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1. Basic information about Monatin

Monatin is a natural high potency sweetener. It is extracted from the root bark of a plant called Sclerochiton ilicifolius, which is found in the Northern Transvaal of South Africa. Monatin was first discovered and elucidated by Vleggar and co-workers in 1992. Physical properties of Monatin are summarized in table 1. The structure is presented in figure 1.1

![Chemical structure of Monatin](image)

Monatin is up to 2700 times sweeter than sugar and contains no calories. The natural occurring compound is the (2S, 4S)-Monatin. The sweetness depends on the absolute configuration and is further explained in the chapter structure. This sweetener proves to be of high quality, because it shows no aftertaste or any toxic physiological effects as far as it is known, which is why it becomes commercially interesting. Another benefit is that there is no harm to teeth by consuming the sweetener. It exhibits a poor solubility, whereas its potassium salt is water soluble. While the molecule is stable to heat, it degrades by exposition to light.

According to IUPAC the exact systematic name of the molecule is:

(2S, 4S)-4-Amino-2-hydroxy-2-(1H-indol-3-ylmethyl)-pentanedioic acid

<table>
<thead>
<tr>
<th>Name</th>
<th>Monatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td><strong>C_{14}H_{16}N_{2}O_{5}</strong></td>
</tr>
<tr>
<td>CAS-Number</td>
<td>146142-94-1</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>292.29 g·mol⁻¹</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>656.4±55.0 °C</td>
</tr>
<tr>
<td>Density</td>
<td>1.525±0.06 g/cm³</td>
</tr>
<tr>
<td>Sweetening Power</td>
<td>up to 2700</td>
</tr>
<tr>
<td>Calories</td>
<td>none</td>
</tr>
</tbody>
</table>

Tab. 1: Physical properties of Monatin.
2. History of sweetener

Natural or synthetic sweeteners are compounds, which are used as substitutes for sugar. They exceed the sweetness of sucrose considerably. They have an intensive sweet taste and no or very low nutritional value. The first artificial sweetener saccharin was discovered by the German chemist Constantin Fahlberg, which is on the market since 1885.\(^4\)

In the food market of sweeteners it is most important that the substitutes accomplish certain criteria. The development of these compounds is dependent on taste and aftertaste, physiological effects, sweetness, stability, nutritional value and many more. The sweetening power is measured in comparison to sucrose. In this scale sucrose sets the standard as 1.
3. Structure

The basic structure of Monatin consists of an indol ring, which is substituted with a glutamic acid molecule in the C3-position of the indol. Therefore Monatin remains to the class of indol derivates or the glutamic acid derivates. There are substituents such as an amino-group in the C4-position and a carboxylic acid- and hydroxy-group in the C2-position. The C4-chain contains two asymmetric centers in C2 and C4-position, which result in four different stereoisomeric structures. Stereoisomerism plays a very important role for the sweetening power of Monatin. It has been reported, that the (2R, 4R)-isomer is the sweetest compound with a relative sweetness of 2700 in comparison to sugar. Also the (2S, 4S)-isomer has been recognized for its intensity of sweetness, while the (2R, 4S) - and (2S, 4R)-Monatin show almost no sweetness. The sweetness of the four stereoisomers is compared in table 3.

![Fig. 3: Identification of functional groups in Monatin structure, a) indole-, b) carboxylic acid-, c) hydroxylic-, d) peptide group.](image)

At a closer examination of the molecule it becomes clear that Monatin is also comparable to the amino acid tryptophan. This suggests Monatin can be synthesized from tryptophan, which is further explained in chapter synthesis.

<table>
<thead>
<tr>
<th>Stereoisomer</th>
<th>(2S, 4S)</th>
<th>(2R,4S)</th>
<th>(2S,4R)</th>
<th>(2R,4R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative sweetness (5% sucrose)a)</td>
<td>50</td>
<td>300</td>
<td>1300</td>
<td>2700</td>
</tr>
<tr>
<td>Relative sweetness (5% sucrose)b)</td>
<td>25</td>
<td>100</td>
<td>800</td>
<td>1700</td>
</tr>
<tr>
<td>Optical purityc)</td>
<td>99.8</td>
<td>99.4</td>
<td>99.2</td>
<td>99.3</td>
</tr>
</tbody>
</table>

Tab. 3: Comparison of sweetness of all Monatin-stereoisomers, a) Relative sweetness values of Monatin sodium salts compared to 5% sucrose solutions, b) Relative sweetness values of Monatin sodium salts [(2S,4R) and (2R,4S)] and potassium salts [(2S,4S) and (2R,4R)] compared to a 10% sucrose solution. c) Optical purities of the stereoisomers determined by HPLC.
4. 3D-Structure

3D structure of Monatin (simulated with Avogadro)

**Fig.4.1:** Showing location of single and double bonds.

**Fig.4.2:** Stick model of the molecule.
5. Synthesis

The Synthesis of Monatin is described mainly by two ways. The total synthesis of optically pure Monatin has been developed by Nakamura. The total synthesis begins with the commercially available indolactid acid as the starting material, which is transformed into the (2S, 4S)-isomer of Monatin over a ten step pathway. In the first step of this synthesis indolactid acid is alkylated by using an alpha-hydroxycarboxylic acid, a pivalaldehyde through a Li-enolate. The enolate of compound 2, which is obtained in a racemic mixture, reacts further with the Garner aldehyde 14 under a second alkylation in two steps. The stereoisomeric mixture of the Boc-protected Compound 15 is reduced by NaH into the compound 16a and 16b. Furthermore the next step is the deprotection of the pivalidene group over Pyridinium p-toluenesulfonate (PPTS) into the structures 17a and 17b. These compounds are oxidized by Pyridinium Dichromate (PDC), so that a carboxylic acid structure 18a and 18b is formed. Subsequently the compounds are converted to lactam formation 19a and 19b, which are separated by a HPLC method. Pure (2S, 4S) 1 and (2R, 4S) - Monatin are obtained by a ring opening in acidic environment.\(^6\)

\[\text{Fig. 5.1: Total synthesis of Monatin.}\]
The production of Monatin through a Biosynthesis is also a possibility. This Synthesis is a complex microbiological procedure, which involves many polypeptides or enzymes. These enzymes convert the amino acid tryptophan to indole-3-pyruvate. Subsequently this intermediate is transformed to 2-hydroxy 2-(indol-3-ylmethyl)-4-keto glutamic acid, which is the Monatin precursor. Finally Monatin is obtained from the Monatin precursor (MP). The biological conversion to the mentioned compounds can be performed through different enzymes. The exact method by which Monatin is produced in the plant is presently unknown. The Biosynthesis is represented in fig.6.2.

Fig.5.2: Biosynthesis of Monatin.
6. Photostability

The exposition of Monatin to UV-light is resulting in the degradation of the structure. This leads to the loss of the indol and therefore to the decrease or complete loss of the sweet taste of Monatin. For the prevention of the degradation of the sweetener or its salt it is any kind of stabilizer needed. An increased stability has been reported by using a radical scavenger, which catches any free radical in the reaction with light. Ascorbic acid, ascorbate, ascorbic acid ester, erythorbic acid, vitamin A, vitamin E, ubiquinol, tryptophan and many more are examples for radical scavenger.\textsuperscript{8}

The use of colorant as an additive to Monatin has also shown preventive effects to the stability, because the colorant exerts a light filtering effect. This is dependent on the wavelength of the light. Another preservation method includes the coexistence of caffeine. The photostability increases also, when chelat complexes like EDTA or Tannic acid are added to soluted Monatin. The choice of packaging or container is also important. The use of transparent yellow PET as the container material has prevented the loss of indol most. By the optimal choice of treatments, additives and container the degradation can be decreased.\textsuperscript{9}
7. Application

Monatin is not used in any way or commercially available yet. Many companies like Cargill and Pepsico are running studies about the sweetening compound and are involved in the development of Monatin. The primary goal is to increase the photostability of Monatin, so that the products do not show any loss of sweetness.

In the future it is definitely considerable, that Monatin is used as a sugar substitute in the wide field of food and beverages. Especially this compound is very suitable for diabetics. Another possibility of use can be pharmaceutical in the form of tablets.

The extraction out of the plant is one possibility to isolate natural Monatin, but it is not interesting for the commercial application, because the amount of Monatin in the plant is about 0.007%.
8. Reference


[4] https://todayinsci.com/F/Fahlberg_Constantin/FahlbergConstantin-Saccharin.htm, 30.01.17


