebaudiana) are one alternative to refined sugars but it is probably better to use natural sugar sources with other components such as iminosugars still present. Stevia plant, for example, contains glycosidase-inhibiting iminosugars (e.g. DMDP and DMDP-N-acetic acid) but they are removed from the processed products; the natural Stevia may, therefore, be better for health than the highly processed steviosides (and related compounds) (10). One of the isolated iminosugar compounds from Stevia (steviamine), also shows potential anti-metastatic activity in assays by inhibition of an enzyme specially produced by cancer cells to aid their spread (11).

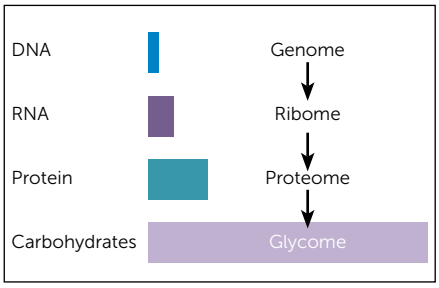
Cucumber is one example of how the active component remained unknown because it was an iminosugar and difficult to detect by usual analytical methods. Known since Roman times to have beneficial anti-inflammatory effects and used by women to improve puffiness and redness around the face, many groups investigated cucumbers but failed to find an active molecule. We now know that certain varieties contain one iminosugar, idoBR1, and it has potent anti-inflammatory activity via a probably novel mechanism (1). Breeding of cucumbers seems to have removed idoBR1 from most modern varieties. IminoTech Inc in the USA has produced a quality-controlled cucumber extract containing measured idoBR1 (Q-actin™) that gave good results in osteo-arthritis from oral use and required over ten times lower doses than glucosamine and chondroitin. Interestingly, our recent research shows that humans and dogs both excrete the idoBR1 eventually unchanged.

Figure 3. Common piperidine iminosugars. DNJ from Mulberry fruit and leaves, fagomine from Buckwheat and some Rice grains, BR1 from Gymnema and idoBR1 from certain cucumbers




Buckwheat and rice contain one iminosugar (D-fagomine) which is related to DNJ. Fagomine if used as a dietary supplement or functional food component is reported to potentially reduce the risks of developing insulin resistance, becoming overweight and suffering from an excess of potentially pathogenic bacteria (12). Interestingly certain rice varieties have more fagomine than buckwheat and can have a wider range of related iminosugars (5). So rice may be more healthy than buckwheat but only if you eat the right variety!

We know the glycome is far more complicated than the genetic code which has just four biochemical letters strung together in lines. We are only just beginning to understand how manipulating the sugar code can be medically useful. For example, with cancer we have known for decades that sugars on cancer cells change and this can make the cells less recognisable to medicines. Studies are underway by Professor Miriam Dwek at the University of Westminster to see if cancer cells dosed with an iminosugar that impedes the growth of the sugar forest on the cancer cell surface can make drugs more effective. Some iminosugars seem also able to induce stronger immune responses (T and NK cell) to cancer cells in animal models and may have wider immunomodulatory benefits (2). It is probable that iminosugars are going to be recognised more and more as health-promoting components of our diet ➜




**Molecular Information**

Figure 4. The Role of Carbohydrates. Carbohydrate complexity and diversity greatly exceeds that of proteins and genes. Carbohydrates and associated receptors present excellent targets and growing market opportunities for iminosugars.

and may be the reason why we and other animals selected foods such as potatoes and cucumbers in the first place. The steeping of plants in hot water to make teas/beverages is the most common way of preparing herbal medicines and this favours the extraction of the stable and water-soluble iminosugars. The water-soluble components of plants comprise most of the weight of plant extractable material but are the least well studied. Many more iminosugars remain to be identified in our common food plants and teas.

As shown earlier, each iminosugar molecule has a nitrogen atom in its ring instead of the usual oxygen atom. It is amazing that such a small change, replacing an oxygen atom in a sugar molecule with a nitrogen atom, can give such wide ranging therapeutic and nutritional benefits. These simple natural molecules promise to open up more avenues for the discovery of new medicines, cosmetic ingredients, health products and supplements. ●

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