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GENERAL

Role of Magnesium in health and disease

SANJAY AGRAWAL

Magnesium - the master cation

Magnesium is the fourth most common mineral in the human body after calcium, sodium, and potassium and is the second most common intracellular cation after potassium.

In a 70 kg individual, there is an average of 25 grams of magnesium in reserve. Of total body Mg2+, ~99% is intracellular, with 53% in bone, 27% in muscle, 19% in soft tissues, and less than 1% in the serum[1]

Magnesium homeostasis

Roughly 30% of ingested magnesium through food or drinking water is absorbed by the intestine, although the extent of absorption depends on the body magnesium status (increased in case of Mg2+ deficiency). Magnesium homeostasis is further regulated through the secretion and reabsorption in the kidneys, where about 95% of the filtered magnesium is reabsorbed.

Primary functions of magnesium

Magnesium (Mg2+) is a critical micronutrient. It is an essential cofactor for over 300 enzymes involved in many of the normal functions of the body. Magnesium is used by every cell to synthesize proteins, repair DNA, and provide energy.

Magnesium is implicated in over 80% of metabolic functions. Mg2+ is a cofactor in the activation of hundreds of enzymatic processes regulating diverse biochemical reactions, including energy metabolism, protein synthesis, muscle and nerve function, blood glucose, and blood pressure control[2].

Magnesium and the cardiovascular system.

Magnesium plays an important role in maintaining normal physiological functions of the cardiovascular system. It influences myocardial metabolism, Ca2+ homeostasis, and endothelium-dependent vasodilation. It also acts as an antihypertensive, antiarrhythmic, anti-inflammatory, and anticoagulant agent[3].

Magnesium is a physiological calcium antagonist. Through this action it produces vasodilation and reduces vascular resistance, improving blood circulation. It also maintains the electrical property of the myocardium, and also has anti-inflammatory activity[4].

Magnesium also inhibits platelet adhesion and platelet aggregation. It is reported that magnesium deficiency can induce oxidative stress, which in turn activates the inflammatory process mediated via activation of nuclear factor kappa-B. This condition ultimately results in various pathological conditions like atherosclerosis, thrombus formation, and vascular calcification[5].

Beneficial actions of magnesium in cardiovascular system

Several clinical studies revealed the relationship between low intake of dietary magnesium with cardiac diseases, and it is reported that the maintenance of the normal physiological level of magnesium has a beneficial effect in various CVD[6]. A systematic review and meta-analysis of prospective studies that included over 300,000 individuals found that elevated magnesium serum levels paralleled a reduced risk of cardiovascular disease; elevated dietary magnesium intakes were shown to be inversely associated with ischemic heart disease[7].

Magnesium and carbohydrate metabolism

It is well known that magnesium acts as an insulin sensitizer by inducing auto phosphorylation of insulin receptors and regulating tyrosine kinase activity on these receptors[8]. In addition, magnesium may directly affect the activity of the glucosetransporter 4 (GLUT4) and help to regulate glucose uptake into the cell[9]. Several studies have reported that a reduced intracellular magnesium level can lead to increased insulin resistance[10].

Consequently, diets with higher amounts of magnesium are related to a significantly lower risk of diabetes. The incidence of hypomagnesemia in patients with type 2 diabetes varies from 13.5–47.7%[11].

Magnesium and bone health

About 50–60% of Mg2 is stored in bones, out of which about 30% is at the surface as hydroxyapatite crystals along with calcium and inorganic phosphate (Pi). Mg2 present at the surface of the bones is only available for ionic exchange. The remaining amount becomes an integral part of the bone and is released during the bone resorption process[12]. Mg2 is involved in regulating the solubility of minerals, thereby

Dr. Sanjay Agrawal,
Leading Pharmaceutical Consultant and Editor-in Chief of IJM Today, Post Graduation Diploma in Naturopathy and Yoga, Visiting Faculty, Global Institute of Healthcare Management, Delhi. 6/146, Malviya Nagar, Jaipur - 302 017. Rajasthan.

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maintaining the size of the crystals. Apart from this, Mg2 also participates in osteoblast proliferation.

Magnesium is required for conversion of vitamin D into its active form which, in turn, supports calcium absorption and metabolism, as well as normal parathyroid hormone function[13].

Magnesium is required for the activity of hepatic 25-hydroxylase and renal 1_-hydroxylase, both crucial to convert 25(OH)D into its biologically active form 1,25(OH)2D3[14]. Magnesium also facilitates the transfer of vitamin D to target tissues through the vitamin D binding protein[15].

Low serum magnesium levels are known to result in low blood concentrations and resistance to action of parathyroid hormone (PTH), and resistance to some of the effects of vitamin D[16].

Many studies have demonstrated that, a moderate or subclinical magnesium deficiency can induce chronic low-grade inflammation or exacerbate inflammatory stress caused by other factors. This low-grade inflammation increases the secretion of pro-inflammatory cytokines, which stimulate the resorption of bone by inducing the differentiation of osteoclasts from their precursors[17].

Several population-based studies have found positive associations between magnesium intake and bone mineral density in both men and women[18].

Magnesium: Recommended Dietary Allowance (RDA)

The current RDA ranges from 80 mg/day for children 1–3 year of age to 130 mg/day for children 4–8 year of age. For older males, the RDA for magnesium ranges from as low as 240 mg/day (range, 9–13 year of age) and increases to 420 mg/day for males 31–70 year of age and older. For females, the RDA for magnesium ranges from 240 mg/day (9–13 year of age) to 360 mg/day for females 14–18 year of age. The RDA for females 31–70 year of age and older is 320 mg/day[19].

Many nutritional experts feel the ideal intake for magnesium should be based on the body weight (e.g.4–6 mg per kg/day).

Magnesium deficiency

Mg2+ deficiency or hypomagnesemia is defined as serum magnesium <0.75 mmol/L[20].

While previously magnesium deficiency was considered rare, more recent findings have suggested that many individuals may have suboptimal magnesium status. Several dietary surveys and epidemiologic studies performed in the USA and EU, revealed that on average people have an intake of dietary magnesium lower than the Recommended Daily Allowance (RDA) of 320 to 420 mg/day[21]. Based on these findings, it is often suggested that over 50% of the normal population may have marginal magnesium deficiency[22].

Reasons of magnesium deficiency:

1. Poor dietary intake- Low consumption of magnesium rich foods and modern farming techniques often deplete magnesium levels in plants.
2. Poor diet – Increased consumption of processed foods. Processed foods contain less magnesium
3. Anti-nutrients - Tannins, oxalic acid, phytic acid in food bind magnesium, preventing its absorption
4. Less magnesium in water – Filtering process removes magnesium from drinking water
5. Poor absorption – Celiac, GI inflammation, malabsorption
6. Chronic alcohol consumption
7. Medications – Long-term use of Acid suppressants, diuretics
8. Fluoridated water – Fluoride binds Mg2+ reducing absorption

Signs and symptoms of magnesium deficiency

Early signs of magnesium deficiency are non-specific and include loss of appetite, lethargy, nausea, vomiting, fatigue, and weakness. More pronounced magnesium deficiency presents with symptoms of increased neuromuscular excitability such as tremor, carpopedal spasm, muscle cramps, tetany and generalized seizures. Hypomagnesemia can cause cardiac arrhythmias including atrial and ventricular tachycardia, prolonged QT interval and torsades de pointes[23].

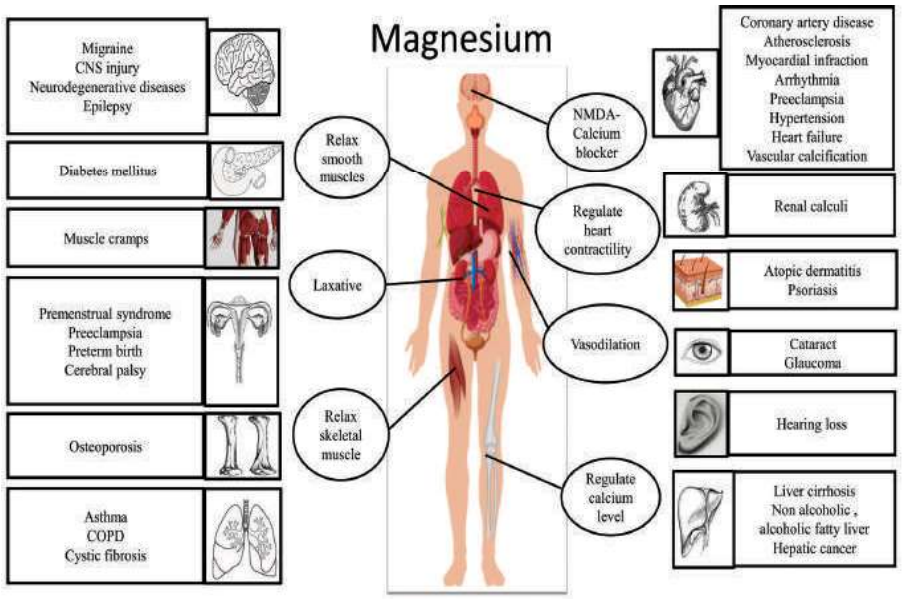
Over the last 30 years several, experimental, clinical, and epidemiological studies have shown that chronic magnesium deficiency is associated with and/or amplifies many major chronic medical conditions including hypertension[24] migraine, diabetes mellitus[25], cardiovascular disease[26] and osteoporosis[27].

Treatment of magnesium deficiency

Multiple studies support magnesium supplementation as a viable and generally

Safe means to treat hypomagnesemia . Typical magnesium supplements include magnesium oxide, magnesium chloride, magnesium sulfate, and other organic magnesium

Formulations. These magnesium salts are known to produce loose stools and diarrhoea, leading to poor GI tolerance and non-compliance to treatment. Recently chelates of magnesium



Physiological role of magnesium in vital systems. Text in the circle represents the physiological role of Mg in various vital organs. Text in the rectangle indicate the diseases or disorders associated with magnesium deficiency

with amino acids such as glycine are made available for treatment of magnesium deficiency. These chelates overcome the short comings of conventional magnesium salts. They are known to be better absorbed from GI tract and are also better tolerated.

Chelation

Chelation is a term that describes an encapsulation process. A mineral, like calcium for example, reacts with another material to form a protective shell around the desired mineral (in this case calcium).

Micronutrients normally have an electrical charge on them. For example, calcium and magnesium are both +2 charge, while chelates are molecules with a neutral charge.

The process of chelation results in the final mineral compound becoming neutral, i.e., containing no electrical charge. This is important because electrically charged mineral compounds can interact with other dietary components, such as phytates and other oppositely charged molecules, and form substances that are not absorbable. In addition, charged mineral compounds are reactive and can deactivate other important nutrient factors, such as vitamin E, ascorbic acid, various B-vitamins, and certain medications.

Mineral - Amino Acid Chelates

The human body is very efficient at absorbing individual amino acids. For instance, the amino acid glycine is readily absorbed across the intestinal wall. When the glycine "grabs" and bonds with a mineral molecule, a mineral-amino acid chelate is formed. This mineral-amino acid chelate doesn't break down in the digestive process. As a result the mineral is easily absorbed, because it gets carried to cells bound to the amino acid.

Glycine is the smallest amino acid and it is often used as a chelating agent. Glycine chelates (also known as glycinates) are a subset of amino acid chelates.

The molecular structure of a mineral amino acid chelate—and particularly a bisglycinate chelate—has several characteristics that help it overcome the 3 key challenges of mineral supplementation: tolerability, bioavailability, and stability.

The chemical stability and non reactivity of the mineral bisglycinate chelates explain much of why these complexes have enhanced bioavailability with fewer side effects than mineral salts. The glycine molecules wrap around and protect the mineral ion at the centre of the chelate, creating a neutral molecule that does not react with other food compounds, like phytates or fiber. This means that more of the mineral is delivered to the site of absorption in the small intestine.

Mineral amino acid chelates have also demonstrated enhanced bioavailability over other forms. The small size of bisglycinate chelates allows them to be absorbed intact into intestinal cells. When the bisglycinate chelate is absorbed this way, it does not compete with other minerals for transport across intestinal cell membranes.

Mineral amino acid chelates have demonstrated superior tolerability to other mineral forms. The 2:1 ratio of glycine molecules to mineral ions makes the bisglycinate chelate pH stable, even within the acidic contents of the stomach. This stability prevents dissociation of the mineral ion, reducing the risk of gastrointestinal side effects.

Benefits of mineral-amino acid chelates:

Molecular Characteristic	Physiologic Significance
Stability	Less interaction with inhibitors (phytates, oxalates, etc.) Less interaction with other vital nutrients Higher bio-availability
Neutral charge	Fewer gastrointestinal side effects increased tolerability increased safety
Small size	Avoids digestive processes priors absorption

Magnesium glycinate: The marvellous magnesium

Magnesium glycinate is one of the most popular magnesium supplement on the market. Magnesium is attached ("chelated") to the amino acid glycine. Technically, it is called bisglycinate,since the compound contains 2 glycine molecules for every 1 magnesium molecule, however, for the sake of convenience, it is usually just referred to as "glycinate".

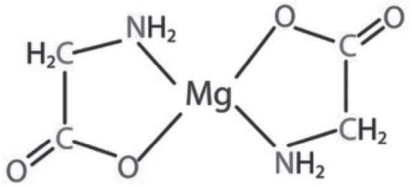


Figure 1: Magnesium Bisglycinate Molecular Structure

Advantages of Magnesium glycinate

Superior bioavailability:

Bioavailability is the measure of the amount of an ingested nutrient that is absorbed and made available to the body for metabolic use. Factors like pH and ionization have influence on the absorption of minerals and their final bioavailability. Chelated minerals don't need ionization and are not pH dependent, which results in an improved absorption and higher bioavailability.

The magnesium bisglycinate combination enables efficient absorption, the glycinate allowing the magnesium to transfer easily across the intestinal wall. Increased absorption means more usable magnesium for body's needs[28].

Better safety and tolerability:

In a study which compared magnesium oxide and magnesium glycinate chelate in ileal resected patients, the magnesium glycinate caused fewer bowel movements and did not produce diarrhea[29].

Another study conducted in healthy adults reported that magnesium glycinate chelates at dosages of 450 mg and 600 mg of magnesium per day had good bowel physiological response as determined by fecal consistency scores[30].

Role of Magnesium in Diabetes

Magnesium supplementation has been suggested as a possible non-pharmacologic, economic and safe treatment for the prevention and the metabolic control of type 2 diabetes.

One randomized, double-blind, placebo-controlled study in 63 individuals with type 2 diabetes mellitus and hypomagnesemia found that those taking an oral magnesium supplement (638 mg/day of elemental magnesium) for 16 weeks had improved measures of insulin sensitivity and glycemic control compared to those taking a placebo[31].

A recent meta-analysis of nine randomized, double-blind, controlled trials concluded that oral supplemental magnesium lowered fasting plasma glucose concentrations in individuals with diabetes[32]. Another meta-analysis of trials that included participants either at-risk of diabetes mellitus or with diabetes mellitus, suggested that evidence to support a benefit of magnesium supplementation on measures of insulin resistance was stronger in subjects who were magnesium deficient than in those with normal serum concentrations of magnesium[33].

According to the recent guidelines of the Association for Magnesium Research, patients with diabetes benefit from four effects of magnesium supplementation: insulin sensitizing effect, calcium antagonism, stress regulating, and endothelium stabilizing effects. In diabetics, the Association for Magnesium Research recommends a daily magnesium supplementation between 240 and 480 mg (10–20 mmol)[34].

Role of Magnesium in osteopenia and osteoporosis

Dietary magnesium deficiency has been hypothesized as a potential risk factor for osteoporosis. Epidemiologic studies have shown that elevated dietary intakes of magnesium were positively and significantly related to bone mineral density (BMD). On the opposite, inadequate dietary magnesium intakes were linked to an increased rate of bone loss in postmenopausal osteoporotic women. In addition, magnesium is necessary for vitamin D synthesis, transport, and activation; hence, magnesium deficiency would impair the production of the active form of vitamin D, 1,25-OH2 D3,

and cause a resistance to PTH and vitamin D actions[35].

As the magnesium content of bone decreases, hydroxyapatite crystals of bone may become larger, leading to more brittle bones. Some studies have found lower magnesium content and larger hydroxyapatite crystals in bones of women with osteoporosis compared to disease-free women[36].

In the Women's Health Initiative study, data analysis from 4,778 participants (mean age, 63 years) followed for about seven years showed that higher magnesium intakes were associated with higher hip and whole-body BMD. Moreover, the highest versus lowest quintile of total magnesium intakes was associated with a 23% increased risk of lower arm and wrist fractures[37].

A recent randomized controlled study conducted in 20 postmenopausal women with osteoporosis suggested that high-dose magnesium supplementation for one month could reduce the rapid rate of bone loss that characterizes osteoporosis[38].

In participants to the cohort "Osteoarthritis Initiative" followed for 8 years, it was found that women with the higher dietary magnesium intake had a 27% reduced risk for future fractures, confirming the positive role of maintaining an adequate magnesium balance on the risk of osteoporosis and fragility fractures[39].

Role of Magnesium in skeletal muscle disorders

Magnesium ions has a key role in all enzymes utilizing or synthesizing muscle ATP, and thus in the production of muscle energy, and indirectly in the muscle contraction and relaxation. Magnesium deficiency has been related to a poor muscle performance. Magnesium deficiency has been suggested to cause muscle weakness, muscle pain and night cramps. It has been proposed that magnesium deficiency may contribute to the development of fibromyalgia[84]. Another study suggested that magnesium supplements may be used to reduce muscle tenderness, pain, and symptom severity in fibromyalgic subjects[40].

In young volunteers, Brilla et al. showed that magnesium supplements (up to 8 mg/kg daily) were able to enhance muscle strength and endurance performance, and to reduce the oxygen consumption[41]. In older subjects, Veronese et al. showed that oral magnesium supplementation (300 mg/day) was able to improve the physical performance, particularly in those subjects with a baseline low magnesium dietary intake, proposing that magnesium supplementation may help in preventing or delaying the decline in physical performance with increasing age[42].

Role of Magnesium in Hypertension

A recent meta-analysis of randomized controlled studies with 2,028 participants found that supplemental magnesium at a median dose of 368 mg/day (range: 238-960mg/day) for a median duration of three months (range: 3 weeks-6 months) increased serum magnesium concentration by 0.05 mmol/L (27 trials) and reduced systolic blood pressure by 2 mm Hg and diastolic blood pressure by 1.78 mm Hg (37 trials) [43].

A 2017 meta-analysis restricted to trials in participants with underlying preclinical (insulin resistance or prediabetes) or clinical conditions (type 2 diabetes mellitus or coronary heart disease) found a 4.18 mm Hg reduction in systolic blood pressure and a 2.27mm Hg reduction in diastolic blood pressure with supplemental doses of magnesium ranging between 365mg/day and 450 mg/day for one to six months[44].

Role of Magnesium in cardiovascular disorders

Endothelial dysfunction, vascular inflammation and oxidative stress are known to promote vasoconstriction, atherosclerosis and increase the risk of thrombus formation, which may lead to myocardial infarction or stroke[45].

A recent systematic review identified six randomized controlled trials that examined the effect of pharmacologic doses of oral magnesium on vascular endothelial function[46]. Three out of six trials, which included individuals with coronary artery disease, diabetes mellitus or hypertension, reported an improvement in flow-mediated dilation (FMD) with supplemental magnesium compared to control.

The measurement of the carotid intima-media thickness (CIMT) is sometimes used as a surrogate marker of atherosclerosis. Higher serum magnesium concentrations were associated with reduced carotid intima-media thickness (CIMT) in all women and in Caucasian men participating in the Atherosclerosis Risk in Communities (ARIC) study[47].

A meta-analysis of seven prospective trials with a total of 241,378 participants observed a modest but statistically significant inverse association between magnesium intake and risk of stroke. An intake increment of 100 mg magnesium/day was associated with a 8% reduction in risk of total stroke (combined RR: 0.92; 95% CI: 0.88, 0.97). Magnesium intake was inversely associated

with risk of ischemic stroke (RR: 0.91; 95% CI: 0.87, 0.96)[48].

Role of Magnesium in Pregnancy

Magnesium deficiency is a common event in pregnancy[49]. Preliminary evidence suggests that magnesium deficiency is a determinant of pregnancy outcomes as well as long-term health of the offspring[50].Oral magnesium supplementation given before the 25th week of gestation compared with placebo, for example, was associated with a lower frequency of preterm births, low birth weight infants, and fewer small for gestational age newborns[51]. Another study showed that magnesium supplementation in pregnancy was associated with lower mean arterial pressure in women along with higher birth weight infants and fewer days spent in the neonatal intensive care unit[52].

A Cochrane database review looking at supplementation with 360 mg/day of magnesium during pregnancy, reported its efficacy in muscle cramps[53].

Magnesium therapy is indicated

For treatment as well as prevention of a number of different diseases and disorders as described below:

A. Therapeutic use :

1. Treatment of magnesium deficiency
2. Treatment of vitamin D3 deficiency- osteopenia and osteoporosis
3. Skeletal muscle cramps and muscle weakness
4. Pregnancy cramps

B. Preventive (Prophylactic) use:

Long-term regular supplementation of magnesium therapy is beneficial in-

- **Maintaining healthy bones-** Synergistic actions of magnesium glycinate and vitamin D3, helps in prevention of osteopenia and osteoporosis.
- **Diabetics-** Both magnesium glycinate and vitamin D3, help in improving control of diabetes and reduce risk of diabetic complications.
- Patients with coronary artery disease- Studies have reported that magnesium, vitamin D3 as well as vitamin C help in reducing risk of CAD complications, improve outcomes and reduce mortality.
- Patients with hypertension- Beneficial actions of magnesium, vitamin D3 and vitamin C help in improving control of hypertension.
- Patients with chronic diarrhoea, malabsorption syndromes and those who have undergone bariatric surgery.
- Elderly- Deficiency of magnesium, vitamin D3, vitamin C and zinc is commonly seen in elderly individuals because of poor dietary intake and decreased intestinal absorption.
- Chronic alcoholics.
- Pregnant and lactating women.

Suggested Dose and Duration

Dose: One to two tablets daily

Duration: The exact duration of magnesium therapy will depend upon patient condition and response to therapy

Safety and tolerability

Magnesium therapy is generally very well tolerated by majority of patients. Occasional patients may complain of mild and transient GI disturbances with Magnesium therapy

Drug-interactions

Reported drug-interactions of magnesium:

Several types of medications have the potential to interact with magnesium supplements or affect magnesium status. A few examples are provided below.

Oral Bisphosphonates

Magnesium supplements can decrease the absorption of oral bisphosphonates, used to treat osteoporosis. Use of magnesium supplements and oral bisphosphonates should be separated by at least 2 hours.

Antibiotics

Magnesium can form insoluble complexes with tetracyclines, as well as quinolone antibiotics, and hence decrease their absorption. These antibiotics should be taken at least 2hours before or 4–6hours after a magnesium-containing supplement[54].

Diuretics

Chronic treatment with thiazide and loop diuretics can increase the loss of magnesium in urine and lead to magnesium depletion. In contrast, potassium-sparing diuretics, such as amiloride and spironolactone, reduce magnesium excretion[55].

Proton pump inhibitors

Proton pump inhibitors (PPIs), when taken for prolonged periods (typically more than a year) can cause hypomagnesemia.[56].

Magnesium therapy Overdose

High doses of magnesium from dietary supplements or medications can result in diarrhea, nausea and abdominal cramping. Forms of magnesium most commonly reported to cause diarrhea include magnesium carbonate, chloride, gluconate, and oxide[57].The diarrhea and laxative effects of magnesium salts are due to the osmotic activity of unabsorbed salts in the intestine and colon and the stimulation of gastric motility.

Very large doses of magnesium-containing laxatives and antacids (typically providing more than 5,000 mg/day magnesium) have been associated with magnesium toxicity[58]. Symptoms of magnesium toxicity, which usually develop after serum concentrations exceed 1.74–2.61mmol/L, can include hypotension, nausea, vomiting, facial flushing, retention of urine, ileus, depression, and lethargy before progressing to muscle weakness, difficulty in breathing, extreme hypotension, irregular heartbeat, and cardiac arrest [59]. The risk of magnesium toxicity increases with impaired renal function or kidney failure because the ability to remove excess magnesium is reduced or lost.

Magnesium therapy Precautions

Long-term use of Magnesium therapy at recommended doses is unlikely to produce any serious side effects in patients with normal renal and liver functions. However, it should be used with caution in patients with impaired renal functions and/or renal stones.

It is advisable to monitor serum magnesium and vitamin D levels in patients on long-term prophylactic therapy with Magnesium .

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Over the years several methods are developed for determining antioxidant capacity of the substance. The oxygen radical absorbance capacity (ORAC) assay developed by scientists at the National Institute of Health and Aging (NIH) to measure the antioxidant capacity of a range of substances found in neutraceuticals pharmaceuticals and different foods has emerged as a lowest cost, highly efficient, robust analytical method. The ORAC assay measures a fluorescent signal from a probe that is quenched in the presence of Reactive Oxygen Species (ROS).

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