Zinc citrate – a highly bioavailable zinc source

Jungbunzlauer

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Zinc, the versatile mineral, is about to become the next star in the minerals category. Profiting from its various health benefits and its relatively low cost in use, zinc sales in supplements have shown a double digit growth in 2012 and are starting to catch up with calcium, magnesium and iron, the category leaders.

Zinc is an essential transition metal that is directly or indirectly involved in a wide variety of physiological processes. After discovering the necessity of zinc for Aspergillus niger, it took another 100 years before its relevance for humans was recognised, when the zinc deficiency syndrome was described for the first time by Prasad and his co-workers at the beginning of the 1960s.

Zinc is a component of about 300 enzymes and 2000 transcriptional factors, and 10% of the human proteome contain zinc-binding motives. Impairment of intestinal zinc absorption results in severe clinical manifestations like skin lesions, developmental retardation, stunted growth and immune deficiency.

Its importance for human health was emphasised by the European health claim regulation, where zinc received more positive opinions (18 in total) than any other mineral. The range of claims (Table 1) includes, amongst others, important health benefits like immunity, bone health, cognitive function and healthy vision. These health benefits can be clearly defined and are easy for the consumer to understand. Even if the EU regulations are not valid outside Europe, they influence other regions in the world.

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because they represent the first comprehensive evaluation of health claims, while the respective dossiers can be used by other authorities as well.

Table 1: Authorised health claims in the EU according to latest wording (status 01.01.2014) of Art. 13.1 health claims list of Regulation (EC) No 1924/2006.

- Normal function of the immune system
- Normal DNA synthesis
- Role in the process of cell division
- Protection of cells from oxidative stress
- Maintenance of normal bones
- Normal cognitive function
- Normal fertility and reproduction
- Normal macronutrient and carbohydrate metabolism
- Normal acid-base metabolism
- Normal metabolism of vitamin A
- Normal metabolism of fatty acids
- Maintenance of normal vision
- Maintenance of normal skin
- Maintenance of normal hair
- Maintenance of normal nails
- Normal protein synthesis
- Maintenance of normal testosterone levels in blood

Good dietary sources for zinc are primarily foods of animal origin, e.g., meat, liver, fish, as well as milk and cheese. Concerning plant origin, high levels are reported for wholemeal products and legumes. However, plant-derived zinc generally displays low bioavailability, as intestinal zinc absorption is in many cases impaired by anti-nutritive factors like phytic acid.

The global prevalence of zinc deficiency was estimated at 31%, ranging from 4–73% across sub-regions. Based on these estimates, zinc deficiency in children aged below five years was estimated to cause 176,000 diarrhoea deaths, 406,000 pneumonia deaths and 207,000 malaria deaths per year. Zinc deficiency is rather uncommon in populations with predominantly Western style nutrition because of the high proportion of animal products and particularly meat in the diet. Nevertheless, people with specialised diets like vegetarians, as well as elderly people and individuals in which gastric dysfunctions (e.g., gastric atrophy and achlorhydria), are at higher risk of suffering from zinc deficiency.

Characteristics of zinc compounds > A wide variety of zinc salts are available for use in functional foods, dietary supplements and drug products. The most common forms are zinc oxide, zinc sulphate and zinc gluconate, the latter two (together with zinc acetate) being recommended by the WHO for use in syrups or dispersible tablets for diarrhoea treatment in infants.

There are various properties that need to be considered when formulating with zinc salts. Taste and solubility, in particular, limit the use of some compounds in specific applications. However, costs and bioavailability are further factors that need to be considered (Table 2).

Table 2: Commonly used zinc salts approved for fortification in the EU according to Regulation (EC) No. 1825/2006.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mineral Content</th>
<th>Solubility</th>
<th>Price per kg Zinc</th>
<th>Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc citrate .3 H2O</td>
<td>31%</td>
<td>3 g/l</td>
<td>$30</td>
<td>Slightly bitter</td>
</tr>
<tr>
<td>Zinc gluconate .H2O</td>
<td>13%</td>
<td>100 g/l</td>
<td>$78</td>
<td>Bitter, astringent</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>80%</td>
<td>Insoluble</td>
<td>$6</td>
<td>Bitter</td>
</tr>
<tr>
<td>Zinc sulfate .7 H2O</td>
<td>23%</td>
<td>960 g/l</td>
<td>$24</td>
<td>Astringent, bitter, metallic</td>
</tr>
</tbody>
</table>

The recommended daily allowance (RDA) of zinc is only 10 mg in the EU and the daily value (DV) is 15 mg in the US, so only small amounts are needed for typical formulations, thus making the usage of zinc very cost efficient. The large variation of mineral content has a huge impact on dosage of the specific zinc form and may thus provide some benefit on overall formulation cost. Additionally, for formulations with limited space (e.g., multi-vitamin or multi-mineral formulations) compounds with high zinc content may be preferred.
Highly soluble salts like zinc sulphate, zinc gluconate and zinc acetate have a strong metallic, bitter and astringent taste that often needs to be masked. Even at the typically low dosage levels of zinc salts in fortified foods, these off-tastes can be noticeable. Particularly in the case of food supplements or drug products like syrups and dispersible or effervescent tablets, off-tastes can limit the applicability of these compounds. However, better tasting zinc oxide is insoluble and existing data indicates that its bioavailability is at the lower end of available zinc compounds. In contrast to the oxide form, zinc gluconate stands out for its high bioavailability, but its low zinc content makes this compound much more expensive. An alternative zinc salt with promising sensory properties is zinc citrate. This compound has a high zinc content of 31%, is slightly soluble in water, is odourless, and has relatively low costs.

Its usability in highly concentrated syrups as well as in compounds for the beverage industry has often been questioned due to its relatively low solubility. However, trials in the Jungbunzlauer Application Technology Centre have shown that the addition of tripotassium citrate (or trisodium citrate) can increase its solubility and zinc citrate, or a combination of zinc citrate and tripotassium citrate, results in significantly less bitter composition, compared to other soluble zinc sources like zinc sulphate or zinc gluconate (Table 3).

### Bioavailability of zinc salts

Intestinal absorption of zinc and its adequate utilisation by the body – in other words, the bioavailability – depends on several factors, such as the chemical form of the zinc salts, dietary factors and physiological condition (Table 4).

It has been demonstrated in animal and human trials that absorbability is strongly related to the specific solubility of zinc compounds in aqueous solution. Therefore, acidic inorganic zinc salts like zinc chloride or zinc sulphate, which are very soluble in aqueous solution, show sufficient bioavailability, where-

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**Table 3: Taste ranking test for bitterness for solutions containing 10 mg Zn²⁺ per 5 ml each;**
(Rank: 1= least pronounced bitterness). Values that do not share a common letter are significantly different (p<0.05)

<table>
<thead>
<tr>
<th>Zinc citrate (dispersed)</th>
<th>Zinc citrate (dissolved w. tripotassium citrate)</th>
<th>Zinc sulfate</th>
<th>Zinc gluconate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average rank</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8ᵃ</td>
<td>1.6ᵃ</td>
<td>3.1ᵇ</td>
<td>3.8ᵇ</td>
</tr>
</tbody>
</table>

Zinc sulfate and zinc gluconate have further been described as having a strong metallic and astringent taste
(Source: Internal tasting panel (n=10) at Jungbunzlauer Ladenburg GmbH, Germany)

**Table 4: Factors affecting bioavailability of zinc**

<table>
<thead>
<tr>
<th>Chemical form of zinc salts</th>
<th>Dietary factors</th>
<th>Physiological conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Solubility</td>
<td>• Amount/concentration of zinc</td>
<td>• Zinc status and foregoing zinc supply / depletion</td>
</tr>
<tr>
<td>• Complexing/chelating anions</td>
<td>• Inhibiting factors (phytic acid)</td>
<td>• Gastric acid, luminal pH</td>
</tr>
<tr>
<td></td>
<td>• Promoting factors (protein, certain amino acids, citric acid)</td>
<td>• Particular requirements (growth, gravidity, lactation, old age)</td>
</tr>
<tr>
<td></td>
<td>• Fe-Zn/Zn-Cu interactions</td>
<td>• Dietary status/eating habits (malnutrition, vegetarianism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased needs due to diseases such as diarrhoea</td>
</tr>
</tbody>
</table>
as zinc absorption from the oxide or carbonate salt, which are practically insoluble in neutral aqueous solution, is significantly lower. Zinc salts with organic anions (zinc acetate, zinc lactate) and particularly with amino acid chelates like zinc histidine and other reversibly complexing anions (e.g., zinc gluconate or zinc citrate) are thought to have a generally higher bioavailability than zinc sulphate. However, human absorption data to support the usage of zinc citrate has so far been very limited.

From the published data on the absorption of zinc from supplements given to humans, it would appear that zinc gluconate, zinc citrate, and zinc sulphate are absorbed at a similar level, while zinc oxide is slightly less well absorbed.

In order to prove this assumption the ETH Zurich, Switzerland recently compared the bioavailability of two assumed high bioavailable salts (zinc citrate and zinc gluconate) with the supposed lower bioavailable zinc oxide. The goal of this trial was to use the double-isotope tracer ratio (DITR) method to compare the absorption of these three compounds when they were given as supplements without food. This procedure is recommended to maximise zinc absorption and is usually advised for the treatment of diarrhoea. The isotope tracer technique which was used included the administration of two stable zinc isotopes (one orally and one intravenously), followed by the quantification of the two isotopes in one spot urine sample four days later.

Fifteen adults were included in this randomised, double masked, 3-way crossover study, meaning each participant acting as his/her own control (Figure 1). Healthy male and female participants aged between 18 and 45 years were selected, who were not vegan, smokers, pregnant, or lactating.

Zinc gluconate, zinc oxide, and zinc citrate were administered as supplements at a dose of 10 mg of zinc each and consumed with water. Each dose consisted of 9 mg of non-labelled and 1 mg of $^{67}$Zn-labelled zinc. Additionally, $^{70}$Zn-labelled ZnCl$_2$ was used for intravenous administration.

The study showed that there was a significantly higher absorption of zinc from zinc citrate (median absorption 61.3 %; $P = 0.006$) and zinc gluconate (median absorption 60.9 %; $P = 0.009$) when compared with the one from zinc oxide (median absorption 49.9 %), see figure 2. The absorption of zinc citrate did not significantly differ from that of zinc gluconate.

One further interesting finding was that two (one male, one female) of the 15 participants did not absorb zinc from zinc oxide and one further participant absorbed the zinc oxide at a low level (14 %). This suggests that there is a portion of the population that is not able to absorb zinc in its oxide form. It was hypothesised by the authors that these individuals cannot dissolve zinc oxide in the gastric juice, probably
as a result of a high intragastric pH making it poorly absorbable.

According to the authors, these results indicate that zinc citrate could be a useful compound for zinc supplementation. At the present time, the WHO recommends the use of the highly-soluble compounds zinc sulphate, zinc acetate or zinc gluconate in the form of syrups or dispersible tablets in the management of diarrhoea. Zinc citrate might be a useful addition to this list and be especially suitable for chewable/crushable tablets because it has better sensory properties than zinc acetate, zinc sulphate, and zinc gluconate, which have an astringent, bitter, or metallic taste. In relation to price and zinc content, zinc citrate would have an advantage over zinc gluconate, because the costs per kilogram of zinc are $30 vs. $78, respectively. The advantage of zinc citrate over zinc sulphate is related to its better sensory qualities and the higher zinc content of citrate (31% vs. 23%) at a similar price and presumably for a similarly high absorption.

The authors conclude “[…] our results indicate that zinc is as well absorbed from zinc citrate as from zinc gluconate and that zinc citrate should be as effective as zinc gluconate in the prevention of zinc deficiency and presumably also in the treatment of diarrhea. Its higher zinc content, good sensory properties, and lower price make it an attractive alternative to zinc gluconate and other water-soluble zinc compounds. Zinc oxide appears to be less well absorbed than other zinc compounds when given without food and may be minimally absorbed by some individuals.” (2; p.136)

Outlook > Awareness of zinc and its various beneficial effects on human health has grown steadily in recent years. Its physiological versatility, which offers various options for new product concepts, combined with its relative low cost in use, demonstrate why zinc is forecasted to continue its growth within fortified foods and supplements. While a number of zinc salts are approved for the usage in food and food supplements, many of them have drawbacks regarding taste, which limit their usage in taste sensitive applications or require extensive work for masking them. Commonly used zinc oxide combines a relative low taste impact at a very low price. The assumed lower bioavailability was recently confirmed and the fact that some individuals can only absorb it minimally questions its general usage for zinc fortification or supplementation.

Zinc citrate combines formulation advantages like preferred sensory properties, relatively low costs in use due to a high zinc content of 31% as well as sufficient solubility. Combined with the recently proven high bioavailability (on the same level as zinc gluconate), this makes zinc citrate a serious option for zinc-fortified foods and zinc supplements.

Zinc Citrate is part of Jungbunzlauer’s Special Salts, which are functional minerals mainly derived from citric acid or gluconic acid. The fully reacted products are manufactured in Europe by neutralisation of these acids with the appropriate alkaline calcium, magnesium, potassium and zinc sources. The resulting organic minerals are known for their high bioavailability, and are used because of their ability to support human health in different applications of food, beverage, dietary supplements or pharmaceutical products.

Further references are available on request.

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