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Review Article

Sulfur in Human Health

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Abstract

Methylsulfonylmethane (MSM) is composed of sulfur, oxygen, and methyl groups and is naturally found in a variety of foods. Because the amount found in foods can significantly decrease as a result of processing and modern agricultural practices, there has been increased interest in the usefulness of supplementing the diet with MSM. MSM is a natural source of sulfur for the diet. However, sulfur is often overlooked as a major nutrient because the majority of dietary sulfur is provided by the sulfur-containing amino acids methionine and cysteine. Sulfur is thought to exert it effects on health via its role in anti-inflammatory antioxidant pathways. There is currently no recommended daily intake of sulfur, only for the sulfur containing amino acids. However, evidence for its independent role in multiple physiological functions critical for human health suggest that recommendation for daily intake should be considered. Therefore, it is the purpose of this paper to review the literature on the role and benefits of sulfur as part of MSM in human health.

Keywords: *Sulfur; Methylsulfonylmethane; Osteoarthritis; Sulfur Containing Amino Acids*

Abbreviations

MSM: Methylsulfonylmethane; Saas: Sulfur-Containing Amino Acids; GAG: Glycosaminoglycans; GSH: Glutathione; SAM: S-Adenosyl Methionine; RDA: Recommended Dietary Allowance; OA: Osteoarthritis; HA: Hyaluronic Acids; RONS: Reactive Oxygen And Nitrogen Species; TAC: Total Antioxidant Capacity; CK: Reduced Creatine Kinase; KOOS: Knee Osteoarthritis Outcome Score; POMS: The Profile of Moods States

Introduction

Methylsulfonylmethane (MSM) is composed of sulfur, oxygen, and methyl groups [1]. MSM is naturally found in a variety of foods, such as milk, fruits, tomatoes, corn, coffee, and tea [2]. Because the amount found in foods can significantly decrease during processing and from modern agricultural practices, there has been increased interest in the usefulness or utility of supplementing the diet with MSM [3]. Earlier pharmacokinetic and metabolic research with oral MSM demonstrates it is rapidly absorbed, well distributed and completely excreted from the body [4]. In humans, serum MSM levels display the rise and fall pattern consistent with fairly rapid absorption from the stomach (within an hour), followed by slower elimination from the bloodstream (over the course of one or two days). Oral MSM appears to be absorbed in a dose-dependent manner without direct dose-dependent impact on sulfate metabolism [5].

The proposed mechanisms of action for MSM are most likely related to its anti-inflammatory [6] and anti-oxidative activity [7]. Dosages of MSM between 1.5 and 6 g/day taken for several weeks to months have been used in human clinical studies with no significant adverse events reported [6,8,9]. While there is abundant research to support the role of MSM in human health [1,6,8-17], less has been reported about sulfur. MSM is a natural source of sulfur for the diet. Sulfur is often overlooked as a major nutrient. Perhaps this is because sulfur has historically been considered for its importance in soil and plant ecology rather than for its importance in human health. In human nutrition, sulfur's better known, yet highly related compounds, include the amino acids methionine and cysteine. In addition, the cellular antioxidant glutathione plays a role in sulfur metabolism and are critical dietary sources of sulfur. Due to the important role it plays in multiple physiological pathways, it is worthy of discussion. Therefore, it is the purpose of this paper to review the literature on the role and benefits of sulfur as part of MSM in human health.

Sulfur

Sulfur is a major inorganic element with biological importance across species because of its integration into many molecules, including: amino acids, proteins, enzymes, vitamins and more [18]. Following calcium and phosphorus, sulfur is the third most abundant mineral in the human body, representing ~0.3% of total body mass. The majority of dietary sulfur is provided by the sulfur-containing amino acids methionine and cysteine, with an estimated requirement for young men of ~14 mg/day per kg body weight [19]. Dietary sulfur comes from proteins, and yet only 2 of the 20 amino acids normally present in proteins contain sulfur.

Although sulfur is found in a variety of foods, dietary intakes have declined due to modern agricultural processes, thereby increasing interest in supplemental sources [1]. However, the majority of the research regarding sulfur intake refers to the sulfur-containing amino acids (SAAs) methionine, cysteine, and taurine as the primary dietary sources rather than sulfur itself [1]. This is because the amino acids methionine and cysteine provide most of the sulfur to meet the body's need and methionine is most abundant in animal sources [1]. Additionally, Glutathione (a natural intracellular antioxidant) provides a source of dietary sulfur and is found in fruits and vegetable [20]. One of these amino acids, methionine, cannot be synthesized by our bodies and must therefore be supplied by the diet. Cysteine, another sulfur containing amino acid, and an important part of a large number of key metabolic intermediates is synthesized by the human body via a sulfur dependent pathway [19].

It has recently been questioned as to whether or not dietary requirements of methionine are being met, which then raises the questions as to whether or not sulfur needs are being met through diet alone [21]. While most Western diets are adequate in methionine, in many parts of the world, including the U.S., the sulfur content of soil is inadequate, effecting other sources, namely glutathione and methionine [22]. In addition to decreased levels in soils, diets that are predominantly vegan or vegetarian may also be low in methionine and therefore sulfur. The relationship between the environmental sulfur and human sulfur is represented in figure 1. This is critical because of the role that the SAAs play in multiple physiological pathways. For example, they provide sulfates for glycosaminoglycans (GAG) and glutathione (GSH), which in turn play a key role in collagen and cartilage health. It should be noted that intake does not have to be deficient to create physiological concerns. It has been suggested that even when intake is marginally sufficient, the sulfur is directed towards synthesis of proteins and other key metabolic intermediates that have critical roles in brain and organ function like GSH and S-Adenosyl Methionine (SAM) [21].

Recommended intake and sources of sulfur

Currently there is no recommended dietary allowance (RDA) for sulfur. However, there are recommended daily intake amounts for sulfur-containing amino acids. For example, intake of the essential sulfur amino acid methionine (combined with cysteine) is recommended at 14 mg/kg BW. However, these recommendations rely on what might be considered inappropriate nitrogen balance studies as an indicator of "sulfur adequacy" and may grossly under-estimate the actual dietary need for sulfur [21]. It is important to point out that the recommendations reflect sulfur's perceived supportive role, for example assuming that the needs will be met through indirect sources such as methionine.

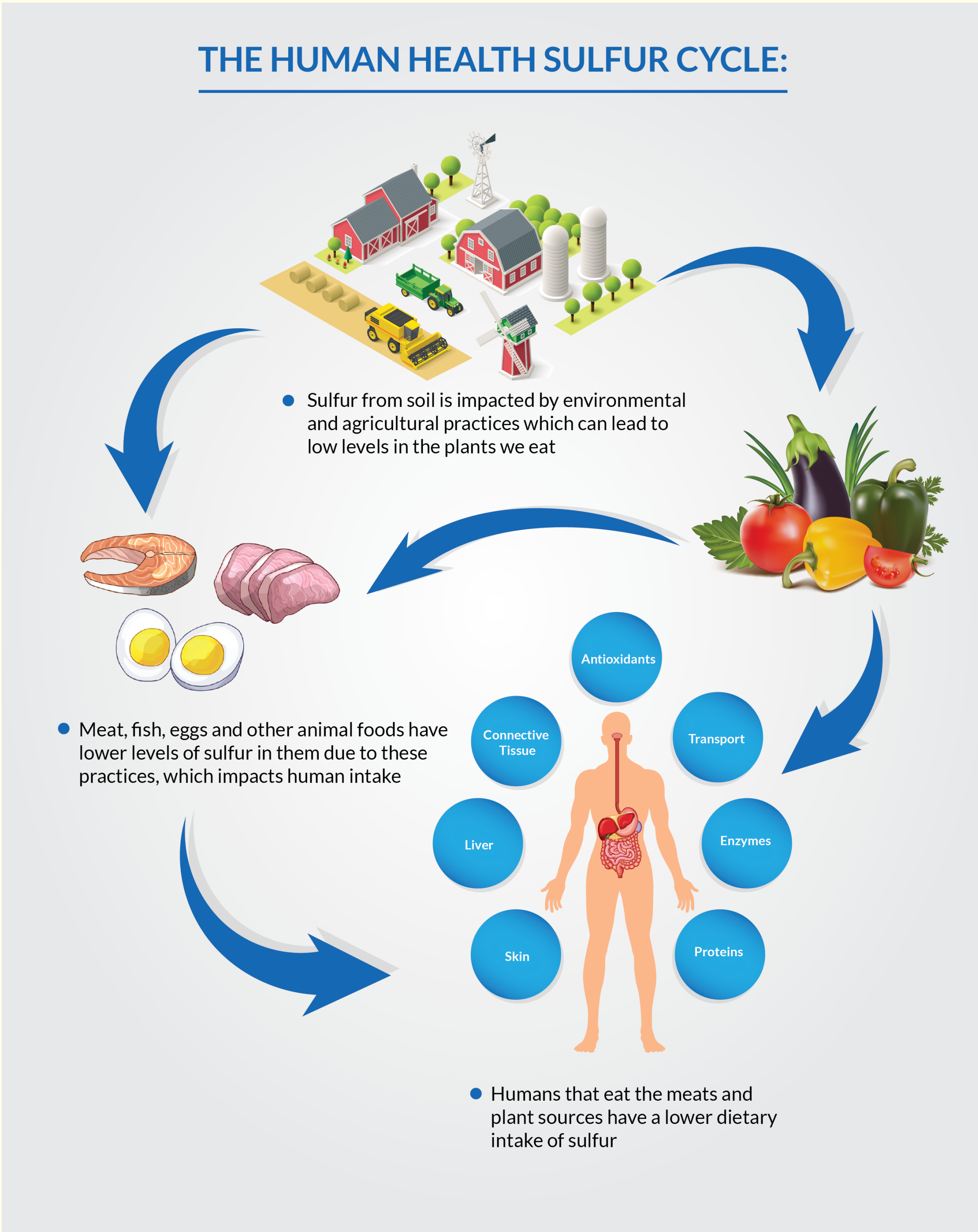
THE HUMAN HEALTH SULFUR CYCLE:
Sulfur from soil is impacted by environmental and agricultural practices which can lead to low levels in the plants we eat
Meat, fish, eggs and other animal foods have lower levels of sulfur in them due to these practices, which impacts human intake
Antioxidants
Connective Tissue
Transport
Liver
Enzymes
Skin
Proteins
Humans that eat the meats and plant sources have a lower dietary intake of sulfur

Figure 1

Sulfur intake is directly correlational to protein intake source. Chicken, fish and beef proteins contain about 5% of SAA. Dairy products contain around 4% because of casein's lower SAA content. If milk proteins are separated, whey protein contains more SAA than casein. Plant proteins average below 4%. The highest content of SAA is found in egg whites, containing around 8% of SAA. Drinking water contains varying amounts of sulfur, brussels sprouts, garlic and onions typically have considerable amounts of sulfur but this varies due to soil variability [21].

MSM as a source of Sulfur

Since directly determining sulfur needs is challenging, it is logical to focus on contributing sources of sulfur, especially when considering supplementation. MSM is one such dietary and supplemental source. MSM is composed of sulfur, oxygen, and methyl groups [1]. Several studies have demonstrated that sulfur from MSM can be incorporated into SAA, proteins and various tissues [23,24]. MSM is naturally found in a variety of foods, such as milk, fruits, tomatoes, corn, coffee, and tea [2]. As stated earlier, changes in agriculture has also changed the sulfur content of the soil, impacting the natural levels of sulfur in a wide variety of foods. Because the amount found in foods can also significantly decrease during food processing and manufacturing, there has been increased interest in the usefulness or utility of supplementing the diet with MSM.

Earlier pharmacokinetic and metabolic research with oral MSM demonstrates it is rapidly absorbed, well distributed and completely excreted from the body [4]. In humans, serum MSM levels display the rise and fall pattern consistent with fairly rapid absorption from the stomach (within an hour), followed by slower elimination from the bloodstream (over the course of one or two days). Oral MSM appears to be absorbed in a dose-dependent manner without direct dose-dependent impact on sulfate metabolism [25].

MSM is sold on the commercial dietary supplement market and often utilized or promoted for joint health. Research has suggested that MSM, alone or along with glucosamine, reduces osteoarthritis (OA) related pain, swelling, and improves function. Improved function includes quality of life scores [8,9,12,26]. This improved quality of life may be explained by results of animal studies that have demonstrated that sulfur-depleted joints affected by OA showed signs of decreased joint degeneration when supplemented with MSM, perhaps due to the abundance of sulfur found in MSM [27]. In a study performed on mice, pretreatment with MSM in doses of 200 and 400 mg/kg significantly decreased ethanol/HCl-induced increase in NF-κB mRNA expression, a key regulator of inflammation in gastric mucosa [28]. The decrease in severity of ethanol/HCl-induced gastric mucosal injury upon supplementation of MSM has been explained by the inhibition of oxidative stress and inflammation (anti-oxidant and anti-inflammatory activity), which may be of interest to prevent peptic ulcer disease as well as other gastrointestinal disorders [28]. MSM may also be effective in suppressing seasonal allergic rhinitis, interstitial cystitis, autoimmune diseases, and supporting cancer chemoprevention [6].

Due to the small size of the sulfur molecule, it can penetrate membranes and therefore spread throughout the body and thus be part of many mechanisms. This can make separating its direct and indirect role challenging. However, it is thought to have its greatest effects on various mechanisms via its role in anti-inflammatory antioxidant pathways [6,7]. Dosages of MSM between 1.5 and 6 g/day taken for several weeks to months have been used in human clinical studies with no significant adverse events reported [6,8,9].

Sulfur and human health

Sulfur has a long history of use for dermatologic issues (example; acne and overall skin appearance), wound healing and acute exposure to radioactive material [20]. Additional functions of sulfur include metal transport, free radical scavenging, regulation of gene expression, protein stabilization and synthesis, tissue integrity and protection, enzyme functionality, DNA methylation and repair, regulation of gene expression, remodeling of extracellular matrix components, lipid metabolism, and detoxification of xenobiotics/signaling molecules in plants and animals [29].

Two of the most important roles sulfur play in the body lie in the connective tissue and the liver. Connective tissue such as skin, tendons, and ligaments rely on sulfur for proper cross-linking and extracellular matrix proteins like GAGs and hyaluronic acids (HA). Disulfide bonds are key to the strong, yet flexible characteristics of connective tissue. ECM proteins, which are highly sulfonated, provide strength, cushion, and retain moisture. In the liver, sulfur plays two key roles. As a major component of glutathione, and as a component of Phase 2 detoxification in the liver. Sulfur is also involved in n-3 and n-6 polyunsaturated fatty acids, minerals such as Selenium, Zinc, Copper and Magnesium, vitamins E and C, antioxidants such as the proanthocyanidins and lipoic acid, many of which are involved in the synthesis of prostaglandins and in the antioxidant cascade [21]. Sulfur is also involved in the stress response and in exercise recovery.

Anti-Inflammation

Oxidative stress, the imbalance between production of free radicals and reactive metabolites (reactive oxygen species), is known to impact inflammatory pathways in mammals including humans [30]. In turn the inflammation is known to lead to damage of cellular structure, cellular function and activity, among other health concerns. Recent research has linked long term oxidative stress to inflammation and cancers [30]. Therefore, strategies for mitigating oxidative stress and the resulting pathways of inflammation have been investigated. Several in vitro studies have demonstrated that MSM inhibits transcriptional activity of nuclear factor kappa-light chain enhancer of activated B cells (NF-kB), which is a pro-inflammatory signaling pathway [6]. MSM has been shown to positively impact tumor necrosis factor α, a pro-inflammatory cytokine, as well as interleukin-6 (IL-6) resulting in an anti-inflammatory effect [31]. As chronic inflammation is associated with multiple chronic diseases, enhancing the sulfur component of the diet through sulfur donors such as oral MSM, may further enhance the balance of oxidative stress and the respondent inflammatory pathways in humans.

Antioxidant

In vivo studies have shown sulfur has an antioxidative effect by reducing the production of reactive oxygen and nitrogen species (RONS) [7]. MSM supplementation may reduce exercise-induced oxidative stress and muscle damage in humans. Supplementation of 50 mg/kg/day in untrained males reduced markers of oxidative stress, increased total antioxidant capacity (TAC) and reduced creatine kinase (CK), and bilirubin levels after exhaustive exercise compared to placebo [10,16]. CK is a marker of muscle damage and bilirubin is an anti-oxidant substrate and marker of oxidative stress. Another study reported reduced perceived muscle soreness and fatigue and increased antioxidant activity in moderately-trained men with a total MSM dose of 3.0 g/day [5]. In this study, healthy men supplementing with 3.0 gm MSM daily experienced an increased and supportive change in total blood antioxidant capacity (Trolox equivalent antioxidant capacity) that was further supported by no change in intracellular glutathione, demonstrating that the anti-oxidative effects of MSM are independent of glutathione metabolism [16]. Similarly, MSM has been shown to decrease inflammatory molecules in response to strenuous exercise [17]. When physically active men were supplemented with either placebo or MSM (3 g/day), MSM not only dampened IL-1β and IL-6 in response to an intense bout of exercise (suggesting that MSM works as an antioxidant) but also increased IL-10 levels in response to exercise [17]. As IL-10 is increased in response to exercised-induced muscle damage and acts as an anti-inflammatory mediator by downregulating proinflammatory cytokines IL-1β and TNF-α, supplementation with MSM reflects anti-inflammatory mechanisms [17]. However, supplementation of 3g/day of MSM over 8 weeks in active individuals performing high impact activities, did not show significant improvements in Knee Osteoarthritis Outcome Score (KOOS) and the Profile of Moods States (POMS) compared to placebo, however this may have nothing to do with impacts on oxidative stress in the body [32]. The conflicting literature indicates the need for further research.

Conclusion

While there is abundant research to support the role of MSM in human health [1,5-9,12,16,17,26,27,32], less has been reported on the specific role of the sulfur moiety of MSM. Sulfur from MSM can be considered a dietary source and most certainly is part of the human sulfur cycle. It is without a doubt that sulfur is important to human health and metabolism. The fact that sulfur is the third most abundant mineral in the body alone denotes its importance to the human body. Further support of its importance is the critical role it plays in achieving a balance between oxidative stress and inflammation, which in turn is linked to long-term chronic diseases. While currently there are no defined daily dietary requirements for sulfur, it may be time to consider the research connecting sulfur to multiple aspects of human health in the development of minimal daily levels needed to maintain health. Interventional studies with sulfur (as part of MSM) have demonstrated an impact for oxidative stress, inflammation, immunity and even perceptions of muscle soreness and exercise recovery, thus indicating a real-world effect that is beyond that of the laboratory alone. This review paper calls for more research to be done surrounding the impacts of sulfur alone on human health and the lifecycle, and to establish a daily minimal intake that humans should aim for as part of healthy living.

Bibliography

1. Parcell S. "Sulfur in Human Nutrition and Applications in Medicine". *Alternative Medicine Review*7.1 (2002): 22-44.
2. Pearson TW., *et al.* "Natural Occurring Levels of Dimethyl Sulfoxide in Selected Fruits, Vegetables, Grains, and Beverages". *Journal of Agricultural and Food Chemistry* 29.5 (1981): 1089-1091.
3. Borzelleca JF., *et al.* "Dossier in Support of the Generally Recognized as Safe (Gras) Status of Optimsm (Methylsulfonylmethane; Msm) as a Food Ingredient". *Food and Drug Administration* Vero Beach, FL, USA (2007).
4. Magnuson BA., *et al.* "Pharmacokinetics and Distribution of [35s] Methylsulfonylmethane Following Oral Administration to Rats". *Journal of Agricultural and Food Chemistry* 55.3 (2007): 1033-1038.
5. Kalman DS., *et al.* "Influence of Methylsulfonylmethane on Markers of Exercise Recovery and Performance in Healthy Men: A Pilot Study". *Journal of the International Society of Sports Nutrition* 9.1 (2012): 46.
6. Butawan M., *et al.* "Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement". *Nutrients* 9.3 (2017).
7. Beilke MA., *et al.* "Effects of Dimethyl Sulfoxide on the Oxidative Function of Human Neutrophils". *Journal of Laboratory and Clinical Medicine* 110.1 (1987): 91-96.
8. Kim LS., *et al.* "Efficacy of Methylsulfonylmethane (Msm) in Osteoarthritis Pain of the Knee: A Pilot Clinical Trial". *Osteoarthritis Cartilage* 14.3 (2006): 286-294.
9. Usha PR and MU Naidu. "Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and Their Combination in Osteoarthritis". *Clinical Drug Investigation* 24.6 (2004): 353-363.
10. Barmaki S., *et al.* "Effect of Methylsulfonylmethane Supplementation on Exercise - Induced Muscle Damage and Total Antioxidant Capacity". *Journal of Sports Medicine and Physical Fitness* 52.2 (2012): 170-174.
11. Barrager E., *et al.* "A Multicentered, Open-Label Trial on the Safety and Efficacy of Methylsulfonylmethane in the Treatment of Seasonal Allergic Rhinitis". *Journal of Alternative and Complementary Medicine* 8.2 (2002): 167-173.
12. Debbi EM., *et al.* "Efficacy of Methylsulfonylmethane Supplementation on Osteoarthritis of the Knee: A Randomized Controlled Study". *BMC Complementary and Alternative Medicine* 11 (2011): 50.
13. Grimble RF. "The Effects of Sulfur Amino Acid Intake on Immune Function in Humans". *Journal of Nutrition* 136.6 (2006): 1660s-1665s.
14. Jacob Stanley Wallace and Jeremy Appleton. "Msm-the Definitive Guide: A Comprehensive Review of the Science and Therapeutics of Methylsulfonylmethane". Freedom Press (2003).

15. Melcher DA., *et al.* "Effects of Methylsulfonylmethane Supplementation on Oxidative Stress, Muscle Soreness, and Performance Variables Following Eccentric Exercise". *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 175 (2016): 1-13.

16. Nakhostin-Roohi B., *et al.* "Effect of Chronic Supplementation with Methylsulfonylmethane on Oxidative Stress Following Acute Exercise in Untrained Healthy Men". *Journal of Pharmacy and Pharmacology* 63.10 (2011): 1290-1294.

17. van der Merwe M and RJ Bloomer. "The Influence of Methylsulfonylmethane on Inflammation-Associated Cytokine Release before and Following Strenuous Exercise". *Journal of Sports Medicine (Hindawi Publ Corp)* (2016): 7498359.

18. Komarnisky LA., *et al.* "Sulfur: Its Clinical and Toxicologic Aspects". *Nutrition* 19.1 (2003): 54-61.

19. van de Poll MC., *et al.* "Adequate Range for Sulfur-Containing Amino Acids and Biomarkers for Their Excess: Lessons from Enteral and Parenteral Nutrition". *Journal of Nutrition* 136.6 (2006): 1694s-1700s.

20. Flagg EW., *et al.* "Dietary Glutathione Intake in Humans and the Relationship between Intake and Plasma Total Glutathione Level". *Nutrition and Cancer* 21.1 (1994): 33-46.

21. Nimni ME., *et al.* "Are We Getting Enough Sulfur in Our Diet?". *Nutrition and Metabolism (Lond)* 4 (2007): 24.

22. S Camberato and J Casteel. "Sulfur Deficiency". Purdue University Department of Agronomy: Soil Fertility Update (2017).

23. Richmond VL. "Incorporation of Methylsulfonylmethane Sulfur into Guinea Pig Serum Proteins". *Life Sciences* 39.3 (1986): 263-268.

24. Wong T., *et al.* "Small Intestinal Absorption of Methylsulfonylmethane (Msm) and Accumulation of the Sulfur Moiety in Selected Tissues of Mice". *Nutrient* 10.1 (2017): E19.

25. Kalman DS and Hewlings SJ. "A Randomized Prospective Comparative Pharmacokinetic and Pharmacodynamic Dose-Escalation Study of Oral Methylsulfonylmethane in Healthy Male Volunteers". *EC Nutrition* 13.11 (2018): 684-695.

26. Lubis AMT., *et al.* "Comparison of Glucosamine-Chondroitin Sulfate with and without Methylsulfonylmethane in Grade I-Ii Knee Osteoarthritis: A Double Blind Randomized Controlled Trial". *Acta Medica Indonesiana* 49.2 (2017): 105-111.

27. Rizzo R., *et al.* "Calcium, Sulfur, and Zinc Distribution in Normal and Arthritic Articular Equine Cartilage: A Synchrotron Radiation-Induced X-Ray Emission (Srixe) Study". *Journal of Experimental Zoology* 273.1 (1995): 82-86.

28. Amirshahrokhi K and AR Khalili. "Methylsulfonylmethane Is Effective against Gastric Mucosal Injury". *European Journal of Pharmacology* 811 (2017): 240-248.

29. Palego L. "Sulfur Metabolism and Sulfur-Containing Amino Acids: I- Molecular Effectors". *Biochemical Pharmacology* 4.1 (2015).

30. Reuter S., *et al.* "Oxidative Stress, Inflammation, and Cancer: How Are They Linked?". *Free Radical Biology and Medicine* 49.11 (2010): 1603-1616.

31. Miller LE. "Methylsulfonylmethane Decreases Inflammatory Response to Tumor Necrosis Factor-Alpha in Cardiac Cells". *American Journal of Cardiovascular Disease* 8.3 (2018): 31-38.

32. Tennent DJ., *et al.* "A Randomized Controlled Trial Evaluating Methylsulfonylmethane Versus Placebo to Prevent Knee Pain in Military Initial Entry Trainees". *US Army Medical Department Journal* 3-17 (2017): 21-25.

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