Sulfur in Human Nutrition and Applications in Medicine

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Abstract

Because the role of elemental sulfur in human nutrition has not been studied extensively, it is the purpose of this article to emphasize the importance of this element in humans and discuss the therapeutic applications of sulfur compounds in medicine. Sulfur is the sixth most abundant macromineral in breast milk and the third most abundant mineral based on percentage of total body weight. The sulfur-containing amino acids (SAAs) are methionine, cysteine, cystine, homocysteine, homocystine, and taurine. Dietary SAA analysis and protein supplementation may be indicated for vegan athletes, children, or patients with HIV, because of an increased risk for SAA deficiency in these groups. Methylsulfonylmethane (MSM), a volatile component in the sulfur cycle, is another source of sulfur found in the human diet. Increases in serum sulfate may explain some of the therapeutic effects of MSM, DMSO, and glucosamine sulfate. Organic sulfur, as SAAs, can be used to increase synthesis of S-adenosylmethionine (SAMe), glutathione (GSH), taurine, and N-acetylcysteine (NAC). MSM may be effective for the treatment of allergy, pain syndromes, athletic injuries, and bladder disorders. Other sulfur compounds such as SAMe, dimethylsulfoxide (DMSO), taurine, glucosamine or chondroitin sulfate, and reduced glutathione may also have clinical applications in the treatment of a number of conditions such as depression, fibromyalgia, arthritis, interstitial cystitis, athletic injuries, congestive heart failure, diabetes, cancer, and AIDS. Dosages, mechanisms of action, and rationales for use are discussed. The low toxicological profiles of these sulfur compounds, combined with promising therapeutic effects, warrant continued human clinical trails.

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Introduction

Sulfur has an atomic weight 32.064, an atomic number of 16, and is represented by the chemical symbol "S". Antoine Lavoisier recognized this nonmetallic element in 1777. Solid sulfur is yellow, brittle, odorless, tasteless, and insoluble in water. The term "thiol" refers to compounds containing sulfur. The structure of sulfur allows for a variety of oxidation states. Figure 1 illustrates the sulfur cycle in biological systems.[1]

The biosynthesis of organic sulfur compounds from sulfate takes place mainly in plants and bacteria, whereas the oxidation of these compounds to sulfate is characteristic of animal species. Sulfur is excreted as sulfate, the urinary excretion of sulfate generally reflecting input from either inorganic or amino acid sources.[2]

Most of the literature regarding sulfur intake considers the sulfur-containing amino acids (SAAs) as the primary source of this element in the diet. Researchers who have examined the role of sulfur in biological systems have controlled the amount of sulfur intake through regulation of protein intake. For ethical reasons, most of the work has been on animals.

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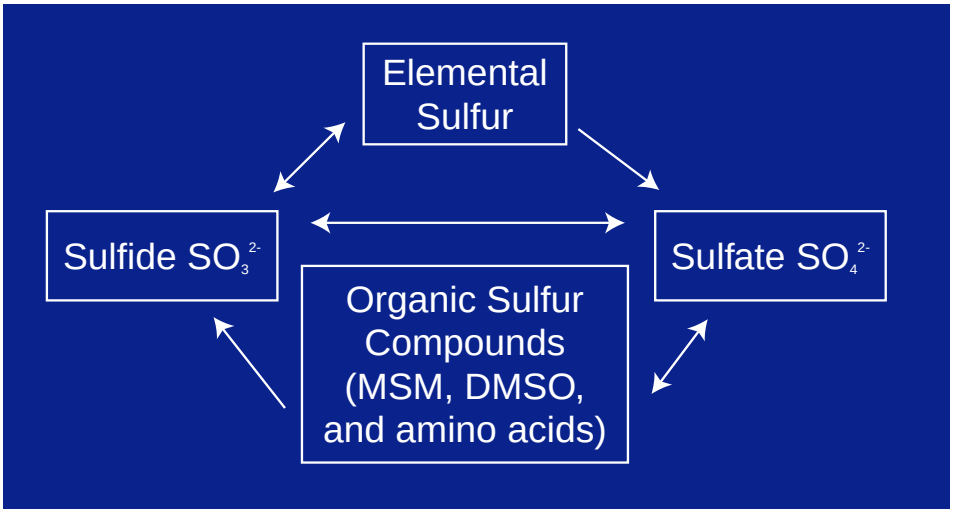
Because the role of elemental sulfur in human nutrition has not been studied extensively, it is the purpose of this article to emphasize the importance of this element in human biology and discuss therapeutic applications of sulfur compounds in medicine. The well-known beneficial actions of organosulfur compounds (isothiocyanates, diallyl sulfide, allicin) found in garlic, onions, and other vegetables will not be discussed because excellent reviews already exist.[3]

Sulfur research on humans has focused on the role of SAAs, low-molecular-weight thiols, and disulfides in redox reactions. Plasma thiols can have pro-oxidant or antioxidant actions depending on the physiological circumstances,[4] but are generally considered antioxidants. The sulfur-containing amino acids include methionine, cysteine, and taurine. Methylsulfonylmethane (MSM), an important volatile component in the sulfur cycle, is another source of sulfur found in the human diet. Sulfur is the sixth most abundant macromineral in breast milk[5] (colostrum has three times more than mature milk) and the third most abundant mineral determined by percentage of total body weight in an adult.[6]

Sulfur has a long history of use for a variety of dermatological disorders, as an ingredient in acne ointments,[7,8] in antidandruff shampoos,[8] and as an antidote for acute exposure to radioactive material.[8] Sulfur aids in wound healing via keratin and has a history of folk usage as a remedy for skin rashes.[8] Topically applied sulfur is keratolytic through the formation of hydrogen sulfide by a reaction that depends on direct interaction between sulfur particles and keratinocytes.[8] Topically, sulfur can induce various histological changes, including hyperkeratosis, acanthosis, and dilation of dermal vessels.[8] Sulfur-containing baths have a long history of use for the treatment of psoriasis, rheumatic pain, and infections,[9-15] and are still prescribed for asthma by medical doctors in France.

Compounds containing sulfur are found in all body cells and are indispensable for life. The primary sulfur-containing compounds of interest in humans are methionine, cysteine, homocysteine, cystathione, S-adenosylmethionine (SAMe), taurine, α-keto-γ-CH_3-thiobutyrate, methanethiol, thiamin, biotin, alpha-lipoic acid (ALA), coenzyme A, glutathione (GSH), chondroitin sulfate, glucosamine sulfate, fibrinogen, heparin, metallothionein, and inorganic sulfate.[16] With the exception of the two sulfur-containing vitamins, thiamin and biotin, all of these sulfur compounds are synthesized from just one parent compound, methionine.[16] In addition, sulfur is needed for a number of chemical reactions involved in the metabolism of drugs, steroids, and xenobiotics.

Figure 1. *The Sulfur Cycle*



Sources of Sulfur

Organic sulfur complexes, notably the amino acids methionine and cysteine, largely meet the sulfur needs of the body.[17] Sulfur-containing amino acids are more abundant in animal and cereal proteins than in legume proteins, with the ratio of methionine to cysteine tending to be higher in animal proteins than in plant sources. Methionine can serve as a source for cysteine through the trans-sulfuration pathway, but the reverse reaction cannot take place,[16] making methionine of critical importance. Soils low in sulfur are common in a number of regions of the world. In the United States, low-sulfur soils are found in the Pacific Northwest and the Great Lakes region.[1] Glutathione is a source of dietary sulfur, with fruits and vegetables contributing over 50 percent of dietary glutathione, while meats contribute less than 25 percent.[18]

Most nutrition textbooks ignore the contribution free sulfate and sulfate bound to parent molecules as sulfoesters make to total available sulfur, because their contribution to total sulfur intake is considered negligible by comparison.[5] However, glutathione, taurine, N-acetyl-methionine, and inorganic sulfate can all have amino acid bioactivity by sparing the need for dietary methionine or cysteine.[16] To discover this, researchers induced an SAA deficiency by feeding animals an SAA-deficient diet, also devoid of sulfate. Sulfur compounds in question, e.g., sulfate, were then administered and weight gain or nitrogen retention recorded. In animal diets deficient in cysteine, sulfate has been demonstrated to spare the physiological need for cysteine and reverse weight loss induced by cysteine-deficient diets.[16] In addition cysteine, but not methionine, becomes labeled with radioactive-S when radioactive sulfate is fed or injected into animals. Thus, sulfate can be incorporated into compounds for which cysteine is a precursor, e.g., taurine and GSH.[16]

Sulfate from dietary sources and endogenous release from SAAs is also used to synthesize the chondroitin matrix of cartilage.[16] The extracellular sulfate pool in humans is among the smallest of animal species[19] and is readily depleted by consumption of a low protein diet or by drugs metabolized by sulfation.[19,20]

The RDA committee recommends a combined SAA intake of at least 13 mg/kg per day. This is equivalent to approximately 910 mg/day for a 70 kg adult. Other authorities believe this figure to be too low and recommend an intake of 25 mg/kg/day of SAA for adults.[21,22] A rule of thumb is 1 gram of protein should contain at least 17 mg of SAAs (e.g., gluten (wheat protein) or zein (corn protein)).

Animal protein has a higher net protein utilization factor (NPU) and usually contains more protein by weight than most plant foods. Therefore, it is harder to obtain individual amino acids from a given gram of plant protein than from a

Table 1. *Needs for SAAs Based on Age*

SAA	Infants 3-4 mo	Children at 2 yrs	Children 10-12	Adults
Methionine plus Cysteine * (mg/kg/day)	58	27	22	13

Based on requirement needed to maintain nitrogen balance and support adequate lean tissue growth. With loss of lean tissue, as in old age, SAA requirements are lower than in healthy younger adults.

gram of animal protein. For this reason, human diets entirely animal free (vegan) may lead to suboptimal sulfur amino acid status.[1] This could occur because the diet may be too low in total protein, composed of proteins of low digestibility, or be low in SAAs. Any of these factors in isolation or occurring together could lead to SAA deficiency.

Analysis of long-term vegans living in California revealed an average protein intake of 64 g/day and an SAA intake of approximately 15 mg/kg/day or 16 mg of SAA per gram of protein.[23] This level of intake would just meet the average requirement but could be marginal for adults with higher than average requirements, such as athletes or people with HIV. Although not conclusive evidence, this does provide evidence that vegan patients should be screened for SAA deficiency.

Not all plant foods are low in SAAs. Some commonly eaten plant foods high in methionine are corn, sunflower seeds, oats, chocolate, cashews, walnuts, almonds, and sesame seeds, in that order.[24] Oats and corn are high in cysteine as well. Corn grits, although low in lysine, have a surprisingly high SAA content of approximately 44 mg/g of corn protein (low NPU), compared to chicken (high NPU) at approximately 41 mg/g.[25] Table 1 illustrates that average requirements for SAA are highest among infants and children.[26]

Conditions Where Thiols Could Be Used In Prevention

Atherosclerosis

Plasma thiols (ALA, GSH or its precursors) have been shown to inhibit oxidation of LDL cholesterol (LDLs).[4] Oxidation of LDLs is regarded as a contributing factor in atherosclerosis. Oxidized LDLs are chemotactic to monocytes, promoting their migration into the intima, their early appearance in the fatty streak, and their transformation and retention in the subintimal compartment as macrophages.[27] Scavenger receptors on the surface of macrophages facilitate the entry of oxidized LDLs into these cells, transferring them into lipid-laden macrophages and foam cells.[27] Oxidized LDLs are also cytotoxic to endothelial cells and may be responsible for their dysfunction or loss from the more advanced lesion.[27]

Overtraining

Excessive physical stress, such as is seen in athletic overtraining, inflicts minor trauma on the athlete's body and can deplete plasma glutathione levels,[28,29] and increase urinary loss of sulfate.[30] For the athlete in training, muscle catabolism or a decrease in plasma GSH are counterproductive. Suboptimal intakes of sulfur amino acids during training may exert a proinflammatory influence because, at low levels of intake, cysteine is preferentially incorporated into protein rather than GSH.[31] It follows that methionine and cysteine could be used to ameliorate loss of lean tissue and GSH stores. Cysteine and methionine are abundant in whey protein. Methionine can be converted into cysteine (cysteine is the rate-limiting step in glutathione synthesis). Lipoic acid could be used to reduce oxidative stress and to preserve vitamin E and C status.

HIV

Low serum thiol levels can predict morbidity in HIV-positive IV drug users.[32] N-acetylcysteine (NAC), glutathione, and alpha-lipoic acid have been shown to interrupt the process of viral activation and CD4 cell death.[33] Sulfur supplementation (as SAA or NAC) has been demonstrated to raise plasma thiol levels.[34,35] In a recent study, the analysis of the daily urinary excretion of sulfate and urea of a group of 19 AIDS patients and 22 asymptomatic HIV-positive subjects confirmed that HIV-positive patients experience massive loss of sulfur.[34] The sulfur loss of asymptomatic patients was equivalent to a mean loss of about 10 g of cysteine per day. If extrapolated, this would correspond to a negative balance of approximately 2 kg of cysteine per year, assuming the normal sulfate excretion (3 g of cysteine per day) is balanced by an adequate diet.[34] The abnormally high sulfate/urea ratio suggests this process drains the glutathione pool.[34] In addition to counteracting catabolism of sulfur, cysteine has also been used to rebuild the immune

function of HIV-positive patients.[35] The immune system is the first to suffer the effects of cysteine depletion and the impairment of immune functions in HIV-positive patients results, at least in part, from cysteine deficiency and depletion of the GSH pool.[35]

To determine the therapeutic effect of SAA supplementation in HIV infection, 40 patients with antiretroviral therapy (ART) and 29 patients without ART were given treatment for seven months with approximately 600 mg NAC administered every other day.[35] The main outcome measures were the change in immunological parameters including natural killer (NK) cell and T-cell functions, and the viral load. N-acetylcysteine caused a marked increase in NK cell activity and raised CD4 counts, serum albumin, and glutamine. The immunomodulating effect of NAC supplementation suggests the HIV-induced cysteine depletion may be a way in which the virus compromises the immune defense of the host.[35]

Therapeutically Relevant Thiols

Glucosamine Sulfate

Glucosamine sulfate (GS) is an aminomonosaccharide (a combination of glutamine and glucose) combined with a sulfate group. Used to treat osteoarthritis, GS is concentrated in joint cartilage where it is a substrate for cartilage glycosaminoglycan (GAG) synthesis. GS supplements are derived from chitin, a substance found in the shells of shrimp, lobsters, and crabs. Synthetic glucosamine sulfate is also available. Glucosamine is currently sold as the sulfate, hydrochloride, N-acetyl, or chlorhydrate salt.[36] Most of the clinical studies have used either the sulfate or chloride salt. Reviews of clinical trials and meta-analyses support the efficacy of glucosamine.[37]

Exactly how glucosamine works is not fully understood. About 90 percent of orally administered glucosamine gets absorbed,[38,39] although a significant portion is catabolized during first pass metabolism and free glucosamine is not detectable in the serum after oral intake (possibly because it is bound to plasma proteins).[38,39] This has led some researchers to speculate it is the sulfate rather than the glucosamine that is the active constituent.

Sulfate is required for GAG synthesis and sulfate depletion inhibits GAG synthesis in human articular cartilage.[40] Hoffer et al[36] recently demonstrated that glucosamine increases serum and synovial sulfate concentrations. This effect was reversed with co-administration of

Table 2. *Pharmacological Actions of Chondroitin Sulfate*[43]

Chondrocytes	Bones	Joint space	Clinical
Stimulates the production of proteoglycans; reduction of apoptosis; blockade of the TNF-alpha receptor (a cytokine involved in cartilage degradation).	Increases the calcium pool; promotes in vitro mineralization; increases the rate of bone repair.	Increases synovial fluid viscosity; inhibits extracellular proteases involved in cartilage degradation; anti-inflammatory effect which protects cartilage matrix against damage from free radicals.	Decreases clinical symptoms in experimental arthritis.

acetaminophen. GAG synthesis in human articular cartilage is sensitive to the sulfate-depleting effects of drugs used in the treatment of rheumatoid arthritis and osteoarthritis.[40] Interestingly, sulfate administration can also increase the clearance of acetaminophen in sulfate-deficient individuals, decreasing its toxicity but potentially reducing the analgesic effect.[41] Increases in serum sulfate may also explain some of the therapeutic effects of MSM and DMSO.

Chondroitin sulfate

Chondroitin sulfate (CS) is a member of the polysaccharides called GAGs. CS is made up of linear repeating units of D-galactosamine and D-glucuronic acid and is found in human cartilage, bone, skin, cornea, and the arterial wall. Sources used in nutritional supplements include bovine and pork cartilage, shark cartilage, and whale septum. Whereas glucosamine sulfate is thought to promote the formation and repair of cartilage, chondroitin sulfate is believed to promote water retention and elasticity in cartilage and inhibit enzymes that break down cartilage.

It was thought that oral chondroitin was not absorbed because of its large molecular size. However, in 1995 researchers found evidence that up to 15 percent of chondroitin is absorbed intact,[42] even though it is a large molecule with molecular weight ranging from 5,000-50,000 daltons. The lower molecular weight chondroitin (less than 16,900 daltons) appears to be absorbed intact.[43] When administered, chondroitin exhibits a tropism for GAG-rich tissues such as the eyes, joints, lumbar disks, and epiphysis at the ends of long bones.[43] The pharmacological actions of chondroitin sulfate are summarized in Table 2.

Glutathione (reduced = GSH; oxidized = GSSG)

Glutathione is a tripeptide consisting of γ-glutamine-cysteine-glycine,[44] and is the most abundant endogenous non-protein thiol.[45] Functions include detoxification of free radicals and peroxides, regulation of cell growth and protein function, and maintenance of immune function.[45] Glutathione deficiency can be induced by protein-deficient diets that are also low in SAAs. GSH is a substrate for GSH transferases and peroxidases, enzymes that catalyze the reactions for detoxification of xenobiotics and reactive oxygen species.[46]

The glutathione pool is of key importance in the defense against oxygen radical pathology.[47] GSH has a mild sparing effect on vitamins C and E through its role as a reducing agent.[48,49] Precursors of GSH include cysteine, N-acetylcysteine, glutathione monoethyl ester, and oxothiazolidine 4-carboxylate (OTC).[49] While administration of oral glutathione increases hepatic GSH levels in fasted rats,[46] it is not completely clear whether the increase in GSH is from direct absorption of the oral GSH or because GSH contains cysteine, the key precursor. There are reports (both animal and human), however, of oral GSH being absorbed intact.[18,50,51]

Low GSH levels in elderly subjects[52] have been theorized to accelerate the aging process.[28] Therefore, maintaining good GSH status during aging may provide a survival advantage in humans.[47]

There is a relationship between GSH, nutrition, and oxidative stress. In diseases where decreased tissue GSH and increased oxidative stress are implicated, or where there is protein-energy malnutrition seen as a secondary manifestation, such as in AIDS, cancer, burns, chronic digestive diseases, alcoholism, or in primary malnutrition, restoration of GSH through administration of cysteine could be beneficial.[47]

Cysteine

Cysteine plays important roles as an extracellular reducing agent, a critical substrate for protein synthesis, and the rate-limiting precursor to GSH and taurine.[45] Cysteine can be given orally to increase GSH[53] or to chelate trace elements in the gut, thereby decreasing absorption of both cysteine and the trace element.[54] Orally administered cysteine markedly improves growth and reduces liver copper deposition in animals fed high levels of inorganic copper.[54] Excessive copper ingestion impairs SAA utilization and increases the dietary requirement for SAA as well. Cobalt and

selenium toxicity can be ameliorated by oral cysteine ingestion.[54] NAC may be a preferred delivery system for cysteine because cysteine readily absorbs moisture and oxidizes; whereas, NAC is more stable and may be better absorbed.

N-acetylcysteine (NAC)

N-acetylcysteine is a derivative of the sulfur-containing amino acid cysteine and an intermediary (along with glutamic acid and glycine) in the conversion of cysteine to glutathione. Made endogenously and found in foods, NAC and cysteine both have sulfhydryl groups that can scavenge free radicals.[53] Oral NAC administration leads to an increase in intracellular cysteine and GSH levels.[55] NAC is the primary antidote for acetaminophen poisoning,[56-60] and can also be useful in the treatment of intoxication due to chromate or borate and is effective at reversing the oliguria associated with these intoxicants.[61] IV administration is preferable for poisoning, since nausea and vomiting may limit the effectiveness of oral therapy.[58] *In vivo*, N-acetylcysteine forms L-cysteine, cystine, L-methionine, and glutathione. L-methionine also forms cysteine, giving rise to glutathione and other products.[59]

HIV-positive patients often have abnormally low GSH and cysteine levels and experience massive sulfur loss.[55] The rate of sulfur loss is not affected by antiviral drugs but may contribute to antiviral treatment failure.[55] Several preliminary clinical trials on NAC treatment of HIV-positive patients have shown significant beneficial effects. These trials did not meet the stringent standards required by health authorities, unfortunately, because they were either too small, too short, not rigorously controlled, or the end-point examined was not a widely accepted marker for survival.[55]

Taurine

Taurine is a conditionally essential sulfonated beta amino acid derived from methionine and cysteine metabolism. Taurine is present in high concentrations in most tissues, particularly in proinflammatory cells such as polymorphonuclear phagocytes and in the retina.[62] Retinal pathologies have been reported for animals and humans deficient in taurine.[63] With the exception of cow's milk, taurine is widely distributed in foods from many animal (but not plant) sources.[64]

Metabolic actions of taurine include bile acid conjugation, detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium levels.[65,66] Although taurine is synthesized from SAA, concern has been expressed about the adequacy of endogenous sources, especially in neonates. Accordingly, proprietary infant formulas are now supplemented with taurine.[64] Clinically, taurine, which achieves good uptake via oral supplementation, has been used with varying degrees of success in the treatment of the following conditions: cardiovascular diseases, hypercholesterolemia, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease, hepatic disorders, alcoholism, and cystic fibrosis.[64,65]

Alpha Lipoic acid (thioctic acid, ALA)

Alpha-lipoic acid plays an essential role in mitochondrial dehydrogenase reactions and is therapeutically useful for preventing free radical cellular damage, reducing oxidative stress, lowering blood sugar, and enhancing the antioxidant potency of other antioxidants (ascorbate and vitamin E).[67] Working in both aqueous and hydrophobic environments, ALA has also been shown to increase coenzyme Q10[68] and intracellular GSH[69] levels. After oral administration, ALA is readily absorbed and converts to its reduced form, dihydrolipoic acid (DHLA).[70] Lipoic acid administration has been shown to be beneficial in a number of conditions including ischemia-reperfusion injury,[71,72] diabetes (hydrophobic binding to protein such as albumin occurs which can prevent glycation reactions),[73-76] cataract formation,[77] neurodegeneration,[78] and radiation injury.[78,79]

DMSO (Dimethyl sulfoxide)

DMSO, a by-product of the wood industry, was first introduced as a therapy to the scientific community in 1963 by a research team headed by Stanley W. Jacob, MD.[80] Unlike MSM, DMSO

is not found in the diet. DMSO can scavenge [OH^-] free radicals,[81] a primary trigger in the inflammatory process, and pass through membranes easily.[82] Additionally, it has been demonstrated that DMSO can exert a protective effect on hyaluronic acid against depolymerization due to insult from [OH^-], gamma radiation, or neutrophil degranulation.[83] Neutrophil-mediated depolymerization with associated release of [OH^-] is theorized to contribute to the breakdown of joint tissue in inflammatory arthritic conditions.[83]

DMSO's ability to penetrate tissues varies with its strength. A 70-90 percent DMSO solution has been found to be the most effective strength, with penetration ability actually dropping with concentrations higher than 90 percent.[80] Two topical formulas used by the DMSO clinic (now closed) at Oregon Health Sciences University are listed in Table 3.

DMSO has the potential to drive with it across membranes other drugs or substances. Possible efficacy exists for DMSO in the treatment of: pain,[84] inflammation,[85-91] arthritis,[85-87,92] wound healing,[93-95] burns,[96,97] amyloidosis,[98,99] and interstitial cystitis.[100] The FDA has approved its use for interstitial cystitis. Side effects of DMSO can include contact urticaria, desquamation, burning sensation, and garlic-like breath odor.[98,99]

Table 3. *Topical DMSO Formulas*

General musculoskeletal support	**60 parts DMSO, 20 parts urea, and 20 parts water. This formula can be gelled or used as a liquid for musculoskeletal applications and will lessen side effects such as itching, skin irritation, and sulfur breath.[81]**
Collagen disorders (scleroderma, Peyronie's disease, Dupuytren's contracture)	**70 parts DMSO, 15 parts urea, 7.5 parts water, and 7.5 parts potassium salt of para-aminobenzoic acid.[81]**

Methylsulfonylmethane (MSM, dimethyl sulfone, crystalline $DMSO_2$, or $DMSO_2$)

MSM is found in foods, including fruit, alfalfa, corn, tomatoes, tea, and coffee;[101] in human and bovine milk; and in human urine (4-11 mg/day of MSM are normally excreted in the urine).[102] Easily soluble in water, MSM contains 34-percent elemental sulfur.[103] A normal oxidation product of naturally occurring DMSO,[101] MSM does not cause a garlic-like body odor[81] (like DMSO) when ingested. When DMSO enters the body, approximately 15 percent of it is converted to MSM.[104] Reported uses for MSM in humans include treatment for conditions such as hyperacidity, parasites, constipation, musculoskeletal pain, arthritis, allergies, and for immunomodulation.[81,100]

There is a metabolic relationship between methionine and MSM. When cows were fed D, L-methionine orally a substantial increase in urinary MSM excretion was observed.[101] Little is known about the pharmacokinetics of MSM in humans. A 1975 study found recovery of MSM administered orally to humans was only three percent, suggesting some type of utilization or modification in the gut or liver.[101] In one case report,[105] using *in vivo* proton magnetic resonance spectroscopy, MSM was detected in the brain of a normal 62-year-old male taking oral MSM, strongly suggesting that MSM is absorbed and can cross the blood-brain barrier, since MSM is not normally found in the brain. The cerebral spinal fluid of this patient was tested for MSM content to rule this out as a source of MSM. The subject had ingested MSM at a dose of 182 mg/kg for seven days followed by 2,000 mg/day as a maintenance dosage. The concentration of this compound in the brain was measured to be 2.4 mmol, with a washout half-life of approximately 7.5 days.[105]

To determine whether sulfur from MSM is incorporated into SAAs, radio-labeled MSM was administered to guinea pigs and incorporation of ^{35}S into methionine and cysteine was measured. One percent of the radioactivity was incorporated into serum methionine and cysteine, none was found in the feces, and most was excreted in the urine.[101] Although this work was done in 1986, a follow-up study has not been performed.

Subjects who showed hypersensitivity to aspirin, oral antibiotics, and other NSAIDS were drug-tolerant when MSM was given with or within an hour of ingesting the sensitizing drug. MSM has been reported to be active *in vivo* and *in vitro* against Giardia, Trichomonas, and round worms, where MSM may compete for binding sites at the mucus membrane, blocking interface between host and parasite.[81]

Methylsulfonylmethane is one of the least toxic substances in biology, similar in toxicity to water. The lethal dose (LD50) of DMSO for mice is over 20 g/kg body weight.[106] Since MSM is a metabolite of DMSO, this should be a reflection of MSM toxicity. According to research done at the MSM clinic at the Oregon Health Sciences University, long-term use of MSM at a dose greater than 2 g/day is well tolerated, producing no adverse effects.[107]

In genetically susceptible mice, both MSM and DMSO were shown to be effective in preventing autoimmune disease and inflammatory joint disease.[108-110] In addition, tumor onset in colon cancer-induced rats was markedly delayed in animals receiving MSM supplementation versus controls, suggesting a chemopreventive effect.[111] Four-percent MSM in drinking water had a similar delaying effect on rat mammary breast cancer.[112] Fewer poorly differentiated tumors were noted in treatment groups. Neither weight loss nor toxicity was observed in animal reports.[111,112]

In clinical studies, MSM was used for treating six patients with interstitial cystitis.[100] Patients were given 30-50 cc of MSM instilled into the bladder at weekly intervals. Five patients became asymptomatic while one had bladder spasms and withdrew from treatment.[100] This case series used DMSO as well, but it was found that MSM provided better results. In addition to scavenging free radicals and inhibiting growth of vascular smooth muscle cells, MSM has been reported to inhibit cell growth more effectively than DMSO.[113]

Because sulfur is needed for the formation of connective tissue, MSM has been studied for its use in treating arthritis. The concentration of sulfur in arthritic cartilage has been shown to be about one-third the level of normal cartilage.[114] A preliminary study was performed on 16 patients suffering from degenerative arthritis. Ten patients, randomly chosen, were treated with 2,250 mg MSM per day while six patients received placebo capsules. Eight of the ten patients experienced some relief within six weeks, while only one person showed minimal improvement on the placebo.[107]

MSM has also been reported to reduce the duration and need for chiropractic visits necessary for treating athletic injuries. A randomized, placebo-controlled clinical trial[104] (sponsored by a supplier of MSM) was conducted on 24 subjects who had sustained acute injuries. Both groups were treated with routine chiropractic manipulation, ultrasound, and muscle stimulation at each visit. The experimental group received three capsules (the exact dose was not given in the study) per day. Patients were discharged from care when all symptoms had resolved. A 58.3-percent symptom reduction on MSM, versus 33.3-percent reduction on placebo was recorded. Symptom resolution and evaluation consisted of the objective findings of the examining doctors at each visit; patient responses regarding symptoms were graded on a scale from 1-10. Patients on MSM had an average of 3.25 visits, while those on placebo had an average of 5.25 visits (an average of two fewer visits in the MSM group) before reaching a recovery phase.

There is very little information in the peer-reviewed literature on the use of MSM alone in humans;[100] therefore, more human trials are called for to fully assess MSM's therapeutic benefits.

Sulfur

Purified sulfur has been used as a therapeutic agent to reduce clinical manifestations of a reaction to combined radiotherapy called autosensitization, a type of autoimmunity associated with

radiation therapy. Thirty-four women with diagnoses of cervical cancer (stages I and II) were given 0.5-1.0 g of purified sulfur mixed with 0.25 g of glucose orally in the morning every 2-3 hours before irradiation. A significant decrease in the reaction to therapeutic irradiation was noted in the sulfur group and no side effects were observed.[115] Because radiation causes damage to DNA through free-radical intermediates, thiols with a net-positive charge may protect against radiation poisoning because they concentrate in the microenvironment of DNA and scavenge free radicals.[53]

S-adenosylmethionine (SAMe)

S-adenosylmethionine is an important methyl donor and metabolite of the sulfur-containing amino acid, methionine.[116] Like methionine, SAMe is involved in numerous metabolic processes in the body that require sulfur.[116] The body typically manufactures all the SAMe it requires from methionine, but a defect in methylation or a deficiency in any of the cofactors required for SAMe production (methionine, choline, folate) is theorized to reduce the body's ability to produce SAMe.

Methylation defects have been implicated in the etiology of psychiatric illness,[117] and depression is the most common neuropsychiatric complication of a deficiency in the methyl donor, folate.[118] Increasing levels of SAMe through supplementation may act as an effective antidepressant by elevating serotonin and dopamine activity in the brain.[118-120] SAMe has performed as well as conventional antidepressant drugs in studies of depression, where it has been demonstrated that SAMe can alter mood. SAMe also has a fundamental role, as a methyl group donor, in transmethylation reactions in which membrane phospholipids are synthesized and is mandatory for the maintenance of membrane fluidity.[121]

Another metabolic pathway involving SAMe, trans-sulfuration, is initiated with the release of a methyl group from the molecule and the formation of S-adenosyl-homocysteine, which is first converted to homocysteine, then cysteine, a precursor of glutathione.[121] Experimental investigations suggest the administration of SAMe exerts analgesic effects and stimulates the synthesis of proteoglycans by articular chondrocytes, with minimal or absent side effects on the gastrointestinal tract and other organs.[122] The effect of SAMe in osteoarthritis is similar to that exerted by NSAIDs, but it is better tolerated.[122] NSAIDs, at normal pharmacological concentrations, have been demonstrated to inhibit glycosaminoglycan synthesis in human articular cartilage,[123] in addition to causing gastrointestinal bleeding and renal problems. Because of the side effects associated with NSAID use for rheumatic pain, SAMe could be used as a safe alternative.

In ethanol-fed baboons, SAMe prevents depletion of glutathione levels, normalizes mitochondrial enzymes, and results in histological improvement of hepatic lesions.[121] In healthy human volunteers it was demonstrated that, after ethanol ingestion, SAMe significantly lowered plasma concentration of ethanol and acetaldehyde.[121] In a two-year double-blind study by Mato et al,[124] SAMe was tested in patients with alcoholic cirrhosis. A 47-percent lower rate of death or need for liver transplantation was noted compared to controls. Patients took 1,200 mg SAMe/day. In people with less severe cirrhosis, the results were even more impressive. SAMe has also been proposed as an alternative to N-acetylcysteine in patients who present late after an overdose of acetaminophen.[121]

Methionine

Methionine is one of the main sources of sulfur in the body and, although it cannot be synthesized by animals, most non-restrictive Western diets supply adequate amounts. Methionine is necessary for the synthesis of proteins and is an important methyl donor. As a methyl donor methionine helps prevent fatty liver through its ability to transmethylate to form choline,[101] necessary to prevent fatty liver disease and eventual cirrhosis.[101] Human studies indicate methionine can lower acetaldehyde levels after alcohol ingestion. Because acetaldehyde is toxic, methionine may be effective in reducing the damaging effects of alcohol.[125] Patients with AIDS have low levels of methionine,[126] and there are reports of its effectiveness in the treatment of Parkinson's disease[127] and acute pancreatitis.[128]

Table 4a. *Therapeutic Indications and Dosage of Sulfur-containing Compounds*

Sulfur Nutrient	Therapeutic Indications	Dosage
NAC	Acetaminophen toxicity/ hepatoprotection [58,59] (human)	250–1500 mg/day. Oral or IV.
	Chronic bronchitis[129,130] (human)	200 mg BID
	HIV infection[33,131-140] (human, *in vitro* and *in vivo*)	800 mg/day
	Chelation of mercury, zinc and copper, chromate, and borate[61,141] (animal)	250–1500 mg/day
Cysteine	To increase GSH; To chelate copper and reduce copper levels in the liver[54] (animal)	Optimal daily intake depends on toxin exposure. Use whey protein or other source of protein high in SAAs.
Methionine	As a precursor to SAMe	Adequate daily intake is between 1,500 mg and 9,000 mg. Take with B12 and folate to prevent elevation of homocysteine and monitor levels of homocysteine in patients at risk.
	Acetaminophen poisoning[142] (human)	2-5 g oral methionine every four hours up to a total dose of 10 g
	Parkinson's disease[127]	1 g/day initially then increase to 5 g/day; decrease dose as improvement occurs.
	Ethanol detoxification[125] (human and animal)	500 mg TID
	Fatty liver (prevents fatty liver via transmethylation to form choline, lack of choline contributes to fatty liver, liver cirrhosis and impaired liver function)	500 mg TID

Table 4b. *Therapeutic Indications and Dosage of Sulfur-containing Compounds*

Sulfur Nutrient	Therapeutic Indications	Dosage
Taurine	Congestive heart failure[143-155] (mostly human studies)	1.5-4 g/day
	Diabetes[156-162] (4 human, 3 animal)	1.5-4 g/day
	Prevention of macular degeneration and other age related eye problems[63,163-165] (animal)	1.5-4 g/day
	Inhibition of platelet aggregation[66,156-158] (human)	1.5-4 g/day
	Hypercholesterolemia[166-169] (animal)	1.5-4 g/day
	Epilepsy[170,171] (human)	200 mg/kg IV
	Alzheimer's disease[65] (review)	1.5-4 g/day
	Alcoholism[172-174] (animal)	0.5 g/kg (animal studies)
	Cystic fibrosis[175-178] (human)	30 mg/kg for steatosis
Glutathione	Adjunct to cisplatin treatment for cancer [179-181] (human)	1.5g-2.5 g/m^2 IV or 600 mg IM
	Optimal aging[18,182] (human)	600-1,200 mg/day of reduced glutathione orally
	Cardiovascular disease	600-1,200 mg/day of reduced glutathione orally (theoretical)
	HIV[183] (human)	600-1,500 mg/day of reduced glutathione orally (theoretical)
	Male infertility[184] (human)	600 mg/day IM

Tables 4a, 4b, and 4c outline clinical indications and dosages for important sulfur-containing compounds.

Table 4c. *Therapeutic Indications and Dosage of Sulfur-containing Compounds*

Sulfur Nutrient	Therapeutic Indications	Dosage
Alpha Lipoic Acid	Diabetic neuropathy[73-76] (human)	14 doses of 600 mg intravenously over a 3-week period or 300-600 mg BID orally
	Diabetes: To inhibit glycosylation[79] (*in vitro*)	100-200 mg/day
	Amanita mushroom poisoning[185] (animal)	100-300 mg/day (theoretical)
	HIV infection (inhibits viral replication *in vitro*)[186-189]	100-300 mg/day (theoretical)
	Daily use as an antioxidant	20-100 mg/day
MSM	Autoimmune disorders[108,109] (animal)	6-8 mg/kg/day
	Inflammatory joint disease[104,107,110] (animal) and degenerative arthritis[107] (human)	2,000-3,000 mg/day for at least six weeks
	Interstitial cystitis and other bladder disorders[100] (nonrandomized and not controlled, human)	30-50 cc instilled into the bladder
	Healing athletic injuries[104] (unpublished, human)	2,000-4,000 mg/day
S-adenosyl-methionine (SAMe)	Depression[117,118,120,190-192] (human)	400 mg TID
	Fibromyalgia[193,194] (human)	400 mg TID
	Arthritis[122,195,196] (human)	600 mg/day for the first two weeks then 400 mg/day thereafter
	Alcohol detoxification[121] (*in vitro*)	400 mg/day
	Alcoholic cirrhosis[124]	1,200 mg/day

Toxicology

With a few exceptions, the sulfur compounds discussed in this article all have very low toxicological profiles. Adverse effects from topically applied sulfur are uncommon and are mainly limited to the skin.[8,201] There are reports of fatalities in infants after massive external application.[8]

In patients with ulcerative colitis (UC), whey protein or other foods high in SAA should be used with caution. There is evidence linking protein fermentation and subsequent formation of sulfide in the pathogenicity of this disease. Hydrogen sulfide, sulfide, and thioacetic acid are produced and cause irritation to the colonic mucosa, resulting in possible damage to colonic epithelial cells, and leading to inflammation.[202-204] One study found 96 percent of patients with UC carry sulfate-reducing bacteria in the colon compared with only 50 percent of healthy individuals.[205] In another study, a diet low in SAAs produced an improvement in UC patients.[204]

SAMe may worsen the symptoms of Parkinson's disease and should be avoided until it is proven safe for these patients.[206,207]

A concern arises in the use of NAC in HIV-positive patients because NAC can raise serum glutamine to above normal levels. Too much NAC may cause glutamine production to be favored over urea production eventually to the point that toxic ammonia accumulates.[35] The dosage schedule can be determined by monitoring plasma glutamine levels. The protocol used by Breitkreutz et al varied the dose from 0.6 g to 3.3 g in order to keep the glutamine levels below 700 microM. By the end of the observation period, the mean dose was 3 g every other day.

Organic sulfur compounds are metabolized by the molybdenum-dependent mitochondrial enzyme sulfite oxidase (sulfoxidation). This is also the process that detoxifies sulfite food additives.[208] Sulfite is toxic to the nervous system and molybdenum is necessary for its metabolism to a nontoxic form, since sulfite oxidase contains molybdenum in its active center. Normally, sulfite oxidase metabolizes sulfites to sulfates, which are excreted in the urine or reused by the body.[208] A deficiency in molybdenum or sulfite oxidase may make an individual more sensitive to sulfur-containing drugs and compounds. Animals can be made deficient in molybdenum by feeding them high amounts of tungsten or copper.[208] Molybdenum deficiency has been described in populations where the soil is low in molybdenum and in patients on long-term total parenteral nutrition.[208] Sulfite oxidase deficiency is also known; it is a rare autosomal recessive disorder, usually presenting at birth. Those with a poorly functioning sulfite oxidase system will demonstrate an increased urinary sulfite:sulfate ratio. Theoretically, molybdenum requirements could increase in patients with increased sulfoxidation or sulfation needs; e.g., sulfur supplementation or drug metabolism.

Conclusion

There are a number of medical conditions for which sulfur compounds could be used therapeutically. Methionine and cysteine can be used to increase SAMe, GSH, taurine, and NAC, and to promote detoxification of xenobiotics via the sulfation pathway. Dietary SAA analysis and SAA or protein supplementation may be indicated for vegan athletes, children, or patients with HIV, because of increased risk of SAA deficiency in these groups. A vegan diet, however, is capable of supplying adequate SAA if foods high in methionine are included. Methylsulfonylmethane may be effective for allergy, pain syndromes, athletic injuries, and bladder disorders. Glucosamine and chondroitin sulfate appear effective for maintaining cartilage matrix integrity. Chondroitin, in particular, has a number of pharmacological properties including effects on bone mineralization, production of proteoglycans, increased synovial fluid viscosity, and inhibition of proteases involved in cartilage degradation. New data support the hypothesis that increases in serum sulfate may mediate the therapeutic effects of glucosamine. Other sulfur compounds such as SAMe, DMSO, taurine, and reduced glutathione also have clinical applications in the treatment of a number of conditions, such as depression, fibromyalgia, arthritis, interstitial cystitis, athletic injuries, congestive heart failure, diabetes, cancer, and AIDS. The low toxicological profile of these sulfur compounds combined with the promising therapeutic effects warrants further human clinical trials.

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