



SUPPLEMENTS, NUTRITION, AND LIFESTYLE MEDICINE TO  
SUPPORT REGENERATIVE MEDICINE

Tal Cohen, DAOM, MS.HNFM

1

Why use  
supplements?

2



**Patients are looking for faster results!**  
 (e.g. less pain and swelling, improved mobility)

3



Certain herbs and supplements can **stimulate and promote the activity of stem cells** and might increase the effectiveness of the treatment.

Udalarnath VL, Jayasinghe CD, Udagama PV. Potential role of herbal remedies in stem cell therapy: proliferation and differentiation of human mesenchymal stromal cells. Stem Cell Research & Therapy. 2016;7(1). doi:10.1186/s13287-016-0366-4.

**stem cell**  
 research & therapy

4



**Patient feels better = more referrals to you!**

5

How many  
American  
adults are  
taking  
supplements?

- A. Unknown
- B. 52 percent of population
- C. 75 percent of population
- D. Only seniors, hypochondriacs, and naturopaths take vitamins

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8



**Supplements provide additional revenue for many clinics.**

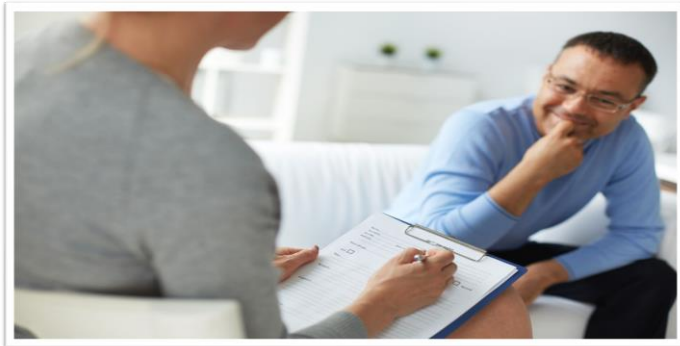
9

**Are you offering the same service as everybody else?**

10

Are you offering the same service as everybody else?

**LOW PRICE  
GUARANTEE**



11

Are you offering the same service as everybody else?

**LOW PRICE  
GUARANTEE**



**LOW PRICE  
GUARANTEE**

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What can you offer that other clinics/doctors don't?



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HOW TO OFFER A UNIQUE  
STEM CELLS PROGRAM  
(and charge more for it)

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**HOW TO OFFER A UNIQUE  
STEM CELLS PROGRAM**  
(and charge more for it)



**Nutritional & lifestyle guide  
for your patients**



**Professional-grade  
supplements to support stem  
cells function and recovery**



**Supporting treatments or other  
valuable products services to  
help your clients achieve their  
health goals.**



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**Nutritional Medicine to  
support stem cells function.**





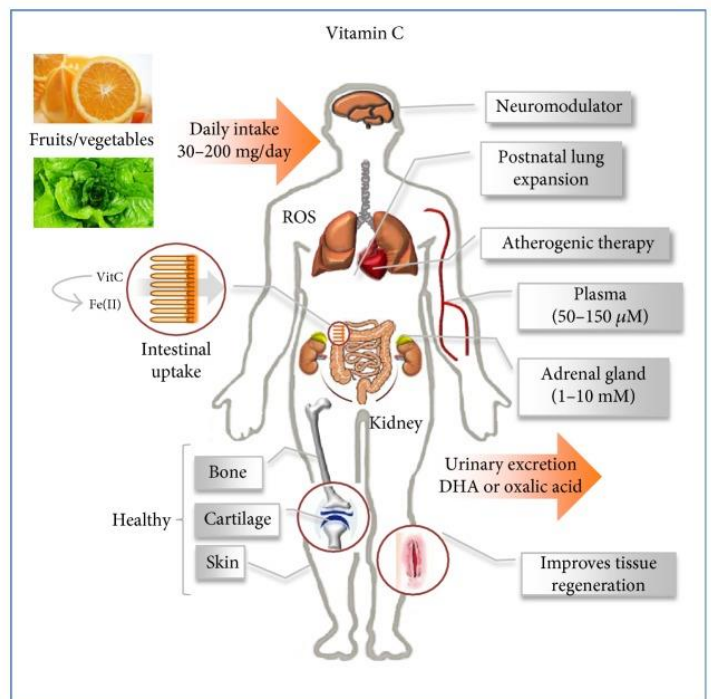
“Recent studies revealed that bioactive compounds, naturally occurring in seaweeds, herbs, fruits and vegetables, possess the ability to modulate self-renewal and differentiation potential of adult stem cells, targeting a broad range of intracellular signal transduction pathways.”

Kornicka, K., Kocherova, I., & Marycz, K. (2017). The effects of chosen plant extracts and compounds on mesenchymal stem cells—a bridge between molecular nutrition and regenerative medicine—concise review. *Phytotherapy Research*, 31(7), 947-958. doi:10.1002/ptr.5812

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Vitamin C is required for healthy function, regeneration of tissue, and can promote the function of Stem Cells.

D'Aniello C, Cermola F, Patriarca EJ, Minchiotti G. Vitamin C in Stem Cell Biology: Impact on Extracellular Matrix Homeostasis and Epigenetics. *Stem Cells Int*. 2017;2017:8936156. doi: 10.1155/2017/8936156. Epub 2017 Apr 20.



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Effect of Vit C activity appears to be dose dependent within a physiological concentration range.

A dosage that is too low or too high can reduce the function of Stem Cells and regeneration process.

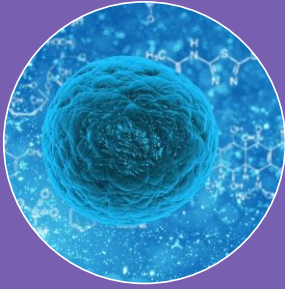


D'Aniello C, Cermola F, Patriarca EJ, Minchiotti G. Vitamin C in Stem Cell Biology: Impact on Extracellular Matrix Homeostasis and Epigenetics. *Stem Cells Int.* 2017;2017:8936156. doi: 10.1155/2017/8936156. Epub 2017 Apr 20.

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## Vitamin D may protect stem cells and play an important role in development and tissue/organ regeneration.

Abdelbaset-Ismail, A., Pedziwiatr, D., Suszyńska, E., Sluczanowska-Glabowska, S., Schneider, G., Kakar, S. S., & Ratajczak, M. Z. (2016). Vitamin D3 stimulates embryonic stem cells but inhibits migration and growth of ovarian cancer and teratocarcinoma cell lines. *Journal of Ovarian Research*, 9, 26. <http://doi.org/10.1186/s13048-016-0235-x>

23

Open Access Original  
Article

DOI: 10.7759/cureus.2741

### Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012)

Naveen R. Parva<sup>1</sup>, Satish Tadepalli<sup>2</sup>, Pratiksha Singh<sup>3</sup>, Andrew Qian<sup>1</sup>, Rajat Joshi<sup>5</sup>, Hyndavi Kandala<sup>1</sup>, Vinod K. Nookala<sup>1</sup>, Pramill Cheriyaath<sup>2</sup>

1. Internal Medicine, PinnacleHealth 2. Internal Medicine, Ocean Medical Center 3. Internal Medicine, Penn State Milton S. Hershey Medical Center

Correspondence

Abstract

Introduction

1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) is a lipid-soluble vitamin that has a wide range of effects on the body. It is essential for bone health and has been shown to have beneficial effects on cardiovascular disease, cancer, diabetes, osteoporosis, and fractures. This study aims to identify the prevalence and change in the pattern of vitamin D deficiency in subpopulations throughout the United States to provide a foundation for further clinical studies correlating the clinical outcomes to vitamin deficiency.

countries, recent literature has demonstrated that subclinical vitamin D deficiency can exist in certain populations and plays a role in downstream clinical consequences, including cardiovascular disease, cancer, diabetes, osteoporosis, and fractures. This study aims to identify the prevalence and change in the pattern of vitamin D deficiency in subpopulations throughout the United States to provide a foundation for further clinical studies correlating the clinical outcomes to vitamin deficiency.

*“Of the 4962 participants surveyed and examined, 1981 (39.92%) were found to be vitamin D deficient”*

Parva, N. R., Tadepalli, S., Singh, P., Qian, A., Joshi, R., Kandala, H., ... Cheriyaath, P. (2018). Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). *Cureus*, 10(6), e2741. doi:10.7759/cureus.2741

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Anne Marie Uwitonze,  
Mohammed S.  
Razzaque. **Role of  
Magnesium in Vitamin D  
Activation and  
Function.** *The Journal of  
the American Osteopathic  
Association*, 2018; 118  
(3): 181  
DOI: [10.7556/jaoa.2018.0  
37](https://doi.org/10.7556/jaoa.2018.037)

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**Low magnesium levels make vitamin D ineffective**  
Up to 50 percent of US population is magnesium deficient

Date: February 26, 2018  
Source: American Osteopathic Association

**Most Popular** *this week*

HEALTH & MEDICINE

New Cause of Cell Aging

near to Lower  
ng

of Estrogen in the  
to Autism

There is a caveat to the push for increased vitamin  
D. Don't forget magnesium

Work in Sync During Music  
Therapy

*Vitamin D can't be metabolized without sufficient magnesium levels, meaning Vitamin D remains stored and inactive for as many as 50 percent of Americans.*

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Vitamin D may protect stem cells that play an important role in development and tissue/organ regeneration.



- ✓ Eat food high in vitamin D: Fatty fish, like mackerel, and salmon.
- ✓ 3oz or one cup of mushrooms
- ✓ Supplementation of 5,000IU of Vitamin D3 (cholecalciferol)

Abdelbaset-Ismail, A., Pedziwiatr, D., Suszyńska, E., Sluczankowska-Glabowska, S., Schneider, G., Kakar, S. S., & Ratajczak, M. Z. (2016). Vitamin D3 stimulates embryonic stem cells but inhibits migration and growth of ovarian cancer and teratocarcinoma cell lines. *Journal of Ovarian Research*, 9, 26. <http://doi.org/10.1186/s13048-016-0235-x>

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**“31% percent of the U.S. population was at risk of at least one vitamin deficiency”**

Women are at higher nutrient deficiency



Bird, J. K., Murphy, R. A., Ciappio, E. D., & McBurney, M. I. (2017). Risk of Deficiency in Multiple Concurrent Micronutrients in Children and Adults in the United States. *Nutrients*, 9(7), 655. doi:10.3390/nu9070655

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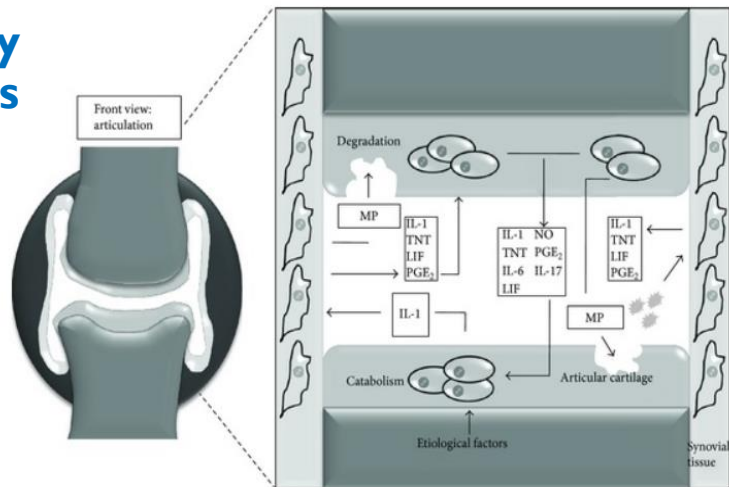


**Supplements & Herbs to support stem cells function.**

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## Physiopathology of osteoarthritis

**Catabolism process is triggered by numerous proinflammatory and proteolytic molecules which generate a local vicious circle.**



Salazar, J., Bello, L., Chávez, M., Añez, R., Rojas, J., & Bermúdez, V. (2014). Glucosamine for osteoarthritis: biological effects, clinical efficacy, and safety on glucose metabolism. *Arthritis*, 2014, 432463.

**IL: interleukin; TNF: tumoral necrosis factor; NO: nitric oxide; PG: prostaglandins; MP: metalloproteases; LIF: leukemia inhibitory factor.**

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## Management (treatment) of OA



### 1 Risk factor management and nonpharmacologic measures.

- Education
- Joint protection
- Physical activity
- Walking aids
- Postural hygiene
- Weight control

### 2 Rapid-acting drugs

- Paracetamol
- Opioids
- NSAIDs
- Intra-articular corticosteroids

### 3 Slow-acting drugs (SYSADOA)

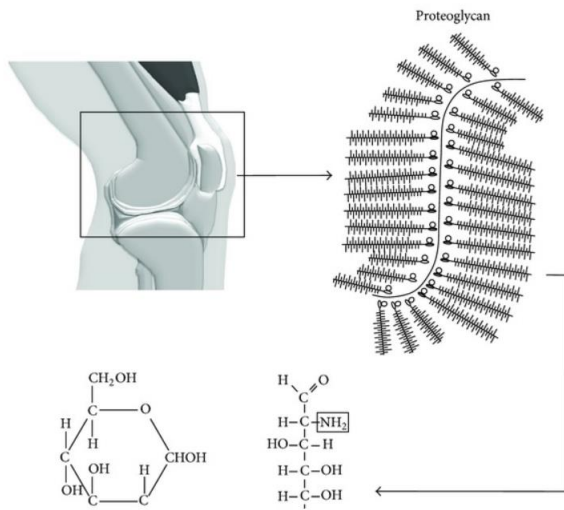
- Glucosamine
- Hyaluronic acid
- Chondroitin
- Diacerein

### 4 Invasive methods

- Articular lavage and infiltration
- Surgical treatment

Salazar, J., Bello, L., Chávez, M., Añez, R., Rojas, J., & Bermúdez, V. (2014). Glucosamine for osteoarthritis: biological effects, clinical efficacy, and safety on glucose metabolism. *Arthritis*, 2014, 432463.

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## What is Glucosamine?

An amino-monosaccharide essential and a noncellular component of connective tissue, cartilage, ligaments, and other structures. (1)

The main compounds:  
glucosamine hydrochloride,  
glucosamine sulfate,  
N-acetylglucosamine. (2)

1. Anderson, JW, Nicolosi, RJ, Borzelleca, JF. (2005) Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food Chem Toxicol.* 43(2), 187-201.
2. Salazar, J., Bello, L., Chávez, M., Añez, R., Rojas, J., & Bermúdez, V. (2014). Glucosamine for osteoarthritis: biological effects, clinical efficacy, and safety on glucose metabolism. *Arthritis*, 432463.

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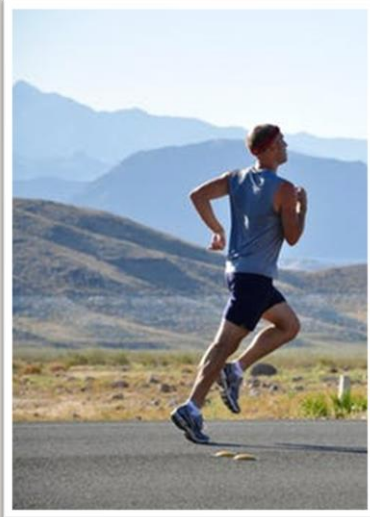
## Systemic review: Clinical effectiveness of glucosamine and chondroitin in OA



- “Inconsistent conclusions with only modest effects on reported pain and function.”
- **“A reduction in joint space narrowing was more consistently observed.”**
- “The biological mechanism of glucosamine sulphate and chondroitin remains uncertain.”

Black, C., Clar, C., Henderson, R., Maceachern, C., McNamee, P., Quayyum, Z., ... Thomas, S. (2009). The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: A systematic review and economic evaluation. *Health Technology Assessment*, 13(52). doi:10.3310/hta13520

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International Journal of  
Rheumatology

Studies demonstrate that glucosamine has many favorable effects on cartilage:

- ✓ **Anabolic effect on cartilage synthesis.**
- ✓ **Support anti-inflammatory cytokines**
- ✓ **Antioxidant activity**
- ✓ **Improves function/mobility of the joint**

In most trials, dosages of 1500 mg/day were used; the dose was as safe as placebo and was tolerated better than NSAIDs.

(2011). Effects of Glucosamine and Chondroitin Sulfate on Cartilage Metabolism in OA: Outlook on Other Nutrient Partners Especially Omega-3 Fatty Acids. International journal of rheumatology, 2011, 969012.

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# eular

fighting rheumatic & musculoskeletal  
diseases together



“In the European League Against Rheumatism (EULAR) recommendation concerning knee OA, they gave CS both the highest evidence grade and the highest recommendation strength, IA and A, respectively.”

ULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).

Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M, Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT.

Ann Rheum Dis. 2003 Dec; 62(12):1145-55.

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**Per general recommendation:**

**What type of medication should patients not take after stem cells procedure?**

**Why?**

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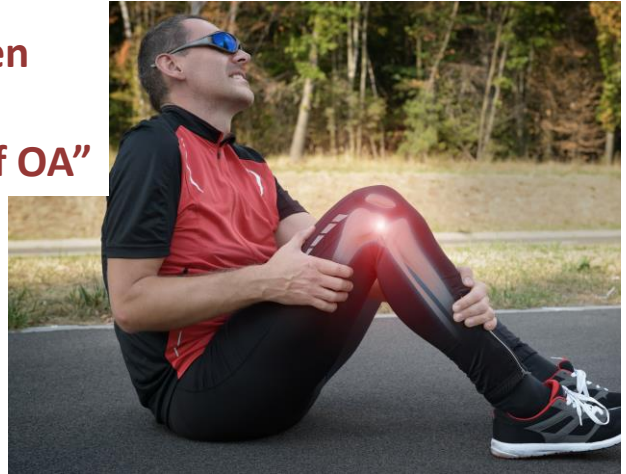
**Harmful inflammation  
vs  
“beneficial inflammation”**

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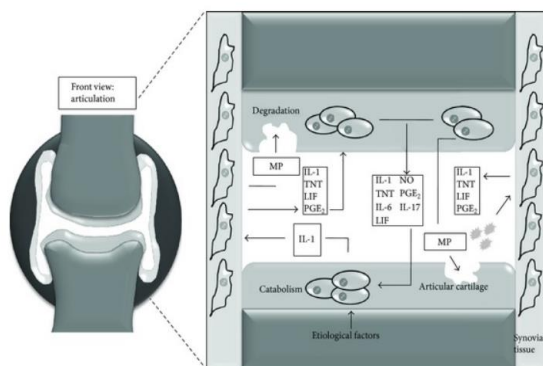
Many patients believe that their joints degenerate because of age, trauma, excess weight, or overuse.

**“Inflammation has now been strongly implicated in the pathogenesis (development) of OA”**

Sokolove, J., & Lepus, C. M. (2013). Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Therapeutic advances in musculoskeletal disease*, 5(2), 77–94. <https://doi.org/10.1177/1759720X12467868>



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**Cytokines that have been implicated in OA pathogenesis include:\***

- Tumor necrosis factor (TNF)- $\alpha$ ,
- Interleukin (IL)-1,
- IL-6,
- IL-2,
- IL-7,
- IL-15,
- IL-21

Picture source: Salazar, J., Bello, L., Chávez, M., Añez, R., Rojas, J., & Bermúdez, V. (2014). Glucosamine for osteoarthritis: biological effects, clinical efficacy, and safety on glucose metabolism. *Arthritis*, 2014, 432463.

\*Miller, R. E., Miller, R. J., & Malfait, A. M. (2014). Osteoarthritis joint pain: the cytokine connection. *Cytokine*, 70(2), 185–193. doi:10.1016/j.cyto.2014.06.019

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“Chronic inflammation leads to oxidative stress, deriving from immune cells”

Oxidative stress can lead to chronic inflammation

**CHRONIC INFLAMMATION**

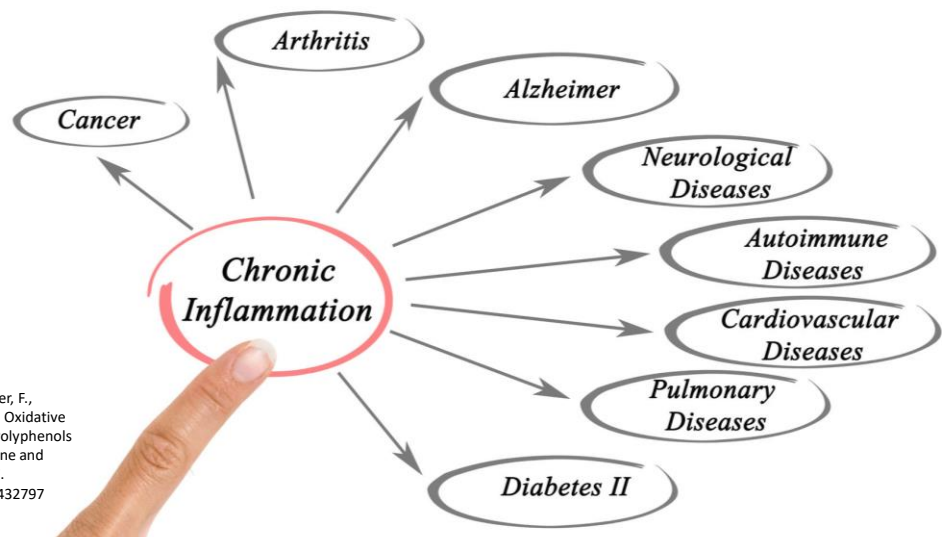
**OXIDATIVE STRESS**

Hardbower, D. M., de Sablet, T., Chaturvedi, R., & Wilson, K. T. (2013). Chronic inflammation and oxidative stress: the smoking gun for Helicobacter pylori-induced gastric cancer?. *Gut microbes*, 4(6), 475–481. <https://doi.org/10.4161/gmic.25583>

Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxid Med Cell Longev*. 2016;2016:7432797. doi: 10.1155/2016/7432797. Epub 2016 Sep 22. PMID: 27738491; PMCID: PMC5055983.

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“The inflammation triggered by oxidative stress is the cause of many chronic diseases.”



Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C., & Rahu, N. (2016). Oxidative Stress and Inflammation: What Polyphenols Can Do for Us?. *Oxidative medicine and cellular longevity*, 2016, 7432797. <https://doi.org/10.1155/2016/7432797>

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“Chronic subclinical systemic inflammation (CSSI) is defined as an elevation of inflammatory cytokines in serum because of the **failure to resolve acute inflammation, oxidative stress, or metabolic malfunction**”



- Ranneh, Y., Akim, A.M., Hamid, H.A. et al. Induction of Chronic Subclinical Systemic Inflammation in Sprague–Dawley Rats Stimulated by Intermittent Bolus Injection of Lipopolysaccharide. Arch. Immunol. Ther. Exp. 67, 385–400 (2019). <https://doi.org/10.1007/s00005-019-00553-6>

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Reducing (harmful)  
**INFLAMMATON** Is  
Essential!



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**Curcumin** is derived from the rhizomes (underground stems) of the plant *Curcuma longa*.

Curcumin has powerful antioxidant and anti-inflammatory properties, and is the most active constituent of turmeric.



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## Curcumin: Clinical Dosage



**Meta-analysis of randomized clinical trials (RCTs) provides evidence that supports the efficacy of turmeric extract (about 1000 mg/day of curcumin) in the treatment of arthritis**

Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Journal of Medicinal Food*, 19(8), 717–729. <http://doi.org/10.1089/jmf.2016.3705>

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367 primary knee osteoarthritis patients with a pain score of 5 or higher were randomized to receive **ibuprofen 1,200 mg/day** or **Curcumin extract 1,500 mg/day** for 4 weeks

**The capsules were identical in appearance and the patients were asked to take only these pills in three dosages**

#### Clinical Interventions in Aging

Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip, C., Saengsuwan, J., Tantayakom, K., ... Laongpech, S. (2014). Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clinical interventions in aging*, 9, 451-8. doi:10.2147/CIA.S58535

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After 4 weeks the study concluded that:

**Curcumin extracts are as effective as ibuprofen for the treatment of knee osteoarthritis.**

Number of events of abdominal pain/discomfort was significantly higher in the ibuprofen group

#### Clinical Interventions in Aging

Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip, C., ... Laongpech, S. (2014). Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clinical Interventions in Aging*, 9, 451-458. <http://doi.org/10.2147/CIA.S58535>

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IL-6 is also involved in pathogenesis of different inflammatory diseases. Curcumin can be considered as potential therapy against IL-6 involved pathologic states.

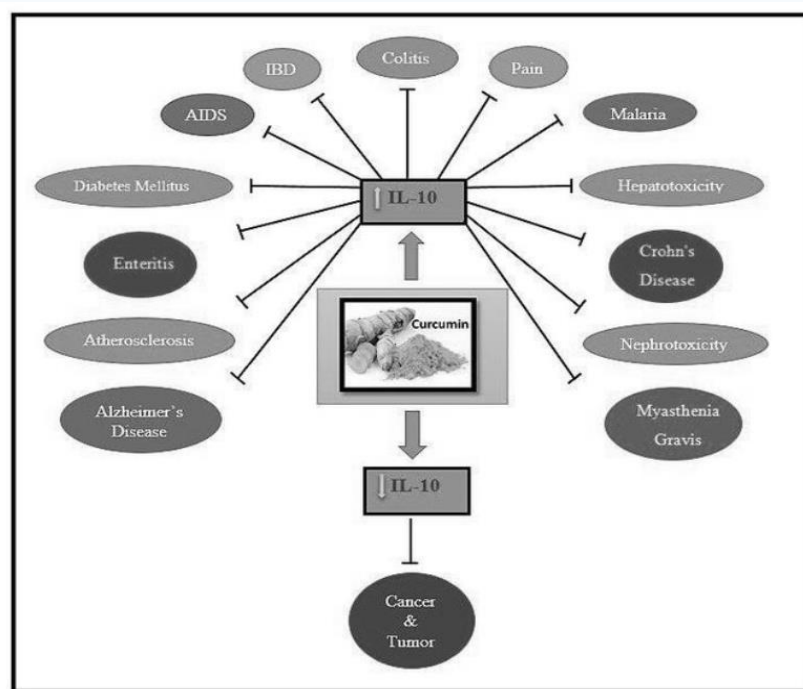
Ghandadi M, Sahebkar A. Curcumin: An Effective Inhibitor of Interleukin-6. *Curr Pharm Des.* 2017;23(6):921-931. doi: 10.2174/1381612822666161006151605. PMID: 27719643.

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Curcumin consumption induces the expression and production of IL-10, potent anti-inflammatory and immunosuppressive cytokine.

IL-10 deregulation plays a role in the development of many inflammatory diseases such as neuropathic pain, Parkinson's disease, Alzheimer's disease, osteoarthritis,

Hamid Mollazadeh, Arrigo F. G. Cicero, Christopher N. Blesso, Matteo Pirro, Muhammed Majeed & Amirhossein Sahebkar (2019) Immune modulation by curcumin: The role of interleukin-10, *Critical Reviews in Food Science and Nutrition*, 59:1, 89-101, DOI: 10.1080/10408398.2017.1358139



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Buhrmann et al. *Arthritis Research & Therapy* 2010, **12**:R127  
<http://arthritis-research.com/content/12/4/R127>



RESEARCH ARTICLE

Open Access

## Curcumin mediated suppression of nuclear factor- $\kappa$ B promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment

Constanze Buhrmann<sup>1</sup>, Ali Mobasher<sup>2</sup>, Ulrike Matis<sup>3</sup> and Mehdi Shakibaei<sup>\*1</sup>

**Curcumin alone does not have chondrogenic effects on MSCs, but it inhibits proinflammatory cytokines (e.g. IL-1 $\beta$ , Nuclear factor- $\kappa$ B) and support the regeneration of articular cartilage (enhanced the production of collagen type II, cartilage specific proteoglycans (CSPGs),  $\beta$ 1-integrin, etc.**

Buhrmann, C., Mobasher, A., Matis, U., & Shakibaei, M. (2010). Curcumin mediated suppression of nuclear factor- $\kappa$ B promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment. *Arthritis research & therapy*, 12(4), R127. doi:10.1186/ar3065

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Animal studies show that

**curcumin stimulated neural stem cells proliferation,**

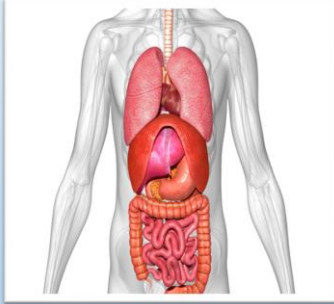
**and in combination with stem cell therapy, induced profound recovery from severe spinal cord injury**

as evidenced by improved functional locomotor recovery, increased body weight, and soleus muscle mass

Ormond, D. R., Shannon, C., Oppenheim, J., Zeman, R., Das, K., Murali, R., & Jhanwar-Uniyal, M. (2014). Stem cell therapy and curcumin synergistically enhance recovery from spinal cord injury. *PLoS one*, 9(2), e88916. doi:10.1371/journal.pone.0088916

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## Curcumin Bioavailability



- Low bioavailability for local GI inflammatory diseases
- Higher bioavailability for systemic inflammation (e.g. joints)
- Adding piperine, the major active component of black pepper, to curcumin has been shown to increase bioavailability by 2000%

Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A Review of Its' Effects on Human Health. *Foods*, 6(10), 92. <http://doi.org/10.3390/foods6100092>

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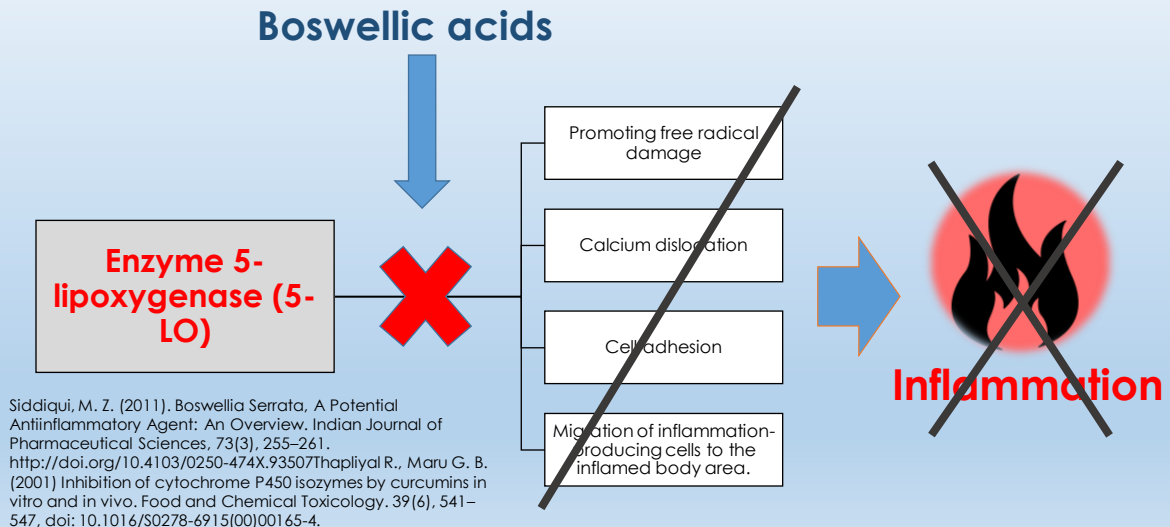
## Boswellia Serrata

A natural and affordable agent that can reduce the inflammatory process



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## Boswellia Serrata



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## Boswellia Serrata

Curcumin combined with boswellic acid extract led to improvement in physical performance and reduction in joint pain and morning stiffness. The use of Boswellia and curcumin supplements was well tolerated and safe. (1)

1. Haroyan, A., Mukuchyan, V., Mkrtychyan, N., Minasyan, N., Gasparyan, S., Sargsyan, A., ... Hovhannisyanyan, A. (2018). Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. BMC Complementary and Alternative Medicine, 18, 7. <http://doi.org/10.1186/s12906-017-2062-z>

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## Boswellia Serrata

Recommended dosage of Boswellia is 500 to 1,000mg twice a day.

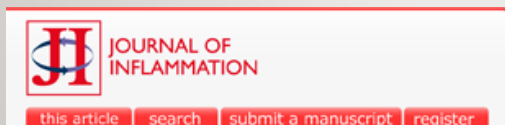
The use of Boswellia and curcumin supplements was well tolerated and safe. (1)



1. Haroyan, A., Mukuchyan, V., Mkrtychyan, N., Minasyan, N., Gasparyan, S., Sargsyan, A., ... Hovhannisyan, A. (2018). Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complementary and Alternative Medicine*, 18, 7. <http://doi.org/10.1186/s12906-017-2062-z>

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**Hesperidin,**  
a flavonoid found in citrus fruits,  
*inhibits secretion of pro-inflammatory  
cytokines IFN- $\gamma$ , IL-2, IL-4 and IL-10,*  
and  
**enhances the formation  
of cartilage by stem cells.**



Xiao, S., Liu, W., Bi, J., Liu, S., Zhao, H., Gong, N., Xing, D., Gao, H., ... Gong, M. (2018). Anti-inflammatory effect of hesperidin enhances chondrogenesis of human mesenchymal stem cells for cartilage tissue repair. *Journal of inflammation* (London, England), 15, 14. [doi:10.1186/s12950-018-0190-y](https://doi.org/10.1186/s12950-018-0190-y)

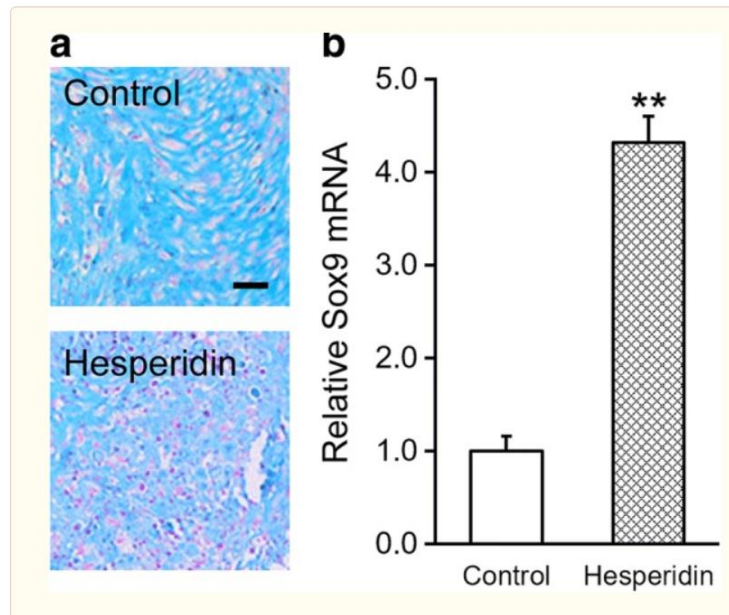
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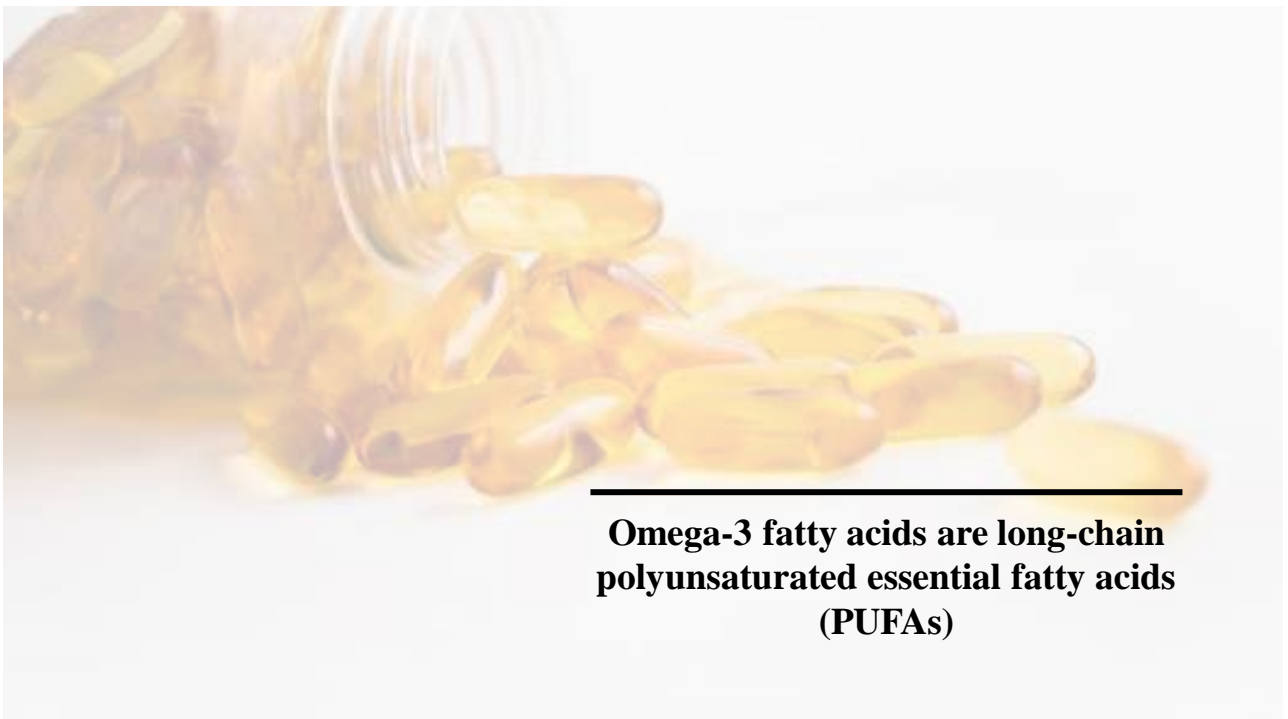
## **Hesperidin**

Hesperidin improves self-renewal ability of MSCs.

At day 14 after differentiation induction in the absence (control) or presence of 5  $\mu$ M hesperidin.



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**Omega-3 fatty acids are long-chain polyunsaturated essential fatty acids (PUFAs)**

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## Omega-3 fatty acids



A randomized, double blind trial, of 12 weeks of treatment with six n-3 PUFA capsules (**3.6 g per day**)

**Significant improvement of morning stiffness and joint tenderness with consumption of omega-3 supplement**

Nielsen GL, Faarvang KL, Thomsen BS, Teglbaerg KL, Jensen LT, Hansen TM, Lervang HH, Schmidt EB, Dyerberg J, Ernst E. (1992) The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. *Eur J Clin Invest*, 22(10), 687-91.

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## Anti-Inflammatory Effect of Fish Oil: Omega 3



**Animal studies show that fish oil could serve as promising source of chondroprotective agents.**

“Our results showed that DHA and EPA as well as omega-3 sources could suppress matrix degradation in cytokine-induced cartilage”

Myers, S. P., & Oliver, C. (2017). Effects of different omega-3 sources, fish oil, krill oil, and green-lipped mussel against cytokine-mediated canine cartilage degradation. *In Vitro Cell Dev Biol Anim*. 2017 doi: 10.1007/s11626-016-0125-y. *In Vitro Cellular & Developmental Biology - Animal*, 53(9), 775-775. doi:10.1007/s11626-017-0188-4

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## Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose

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**Handling editor** Tore K Kvien

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2014-207169>).

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### ABSTRACT

**Objectives** To determine whether high-dose fish oil is superior to low-dose supplementation for symptomatic and structural outcomes in knee osteoarthritis (OA).

**Methods** A randomised, double-blind, multicentre trial enrolled 202 patients with knee OA and regular knee pain. They were randomised 1:1 to high-dose fish oil (4.5 g omega-3 fatty acids) 15 mL/day or (2) low-dose fish oil (blend of fish oil and sunola oil; ratio of 1:9; 0.45 g omega-3 fatty acids) 15 mL/day. The primary

Since synovitis and cartilage degradation are common to both RA and OA, it is possible that fish oil may be useful in OA.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main omega-3 fatty acids in fish oil, decrease synthesis of the cyclooxygenase omega-6 fatty acid metabolite, prostaglandin E2 also a target of NSAID action. EPA and DHA are also precursors of the E-resolvins and D-resolvins that suppress inflammatory cytokine production

**A total of 302 participants:**

**High-dose fish oil supplying 4.5 g EPA+DHA per day vs low dosage of 0.45 g EPA+DHA per day, (equivalent to 1.5 standard 1 g fish oil capsule daily)**

No change in serum C reactive protein. Low-dose fish oil resulted in better pain and function scores at 18 and 24 months compared with high-dose fish oil.

Hill CL, March LM, Aitken D. (2016) Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose *Annals of the Rheumatic Diseases*. 75, 23-29.

Received 17 December 2014  
Revised 17 August 2015  
Accepted 19 August 2015

**Conclusions** In people with symptomatic knee OA, there was no additional benefit of a high-dose fish oil compared with low-dose fish oil. The combination

spread. An Australian study of 260 000 people reported 32.6% had taken omega-3 supplements within the past four weeks with presence of OA

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**If you increase consumption of omega-6 and reduce the consumption of omega-3, you increase the risk of chronic diseases and inflammation**

Journal of the  
**American College  
of Nutrition**

Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr*. 2002 Dec;21(6):495-505.

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## Anti-Inflammatory Effect of Fish Oil: Omega 3



- ✓ Altered cell membrane phospholipid fatty acid composition
- ✓ Balance excess in n-6 linoleic acid which is typically consumed in 5 to 20-fold greater amounts than  $\alpha$ -linolenic acid
- ✓ Inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B
- ✓ Reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor NRIC3.

Calder P.C. (2013). Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology?. British journal of clinical pharmacology, 75(3), 645-62.

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## Combining Glucosamine Chondroid and Omega 3



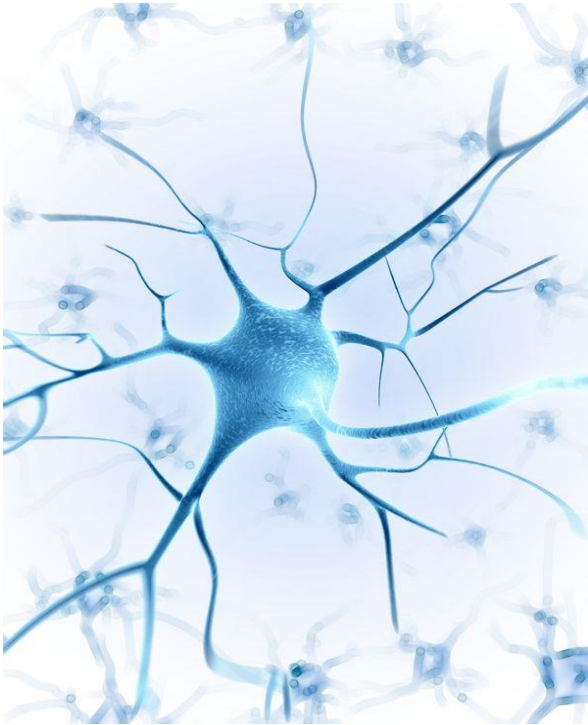
“...the treatment with chondroprotectives, such as **glucosamine** sulfate, **chondroitin** sulfate, hyaluronic acid, **collagen** hydrolysate, or nutrients, such as **antioxidants** and **omega-3** fatty acids is a promising therapeutic approach.”

Jerosch J. (2011). Effects of Glucosamine and Chondroitin Sulfate on Cartilage Metabolism in OA: Outlook on Other Nutrient Partners Especially Omega-3 Fatty Acids. International journal of rheumatology, 2011, 969012.

International Journal of Rheumatology

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*Nutritional & Supplements Protocol for Nerve Regeneration*

70



*Common Conditions*



71

## Neurogenesis decreases with age.

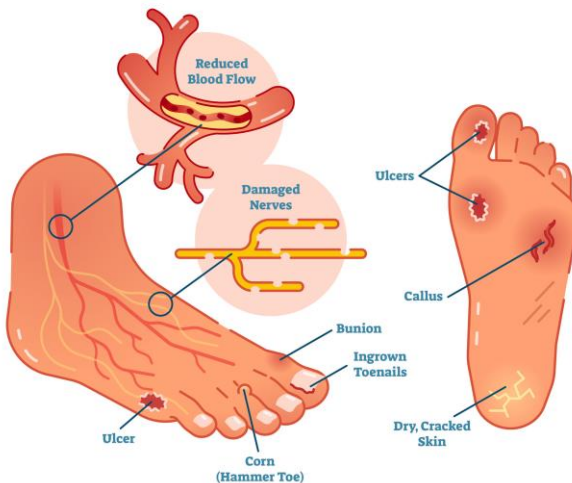
Several factors, such as oxidative stress and inflammation, have been shown to decrease neurogenesis



Poulose, S. M., Miller, M. G., Scott, T., & Shukitt-Hale, B. (2017). Nutritional Factors Affecting Adult Neurogenesis and Cognitive Function. *Advances in nutrition (Bethesda, Md.)*, 8(6), 804–811. <https://doi.org/10.3945/an.117.016261>

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## Diabetes Neuropathy

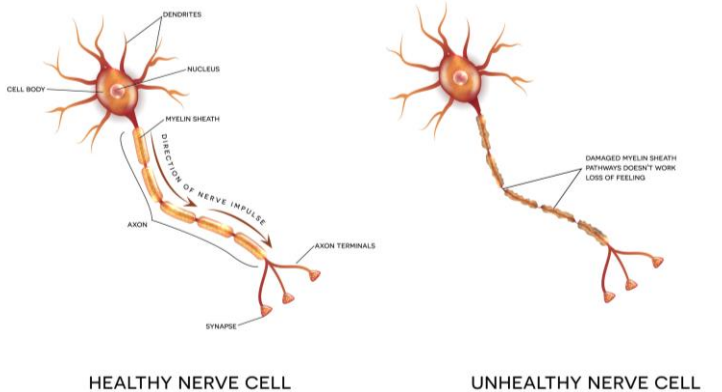


*Comprehensive approach includes:*

- Supporting nerve regeneration
- Blood vessels regeneration
- Nerve function

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*“Alpha lipoic acid (ALA), a small antioxidant molecule, affects cell apoptosis by lowering the ROS level. In this study, we show that ALA promoted production of human pluripotent stem cells (hPSCs)”*



Dong Y, Bai J, Zhang Y, Zhou Y, Pan X, Li X, Zhou Q, Chen Y, Lai M, Mao B, Bian G, Feng J, Xie F, Chen B, Nakahata T, Zhang Y, Ma F. Alpha lipoic acid promotes development of hematopoietic progenitors derived from human embryonic stem cells by antagonizing ROS signals. *J Leukoc Biol.* 2020 Dec;108(6):1711-1725. doi: 10.1002/JLB.1A0520-179R. Epub 2020 Jul 8. PMID: 32640500; PMCID: PMC7754144.

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*“Randomized, double-blind, placebo-controlled trial, 181 diabetic patients in Russia and Israel received once-daily oral doses of 600”*

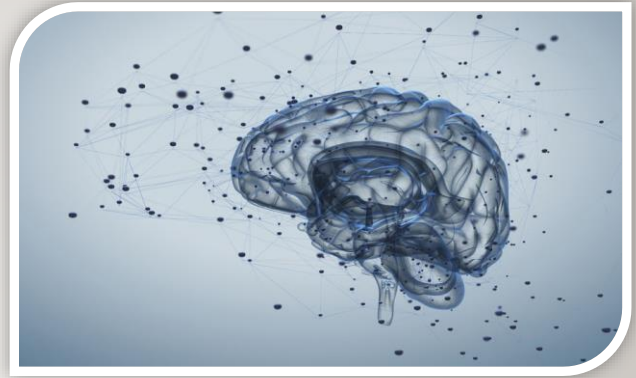
*Reduction of 51% in Total Symptom Score (TSS) after 5 weeks.*

Ziegler D, Ametov A, Barinova A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care.* 2006 Nov;29(11):2365-70. doi: 10.2337/dc06-1216. PMID: 17065669.



75

## Zinc deficiency impairs the renewal of neural stem cells in the hippocampus.



Han J, Zhao J, Jiang J, Ma X, Liu X, Wang C, Jiang S, Wan C. Zinc deficiency impairs the renewal of hippocampal neural stem cells in adult rats: involvement of FoxO3a activation and downstream p27(kip1) expression. *J Neurochem*. 2015 Sep;134(5):879-91. doi: 10.1111/jnc.13199. Epub 2015 Jul 7.

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## Resveratrol



Resveratrol is a natural polyphenol that is found in the skin of red grapes, cranberries, peanuts and root extracts of the weed *Polygonum Cuspidatum*

Camins, A., Junyent, F., Verdaguer, E., Beas-Zarate, C., Rojas-Mayorquin, A. E., Ortuño-Sahagún, D., & Pallás, M. (2009). Resveratrol: An Antiaging Drug with Potential Therapeutic Applications in Treating Diseases. *Pharmaceuticals (Basel, Switzerland)*, 2(3), 194-205.

77



*“Resveratrol treatment significantly increased the mRNA and protein expression levels of neuronal markers”*

**Resveratrol improved the ratio of neuron-like cells from about 5% to 50% within one hour.**

Guo, L., Wang, L., Wang, L., Yun-Peng, S., Zhou, J. J., Zhao, Z., & Li, D. P. (2017). Resveratrol Induces Differentiation of Human Umbilical Cord Mesenchymal Stem Cells into Neuron-Like Cells. *Stem cells international*, 2017, 1651325.

INTERNATIONAL  
JOURNAL OF STEM CELLS

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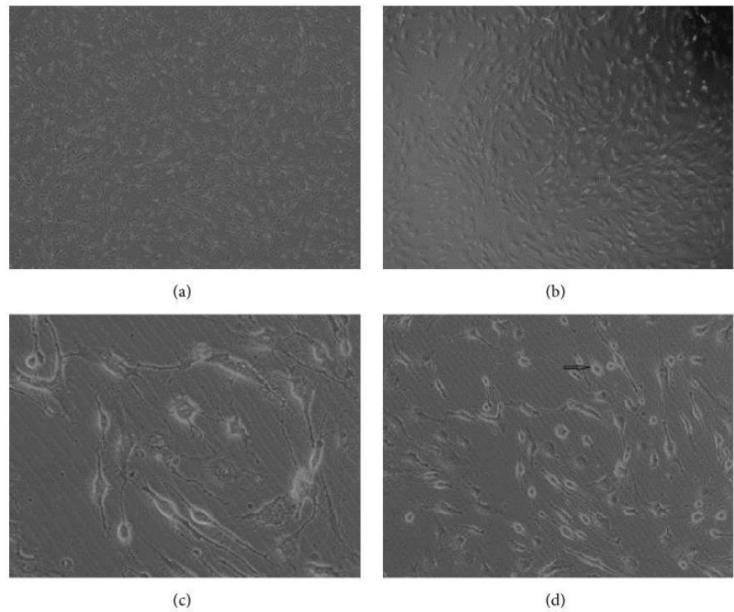
*“Furthermore, the cells appeared connected into a net-like pattern. After 6 h treatment with resveratrol (30 mg/L), 85%~90% of the hUC-MSCs displayed neuron-like shape”*

INTERNATIONAL  
JOURNAL OF STEM CELLS

Guo, L., Wang, L., Wang, L., Yun-Peng, S., Zhou, J. J., Zhao, Z., & Li, D. P. (2017). Resveratrol Induces Differentiation of Human Umbilical Cord Mesenchymal Stem Cells into Neuron-Like Cells. *Stem cells international*, 2017, 1651325.

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Images showing that different concentrations of resveratrol (0.0 mg/L (a), 7.5 mg/L (b), 15.0 mg/L (c), and 30.0 mg/L (d)) induce differentiation of hUC-MSCs into neuron-like cells.



Guo, L., Wang, L., Wang, L., Yun-Peng, S., Zhou, J. J., Zhao, Z., & Li, D. P. (2017). Resveratrol Induces Differentiation of Human Umbilical Cord Mesenchymal Stem Cells into Neuron-Like Cells. *Stem cells international*, 2017, 1651325.

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*What's the dosage?*

**500mg Japanese Knotweed (*Polygonum cuspidatum*) Root Extract (standardized for 50% Trans-Resveratrol, yielding 250 mg)**

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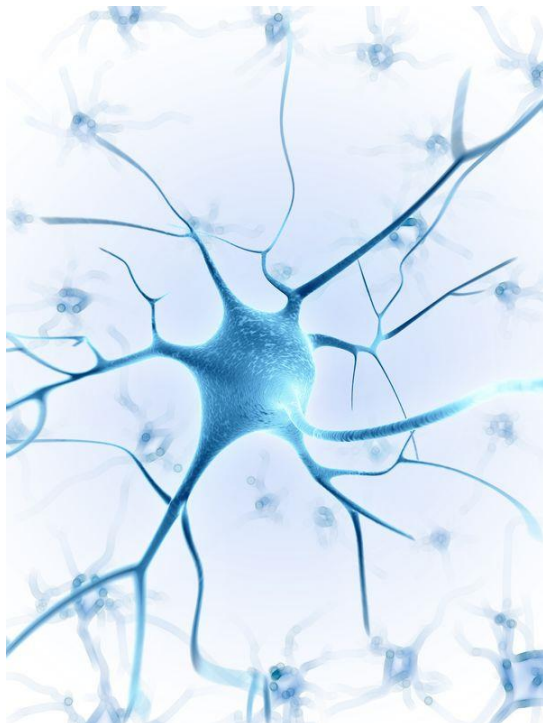
## Zinc deficiency impairs the renewal of neural stem cells in the hippocampus.



Eat food high in zinc:  
beef, lamb, spinach, pumpkin seeds,  
squash seeds, nuts, dark chocolate,  
chicken, beans, and mushrooms

Han J, Zhao J, Jiang J, Ma X, Liu X, Wang C, Jiang S, Wan C. Zinc deficiency impairs the renewal of hippocampal neural stem cells in adult rats: involvement of FoxO3a activation and downstream p27(kip1) expression. *J Neurochem*. 2015 Sep;134(5):879-91. doi: 10.1111/jnc.13199. Epub 2015 Jul 7.

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***Ginkgo Biloba*** enhances proliferation of neural stem cells in the subventricular zone and dentate gyrus, and significantly improves learning and memory in rats with vascular dementia.

**Neural Regeneration Research**



Wang, J., Chen, W., & Wang, Y. (2013). A ginkgo biloba extract promotes proliferation of endogenous neural stem cells in vascular dementia rats. *Neural regeneration research*, 8(18), 1655-62.

83

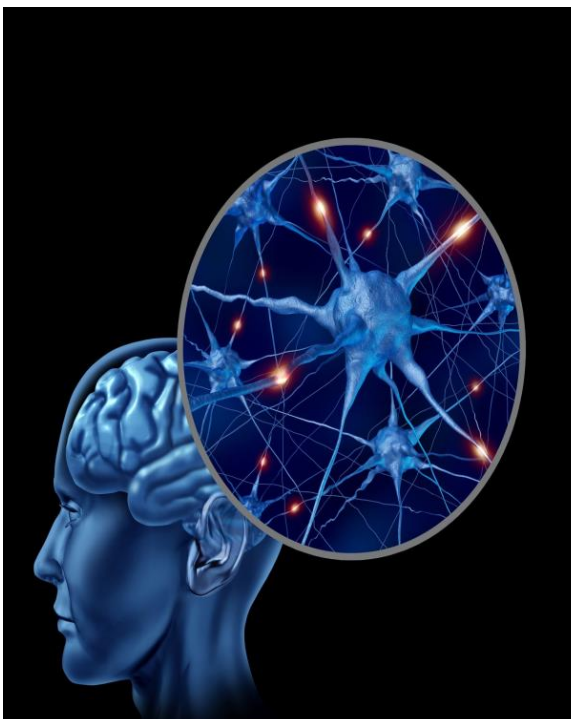


**A 24-week randomized controlled trial with 404 outpatients  $\geq$  50 years diagnosed with mild to moderate dementia, Alzheimer's disease, or vascular dementia, with neuropsychiatric features. 240 mg once-daily preparation of Ginkgo biloba extract.**

**Pharmacopsychiatry**

Ihl R, Tribanek M, Bachinskaya N, GOTADAY Study Group. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial.  
Pharmacopsychiatry 2012; Mar; 45(2):41-6

84



**240 mg of Ginkgo Biloba once-daily improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia**

**Pharmacopsychiatry**

Ihl R, Tribanek M, Bachinskaya N, GOTADAY Study Group. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial.  
Pharmacopsychiatry 2012; Mar; 45(2):41-6

85



**“Aging of Human mesenchymal stem cells (hMSCs) is associated with a rise in intracellular reactive oxygen species, loss of telomerase activity, decrease in human telomerase reverse transcriptase (hTERT) expression and finally eroded telomere ends.”**

1. Farahzadi, R., Mesbah-Namin, S. A., Zarghami, N., & Fathi, E. (2016). L-carnitine Effectively Induces hTERT Gene Expression of Human Adipose Tissue-derived Mesenchymal Stem Cells Obtained from the Aged Subjects. *International journal of stem cells*, 9(1), 107–114. doi:10.15283/ijsc.2016.9.1.1072. *Exp Gerontol.* 2005 Dec;40(12):926-30. Epub 2005 Aug 25. Mesenchymal stem cell aging. Fehrer C I, Lepperdinger G.

86

**“L-carnitine could significantly increase the human telomerase reverse transcriptase gene expression and telomere length”**

Farahzadi, R., Mesbah-Namin, S. A., Zarghami, N., & Fathi, E. (2016). L-carnitine Effectively Induces hTERT Gene Expression of Human Adipose Tissue-derived Mesenchymal Stem Cells Obtained from the Aged Subjects. *International journal of stem cells*, 9(1), 107–114. doi:10.15283/ijsc.2016.9.1.107

87

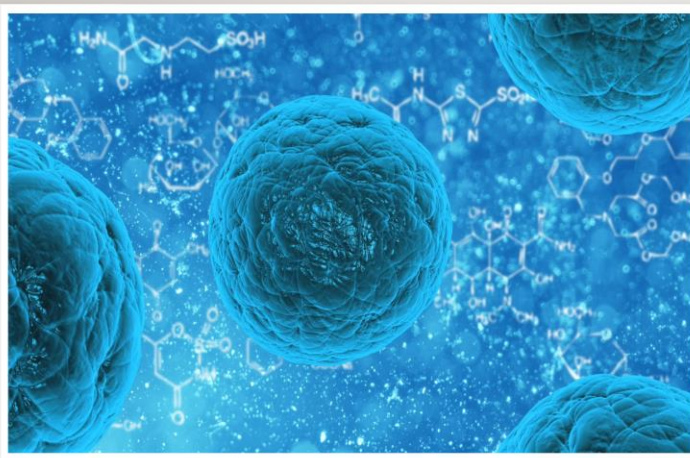
## “L-carnitine could be used as a good candidate for extending the replicative life-spans of aged MSCs.”

According to a systematic review and meta-analysis study:  
**L-carnitine supplementation has been associated with a significant reduction in all-cause mortality. Dosage of more than 2g per day did not improve results.**

1. Fathi, E., Farahzadi, R., & Charoudeh, H. N. (2017). L-carnitine contributes to enhancement of neurogenesis from mesenchymal stem cells through Wnt/ $\beta$ -catenin and PKA pathway. *Experimental biology and medicine (Maywood, N.J.)*, 242(5), 482–486. doi:10.1177/1535370216685432
2. Shang, R., Sun, Z., & Li, H. (2014). Effective dosing of L-carnitine in the secondary prevention of cardiovascular disease: a systematic review and meta-analysis. *BMC cardiovascular disorders*, 14, 88. doi:10.1186/1471-2261-14-88

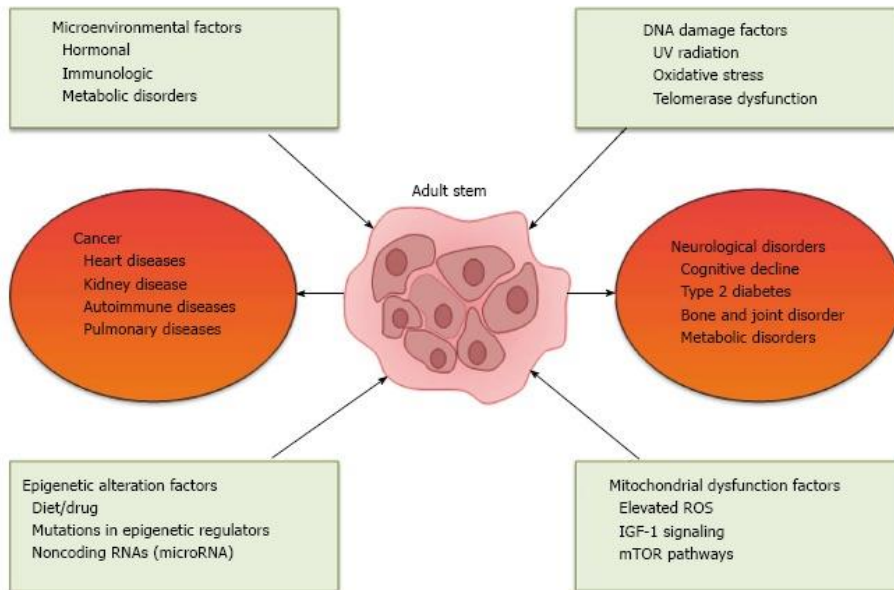
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## Protect Stem Cells From Damage



What can inhibit stem cells or reduce their ability to regenerate new tissue?

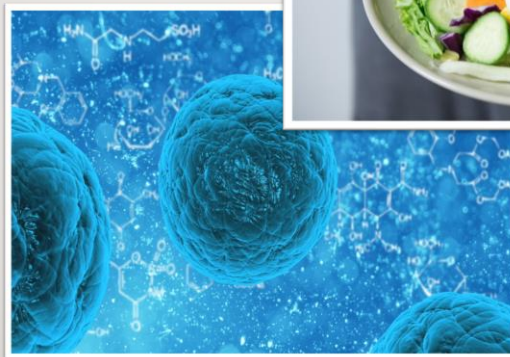
89



Ahmed, A. S. I., Sheng, M. H., Wasnik, S., Baylink, D. J., & Lau, K.-H. W. (2017). Effect of aging on stem cells. *World Journal of Experimental Medicine*, 7(1), 1–10. <http://doi.org/10.5493/wjem.v7.i1.1>

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## Dietary Changes to Support Stem Cells Therapy



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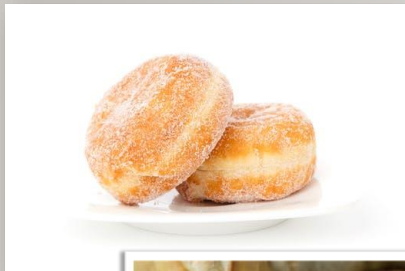


## The science of epigenetic and nutrigenetic

**“Nutrition may exert its impact on health outcomes by directly affecting expression of genes”**

Fenech, M., El-Sohehy, A., Cahill, L., Ferguson, L. R., French, T. A., Tai, E. S., Milner, J., Koh, W. P., Xie, L., Zucker, M., Buckley, M., Cosgrove, L., Lockett, T., Fung, K. Y., & Head, R. (2011). Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *Journal of nutrigenetics and nutrigenomics*, 4(2), 69–89. <https://doi.org/10.1159/000327772>

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## Remove Foods that Increase Inflammation:

1. **Sugar**
2. **Gluten (wheat)**
3. **Processed or fast food**



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*“Sugar Sweetened Beverages may also increase T2DM and cardiovascular risk independent of obesity, as a potential contributor to a high dietary glycemic load and*

**increased fructose metabolism leading to inflammation,**

*insulin resistance, impaired beta-cell function, and high blood pressure.”*

Malik, V. S., Popkin, B. M., Bray, G. A., Després, J. P., & Hu, F. B. (2010). Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*, 121(11), 1356-64.

94

**“Fructose and its metabolites directly and/or indirectly cause oxidative stress, chronic inflammation, endothelial dysfunction, autophagy and increased intestinal permeability, and then further aggravate the metabolic syndrome with tissue and organ dysfunctions.”**

Zhang, D. M., Jiao, R. Q., & Kong, L. D. (2017). High Dietary Fructose: Direct or Indirect Dangerous Factors Disturbing Tissue and Organ Functions. *Nutrients*, 9(4), 335. <https://doi.org/10.3390/nu9040335>



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Regular consumption of sugar-sweetened soda, but not diet soda, is **associated with increased risk of seropositive RA** in women, independent of other dietary and lifestyle factors.



Hu, Y., Costenbader, K. H., Gao, X., Al-Daabil, M., Sparks, J. A., Solomon, D. H., Hu, F. B., Karlson, E. W., ... Lu, B. (2014). Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women. *The American journal of clinical nutrition*, 100(3), 959-67.

96

**Animal study published in 2013 reported that gluten-containing diet changed the immune system to express more **inflammatory cells**.**

Antvorskov, J. C., Fundova, P., Buschard, K., & Funda, D. P. (2013). Dietary gluten alters the balance of pro-inflammatory and anti-inflammatory cytokines in T cells of BALB/c mice. *Immunology*, 138(1), 23–33. <https://doi.org/10.1111/imm.12007>



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“Gluten-containing diet increased the level of potent pro-inflammatory (IL-17, IFN- $\gamma$ ) cytokines, as well as of IL-2 and IL-4.”

# Immunology

British Society for  
immunology 

Antvorskov, J. C., Fundova, P., Buschard, K., & Funda, D. P. (2013). Dietary gluten alters the balance of pro-inflammatory and anti-inflammatory cytokines in T cells of BALB/c mice. *Immunology*, 138(1), 23-33.

98

Evidence from *in vitro*, *in vivo* and human intervention studies that describe how the consumption of wheat, but also other cereal grains, can contribute to the manifestation of chronic inflammation and autoimmune diseases by

**increasing intestinal permeability and initiating a pro-inflammatory immune response.**

de Punder, K., & Pruimboom, L. (2013). The dietary intake of wheat and other cereal grains and their role in inflammation. *Nutrients*, 5(3), 771-87. doi:10.3390/nu5030771

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Remove Foods that Increase Inflammation:

1. **Sugar**
2. **Gluten (wheat)**
3. **Processed or fast food**

100

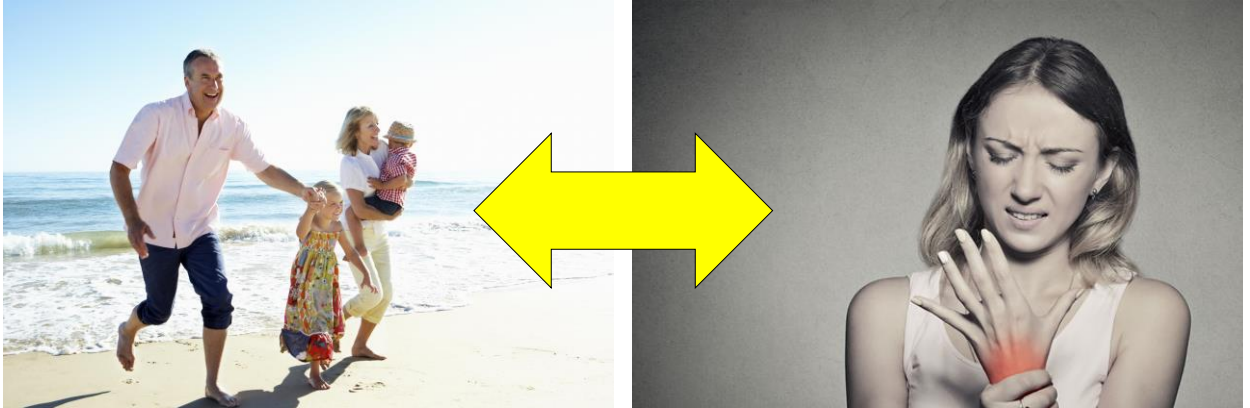


**Are your patients  
eat pro or anti-  
inflammatory  
foods?**

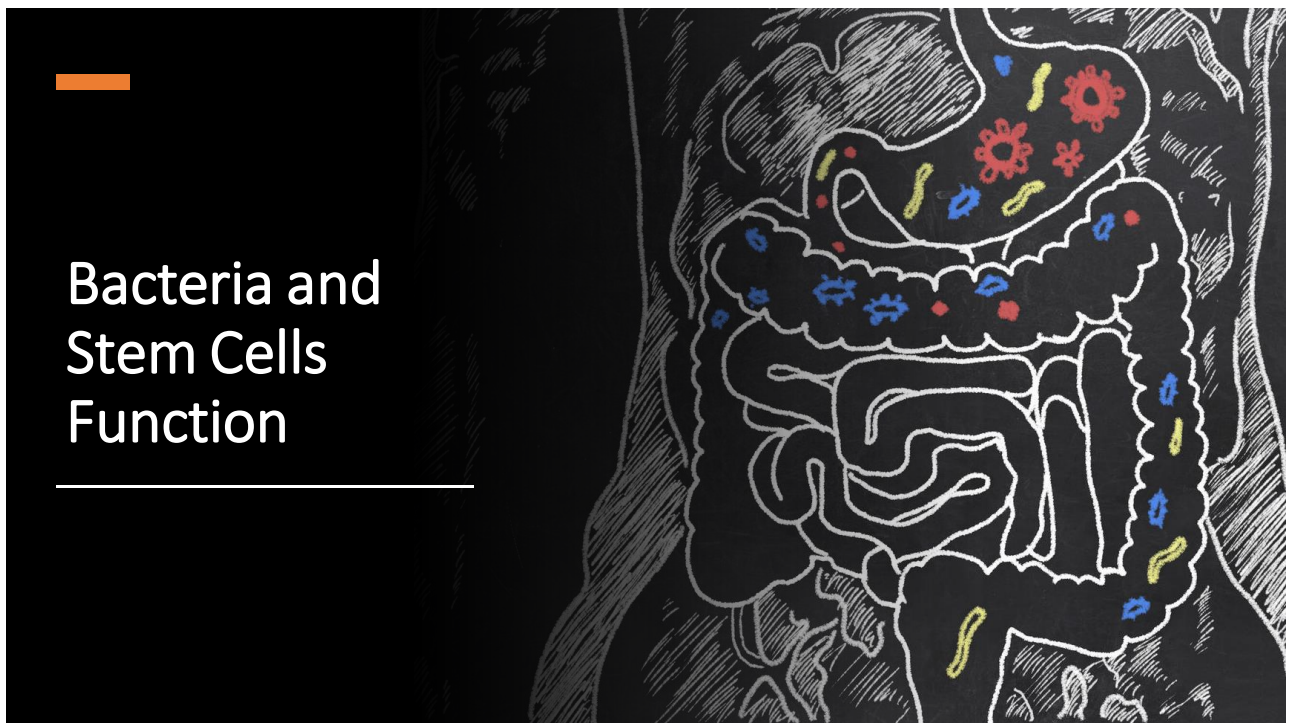
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## How is the food they eat effect expression of their genes?



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## The oral bacteria *Porphyromonas gingivalis* might increase inflammation and inhibit function of MSCs, thereby accelerating MSC dysfunction and delaying wound healing

Han, N., Jia, L., Guo, L., Su, Y., Luo, Z., Du, J., Mei, S., & Liu, Y. (2020). Balanced oral pathogenic bacteria and probiotics promoted wound healing via maintaining mesenchymal stem cell homeostasis. *Stem cell research & therapy*, 11(1), 61. <https://doi.org/10.1186/s13287-020-1569-2>

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“We discovered that 50 µg/ml **Lactobacillus Reuteri** extracts increased the capacities of migration, expression of stem cell markers, osteogenic differentiation, and proliferation of (Human gingiva-derived mesenchymal stem cells) GMSCs”

How, K. Y., Song, K. P., & Chan, K. G. (2016). *Porphyromonas gingivalis*: An Overview of Periodontopathic Pathogen below the Gum Line. *Frontiers in microbiology*, 7, 53. <https://doi.org/10.3389/fmicb.2016.00053>

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- **probiotic *Lactobacillus casei* Shirota benefited patients with knee osteoarthritis (reduction of serum levels of high sensitivity C-reactive protein)**

Lei M, Guo C, Wang D, Zhang C, Hua L. The effect of probiotic *Lactobacillus casei* Shirota on knee osteoarthritis: a randomised double-blind, placebo-controlled clinical trial. *Benef Microbes*. 2017 Oct 13;8(5):697-703. doi: 10.3920/BM2016.0207. Epub 2017 Jul 20. PMID: 28726510.

- ***Lactobacillus rhamnosus* GG protects the intestinal epithelium from radiation injury through release of lipoteichoic acid, macrophage activation and the migration of mesenchymal stem cells**

Riehl TE, Alvarado D, Ee X, Zuckerman A, Foster L, Kapoor V, Thotala D, Ciorba MA, Stenson WF. *Lactobacillus rhamnosus* GG protects the intestinal epithelium from radiation injury through release of lipoteichoic acid, macrophage activation and the migration of mesenchymal stem cells. *Gut*. 2019 Jun;68(6):1003-1013. doi: 10.1136/gutjnl-2018-316226. Epub 2018 Jun 22. PMID: 29934438; PMCID: PMC7202371.

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### Healthy Fats: (up your intake, it fuels your brain and reduce inflammation)

- Avocado
- Coconut oil
- Olive oil
- Butter or Ghee from Grass Fed Cows
- Omega 3 from fish, seafood, or seaweed.

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## Healthy Protein (without hormones or antibiotics).

- Grass-fed Beef or Bison
- Pastured Eggs (organic/free range)
- Sockeye Salmon (wild caught)
- Chicken (organic, free range, anti-biotic free)

Avoid tuna fish or canned food!



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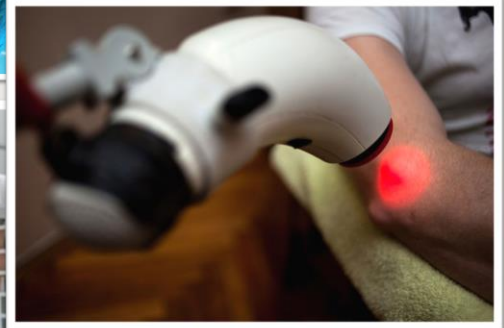
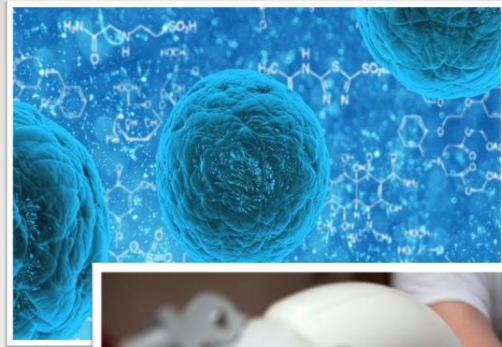


Healthy carbs: (up your intake, it fuels your brain and reduce inflammation)

- Replace sugar with Stevia or xylitol
- Quinoa
- Organic brown rice
- Lintel noodles/pasta (gluten free)
- Yams and other root vegetables
- Legumes: Hummus, beans

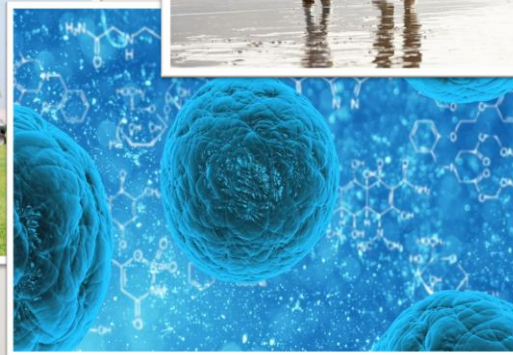
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## Supporting Treatments to improve clinical results and create your unique program



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## Guidelines After Stem Cell Therapy



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*Guideline: Stay active, but do not over use.*

After joint injection:

- Ankle, knees, hips, or lower back injection avoid running or weights training for at least 30 days.
- Shoulders or back do not lift heavy for 2 months.
- Fingers or thumbs – avoid texting.



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**Considerations  
in treatment of  
patients with  
supplements**

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## Herbs & Supplements: Interaction with Medication

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- Curcumin in high dosages and blood thinners (e.g. Coumadin)
- Fish oil is safe to consume (my experience: 2g daily)
- Ginkgo in small amounts no interaction with warfarin
- Ginkgo in high dosages demonstrated antiplatelet activity when combined with NSAID drugs, especially aspirin, might cause severe bleeding, including intracranial bleeding
- Resveratrol might interact with some medications. Use low amount (250mg/day)
- Do not recommend consumption of green vegetables with anti-coagulant drugs



American Academy of Family Physicians. (2018) Herbal and Dietary Supplement–Drug Interactions in Patients with Chronic Illnesses. Retrieved from <https://pdfs.semanticscholar.org/0685/6ae00b3ca62eb770e4a7684d3a6299656fc2.pdf>

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## Advantages for Use of Supplements in Stem Cell Therapy

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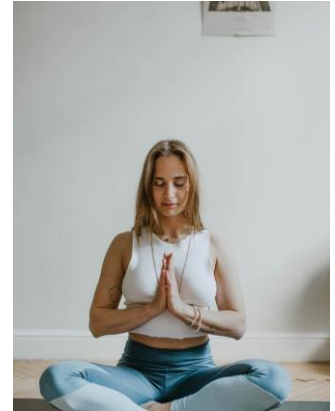
- ✓ **Improve results** (support reduction in inflammation, pain, etc.)
- ✓ Improve your unique selling proposition (offer a comprehensive approach)
- ✓ Charge for a **Stem Cell Program** instead of Stem Cell Injection.

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## Environmental factors with epigenetic effects include behaviors, nutrition, and chemicals and industrial pollutants.

Tiffon C. (2018). The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. *International journal of molecular sciences*, 19(11), 3425. <https://doi.org/10.3390/ijms19113425>



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**“Understanding the molecular effects of behavior, nutrients, and pollutants might be relevant for developing preventative strategies and personalized health programs.”**

Tiffon C. (2018). The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. *International journal of molecular sciences*, 19(11), 3425. <https://doi.org/10.3390/ijms19113425>



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# Get Certified As a FUNCTIONAL MEDICINE Provider

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# Supplements, Nutrition, and Lifestyle Medicine to Support Regenerative Medicine

Thank you!

Tal Cohen, DAOM, MS-HNFM

TAL.COHEN@ANewWay.Clinic

