SUPPLEMENTS, NUTRITION, AND LIFESTYLE MEDICINE TO SUPPORT STEM CELL THERAPY

Tal Cohen, DAOM, MS.HNFM

Why use supplements?


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

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

Udalamaththa 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

Patient feels better = more referrals to you

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

2% of US adults report of supplements in 2011–2012

JAMA The Journal of the American Medical Association

Kantor, E. D., Rehm, C. D., Du, M., White, E., & Giovannucci, E
(2016). Trends in Dietary Supplement Use among US Adults Fr
1999–2012. *JAMA*, *316*(14), 1464–1474.
http://doi.org/10.1001/jama.2016.14403

Published survey 2017): by The Council for Responsible Nutrition

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http://doi.org/10.1001/jama.2016.14403

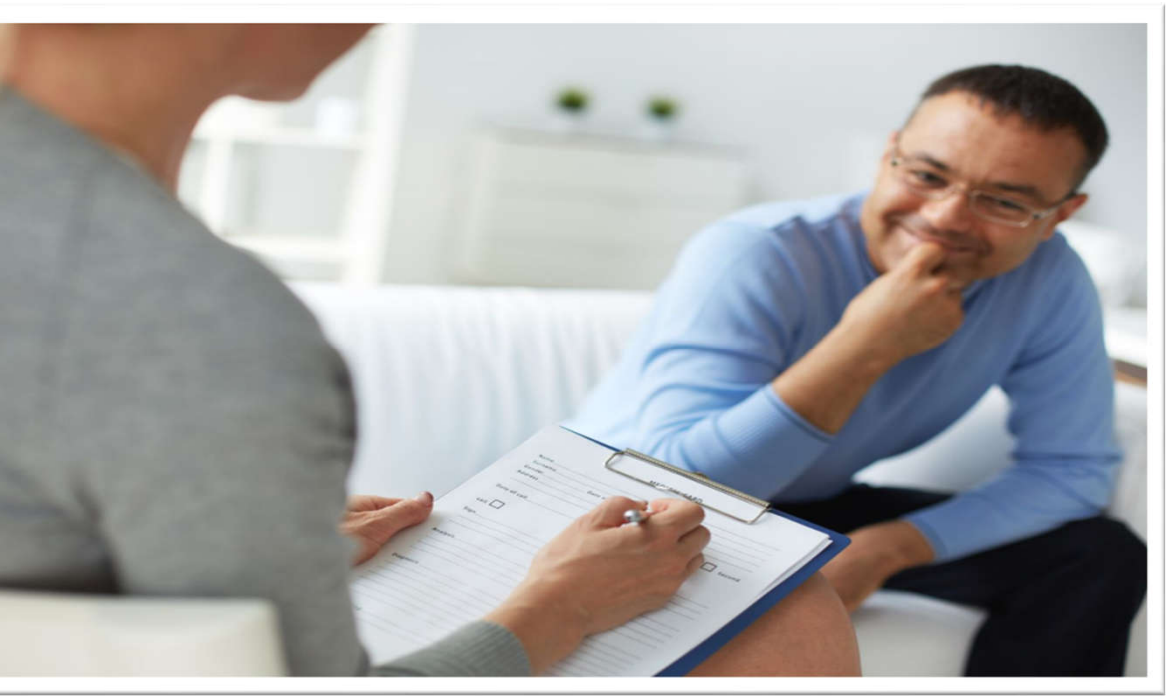
Published survey 2017): by The Council for Responsible Nutrition

JAMA The Journal of the American Medical Association

Supplements provide additional revenue fo many clinics.

Are you offering the same service as everybody else?

Are you offering the sam
service as everybody els



Are you offering the sam
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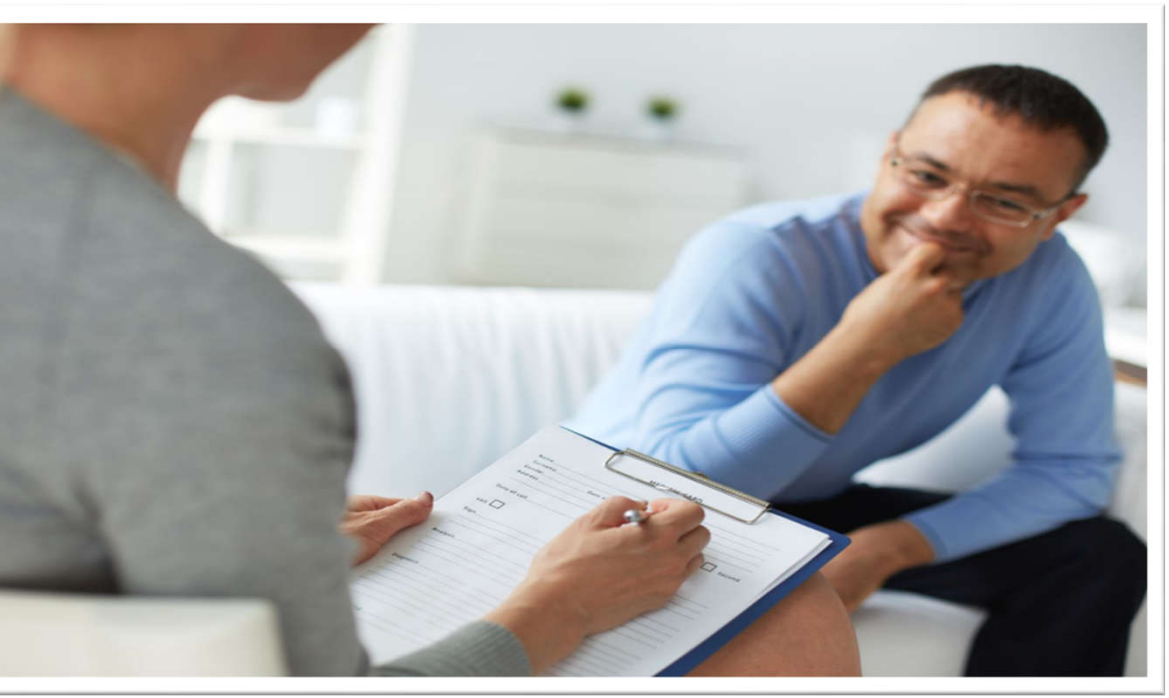


Are you offering the sam
service as everybody els

What if you could offer something unique?

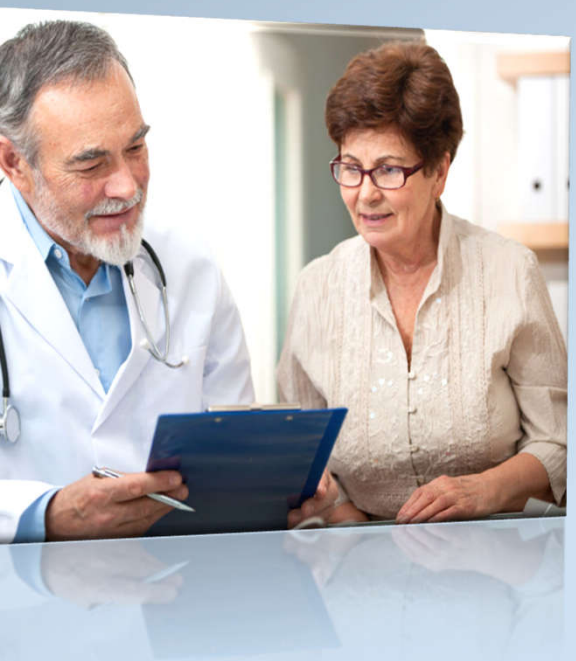
What can you offer that other clinics/doctors don't?

HOW TO OFFER A UNIQUE STEM CELLS PROGRAM

(and charge more for it)

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.

STEM CELL • REPAIR • REGEN • RESTO

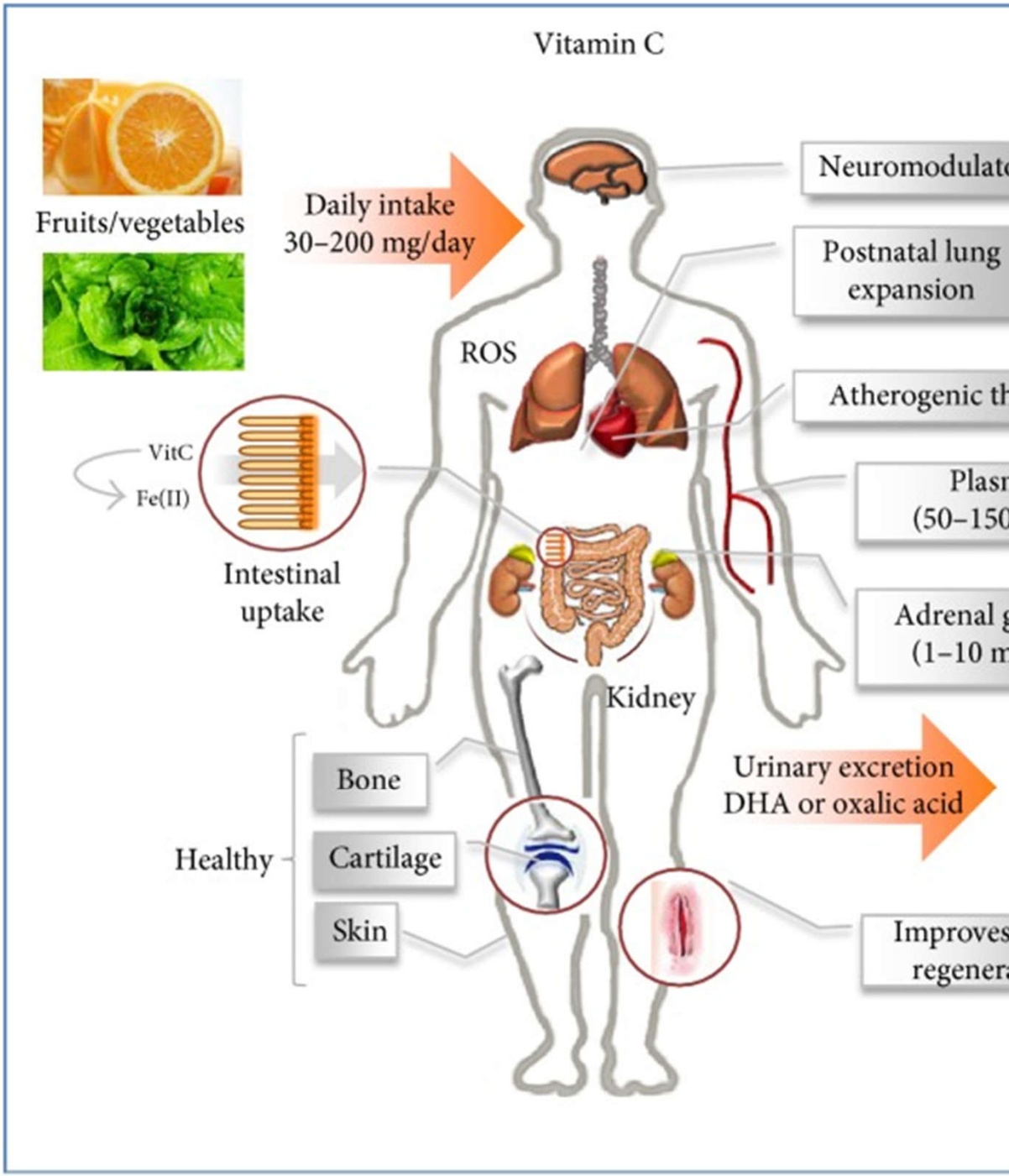

Nutritional Medicine to
support stem cells function.

"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

tamin C is required for healthy function, generation of tissue, and n promote the function of Stem Cells.

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

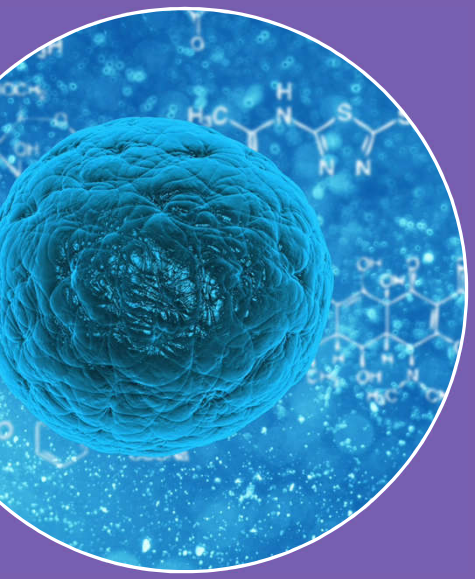


Effect of Vit C activity appears to be dose dependent within a physiological concentration range.

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.


tamin C 250 to 500mg Twice Daily
l berries, kale, Brussels Sprouts, broccoli



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

n Access Original
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DOI: 10.7759/cureus.2741

revalence of Vitamin D Deficiency and ssociated Risk Factors in the US opulation (2011-2012)

veen R. Parva [1], Satish Tadepalli [2], Pratiksha Singh [2], Andrew Qian [1], Rajat Joshi [3], ndavi Kandala [1], Vinod K. Nookala [1], Pramil Cheriyath [2]

nternal Medicine, PinnacleHealth 2. Internal Medicine, Ocean Medical Center 3. Internal Medicine, n State Milton S. Hershey Medical Center

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

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

Parva, N. R., Tadepalli, S., Singh, P., Qian, A., Joshi, R., Kandala H., … Cheriyath, P. (2018). Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Populatio (2011-2012). Cureus, 10(6), e2741. doi:10.7759/cureus.274

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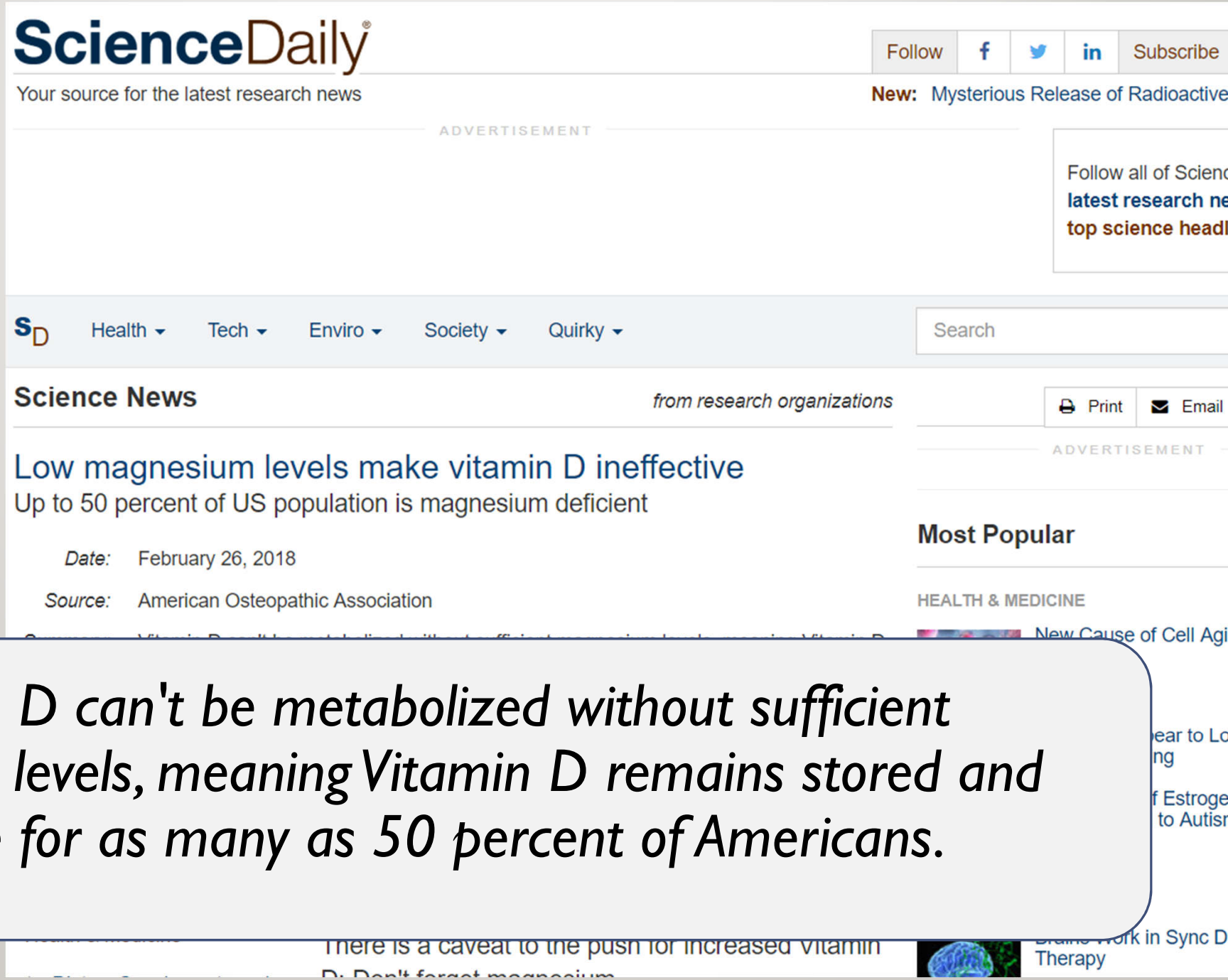


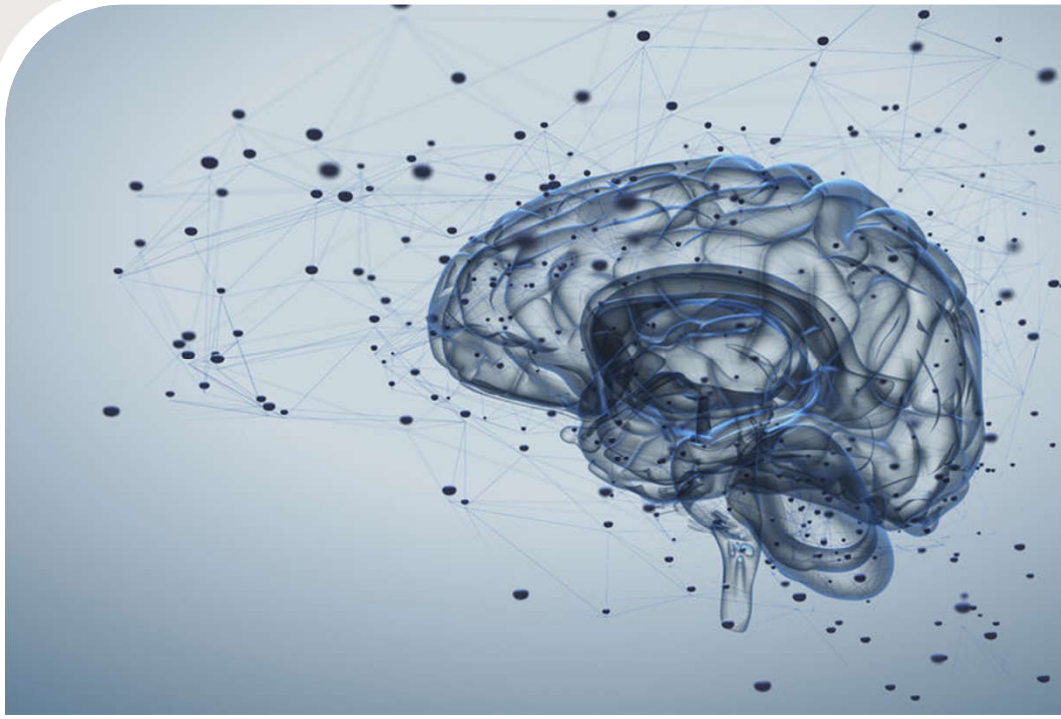
Vitamin D can't be metabolized without sufficient magnesium levels, meaning Vitamin D remains stored and inactive for as many as 50 percent of Americans.

tamin 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 (cholecalcife

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

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



Journal of Neurochemistry
JNC

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.

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

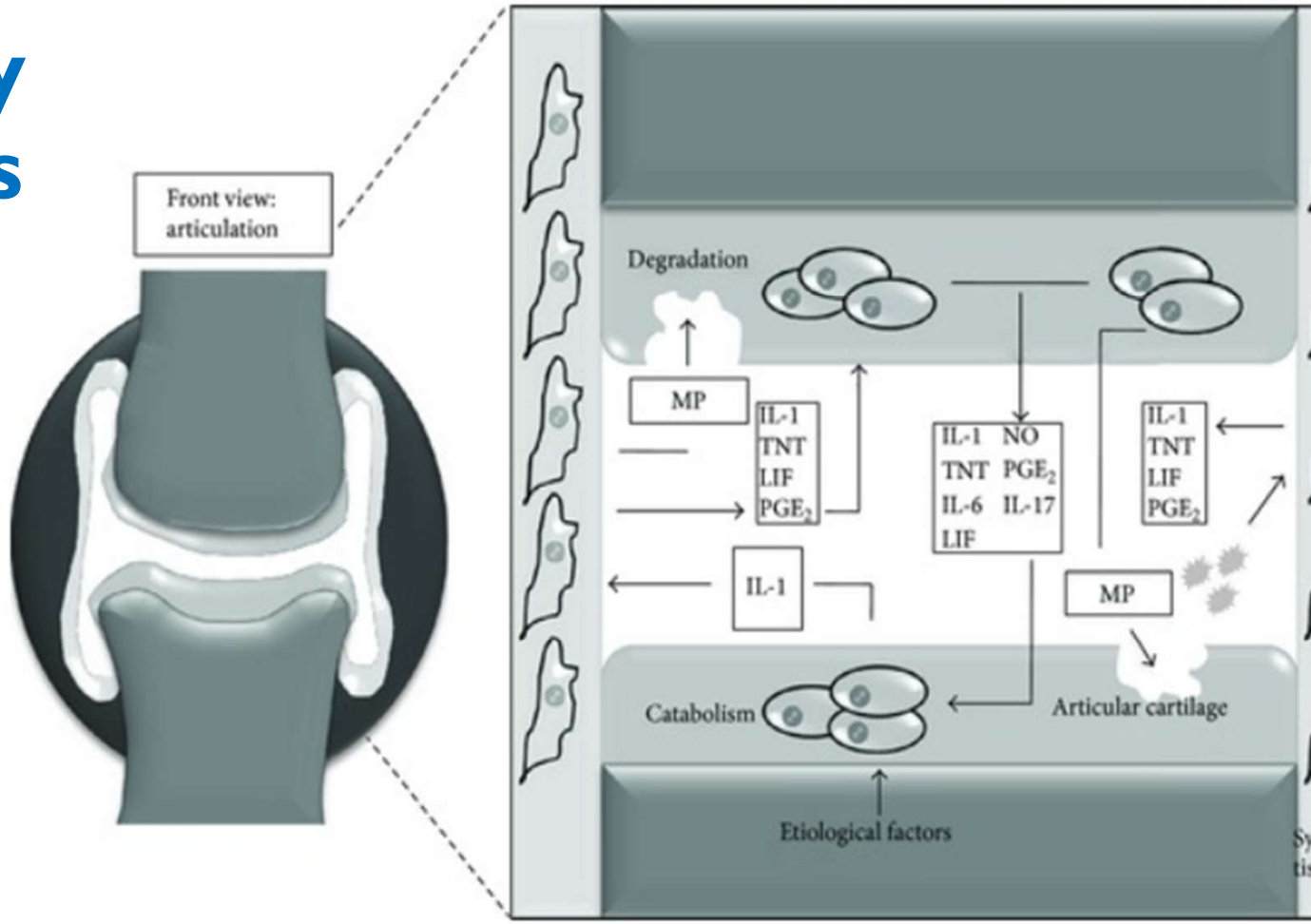
Women are at higher nutrient deficiency

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


upplements & Herbs to
upport stem cells function.

Physiopathology of osteoarthritis

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



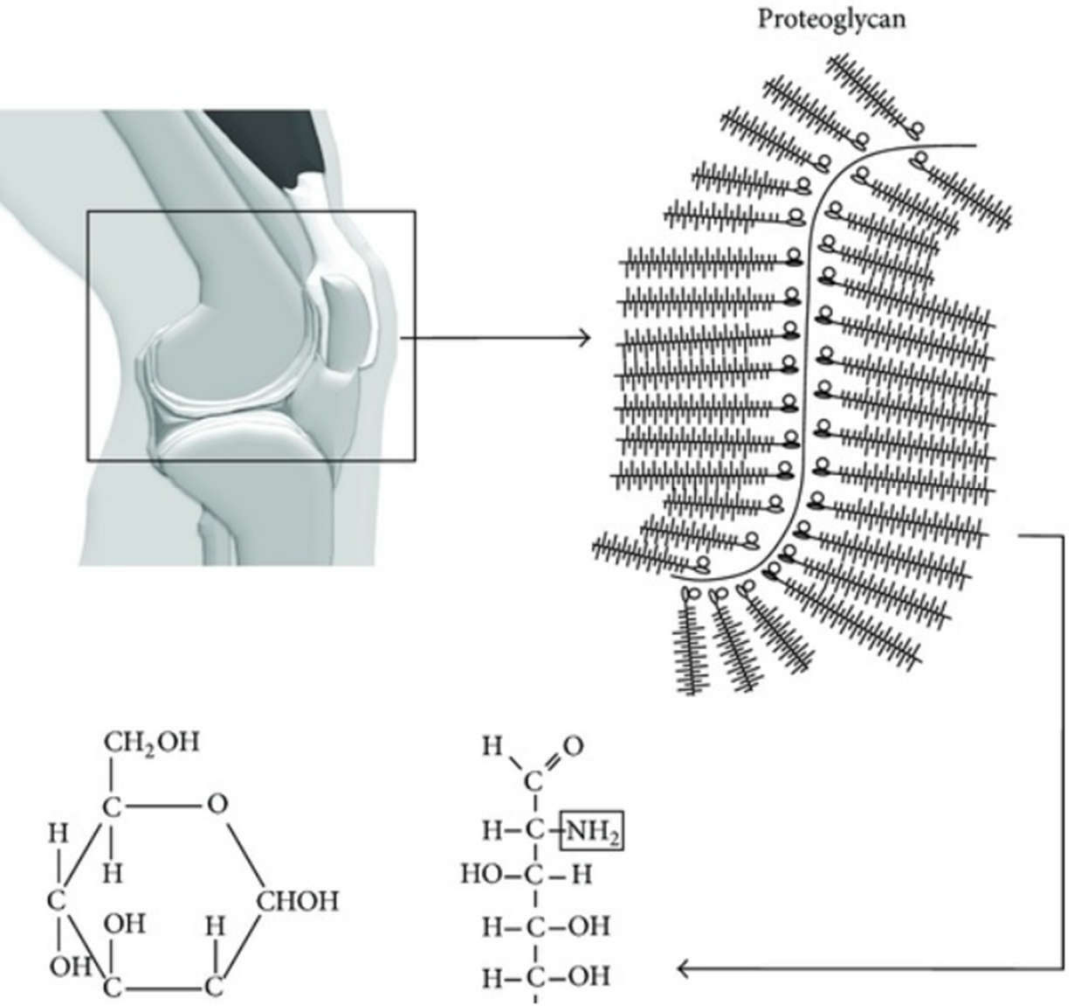
IL: interleukin; TNF: tumoral necros factor; NO: nitric oxide; PG: prostaglandins; MP: metalloprotease LIF: leukemia inhibitory factor.

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.

Management (treatment) of OA

1. Risk factor management and nonpharmacologic measures.
   - Education
   - Walking aids
   - Joint protection
   - Postural hygiene
   - Physical activity
   - Weight control
2. Rapid-acting drugs
   - Paracetamol
   - NSAIDs
   - Opioids
   - Intra-articular corticosteroids
3. Slow-acting drugs (SYSADOA)
   - Glucosamine
   - Chondroitin
   - Hyaluronic acid
   - 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.



What is Glucosamine?

An amino-monosaccharideessential and a noncellular component of connective tissue, cartilage, ligament and other structures. (1)

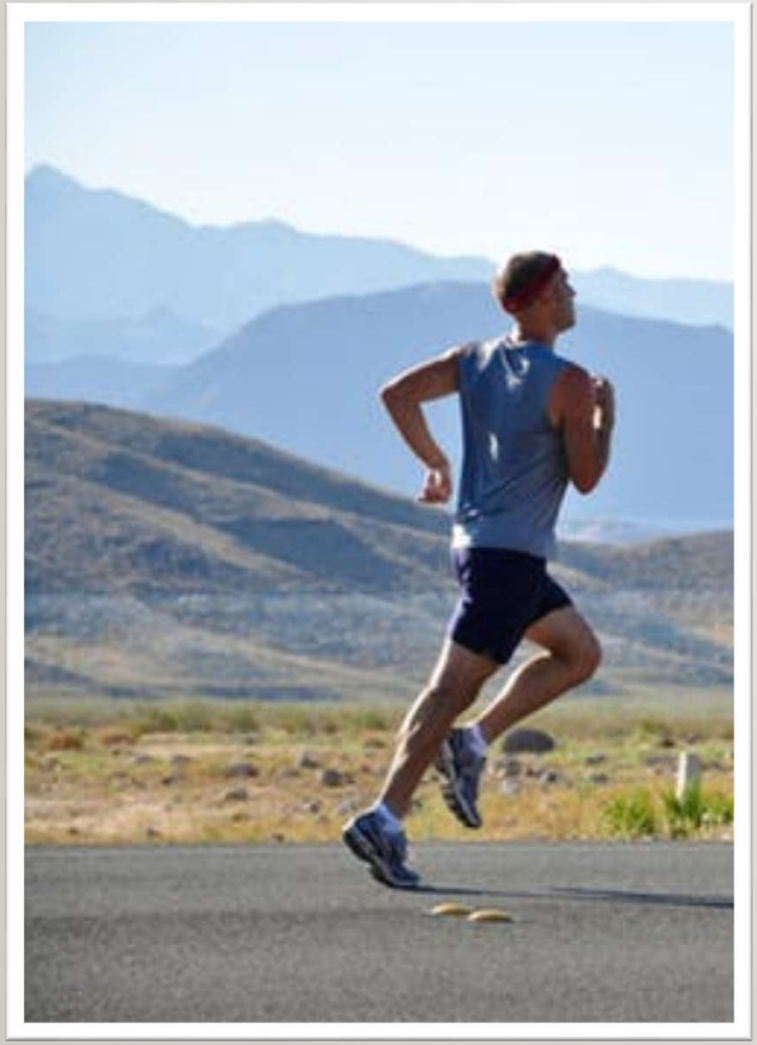
The main compounds:
glucosamine hydrochloride,
glucosamine sulfate,
N-acetylglucosamine. (2)

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.

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



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.

International Journal of Rheumatology

(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.

eular

fighting rheumatic & musculoskeletal diseases together

"In the European League Against Rheumatism (EULAR) recommendation concerning knee C they gave CS both the highest evidence grade and the highest recommendation strength, 1A and A respectively."

Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Com for International Clinical Studies Including Therapeutic Trials (ESCISIT).
KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S esne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M, S Committee for International Clinical Studies Including Therapeutic Trials ESCISIT.
Ann Rheum Dis. 2003 Dec; 62(12):1145-55.

"Deeply investigated, herbal extract which increases tissue regeneration and promotes stem cell growth may be successfully applied in the field of biomaterials. Promoting the endogenous stem cell multipotency and their differentiation ***potential may additionally support the regenerative processes after MSCs transplantation.***"

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

Per general recommendation:

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

Why?

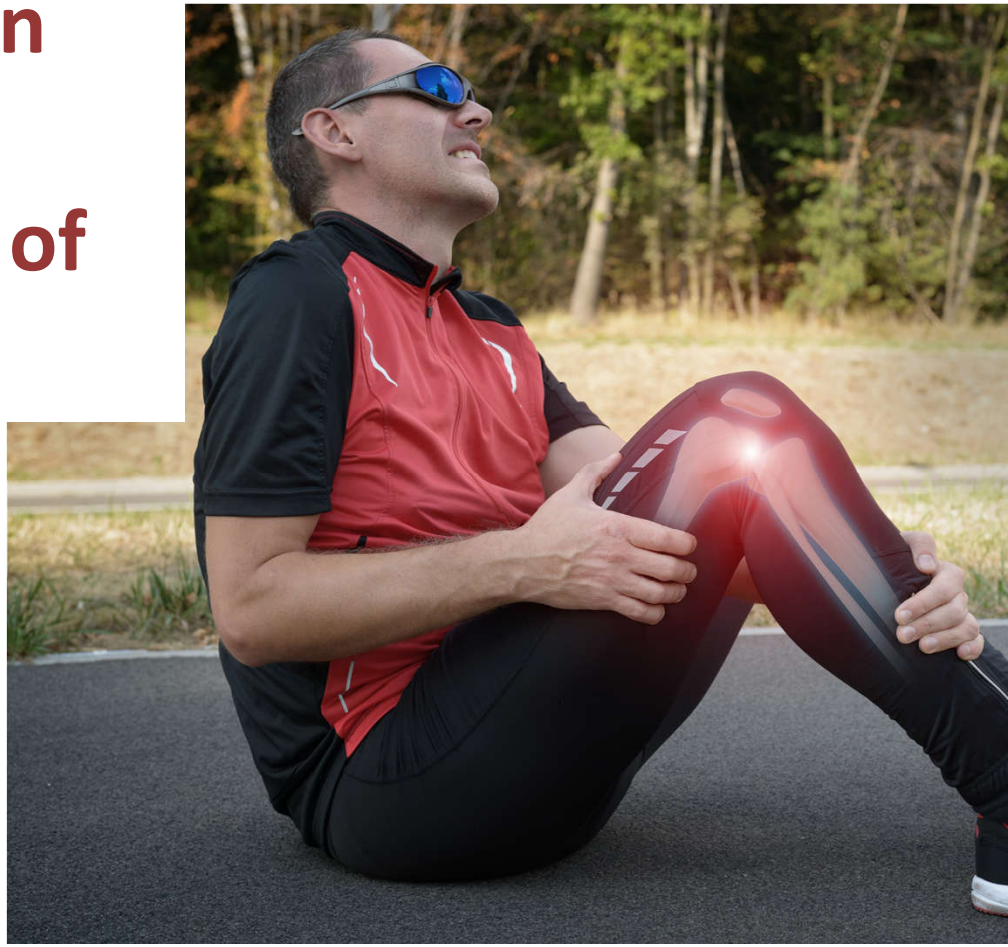

May
Inflammation
Be With You!

Infections, wounds, and any damage to tissue would not be able to heal without an inflammatory response.

Harmful inflammation
vs
“beneficial inflammation”

We used to think that our joints degenerate because of age, rauma, excess weight, or overuse.

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



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

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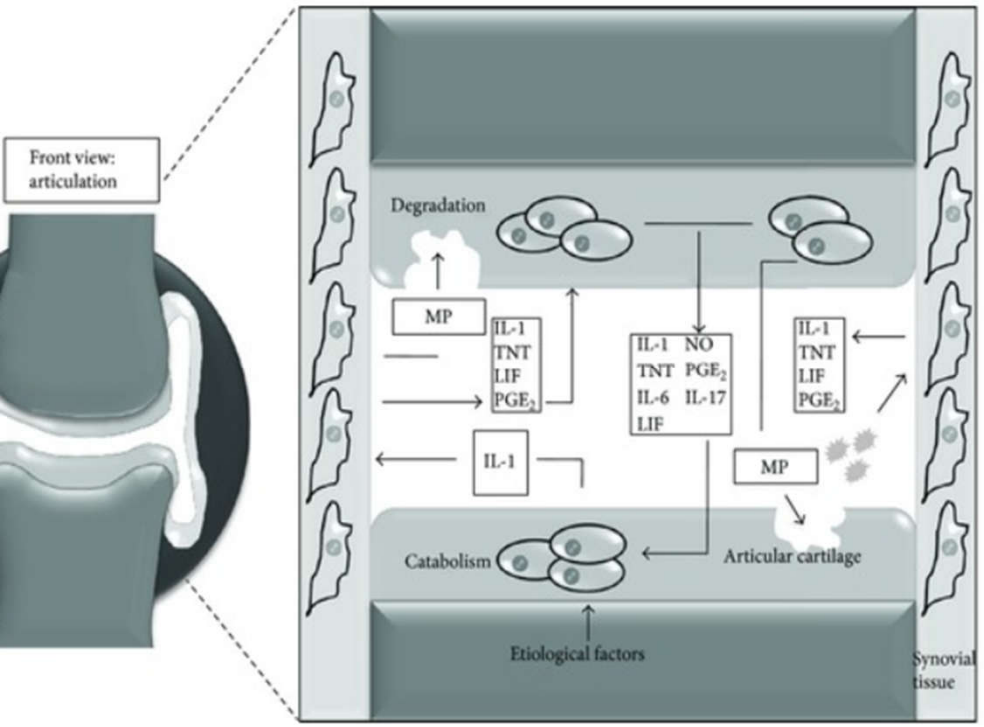
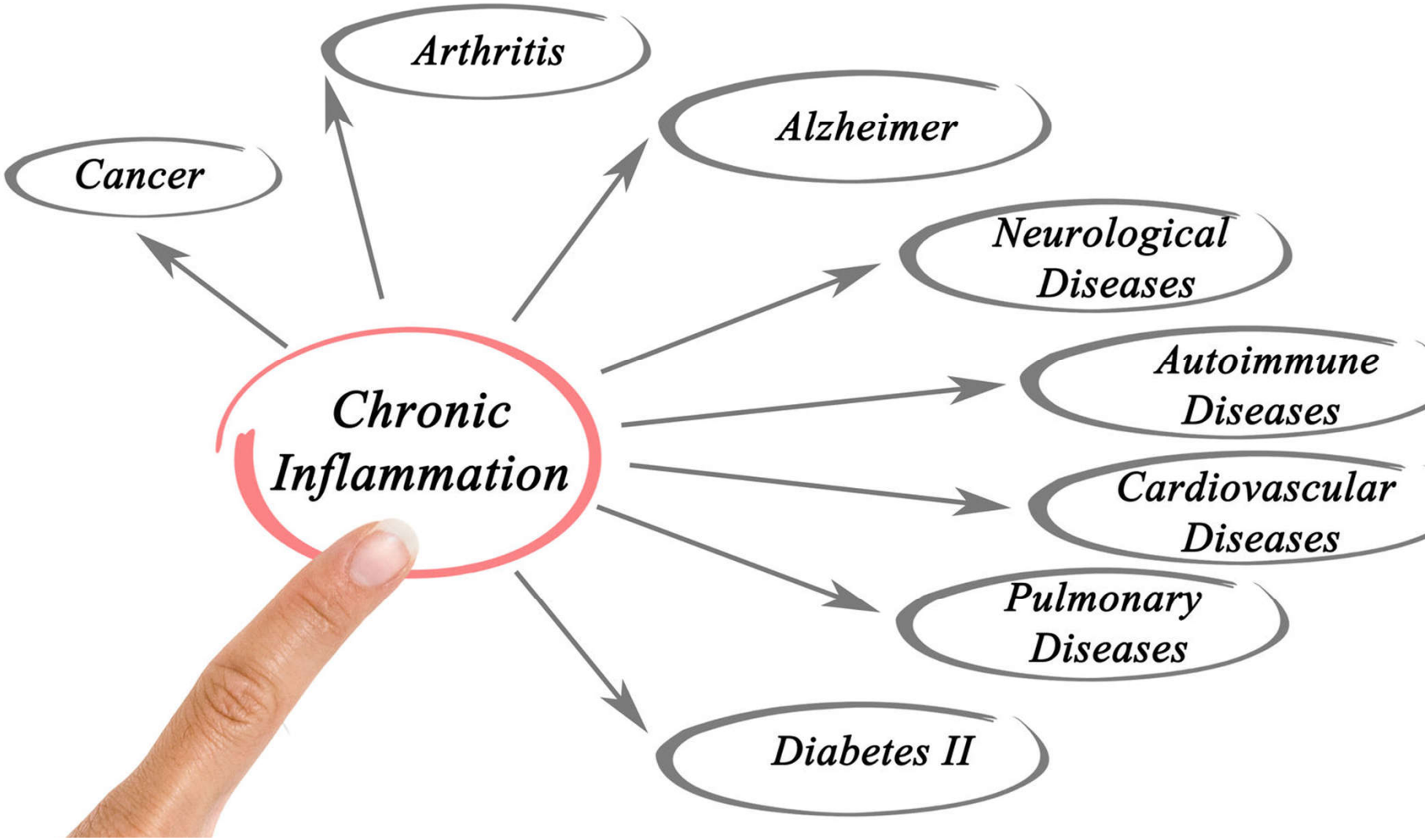


Cytokines that have been implicated in OA pathogenesis include:*

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

source: Salazar, J., Bello, L., Chávez, M., Añez, R., Rojas, J., & Bermúdez, V. (2014). Glucosamine for osteoarthritis: biological effects, clinical effica
n glucose metabolism. Arthritis, 2014, 432463.
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.

hronic inflammation has a key role in evelopment of many chronic diseases.



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

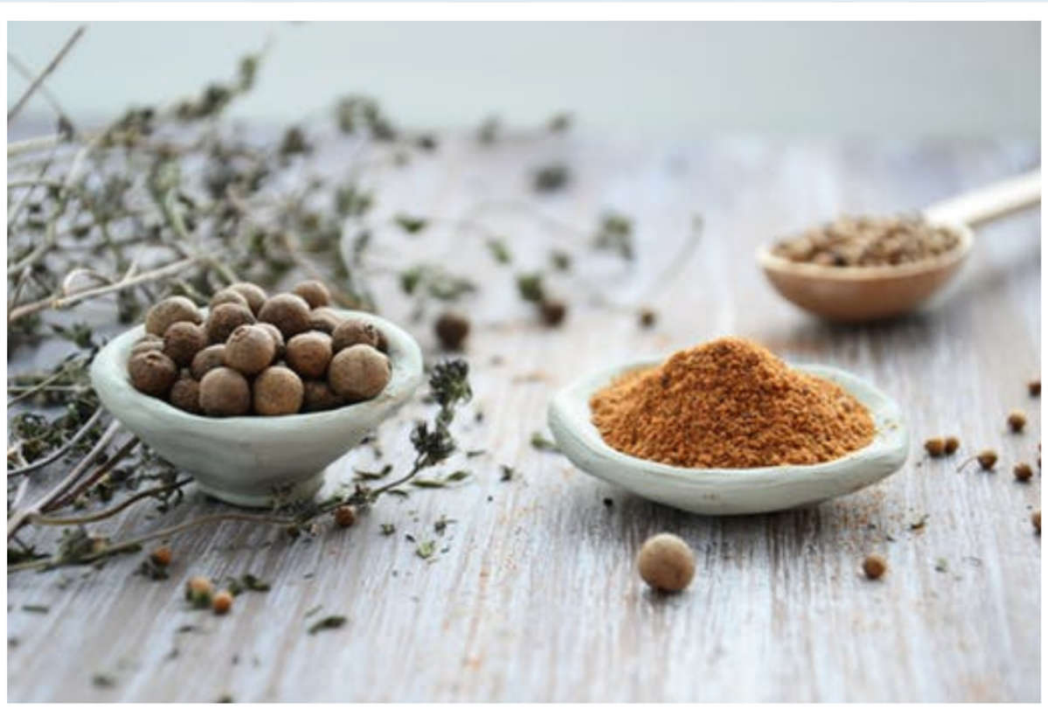
Ranneh, Y., Akim, A.M., Hamid, H.A. et al. Induction of Chronic ubclinical Systemic Inflammation in Sprague–Dawley Rats imulated by Intermittent Bolus Injection of Lipopolysaccharide. rch. Immunol. Ther. Exp. 67, 385–400 (2019). ttps://doi.org/10.1007/s00005-019-00553-6

educing
FLAMMATON Is
sential!

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.

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

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., … Laongp
(2014). Efficacy and safety of Curcuma domestica extracts compared with ibup
patients with knee osteoarthritis: a multicenter study. Clinical interventions in agi
451-8. doi:10.2147/CIA.S58535

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 safet 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

IL-6 is also involved in pathogenesis of differe inflammatory diseases Curcumin can be considered as potentia therapy against IL-6 involved pathologic sta

Ghandadi M, Sahebkar A. Curcumin: An Effective Inhibitor of Interleukin-6. Curr Des. 2017;23(6):921-931. doi: 10.2174/1381612822666161006151600 PMID: 27719643.

rcumin consumption
uces
expression and production
L-10, potent anti-
ammatory and
munosuppressive cytokine.

10 deregulation plays a role
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ammatory diseases such
neuropathic pain,
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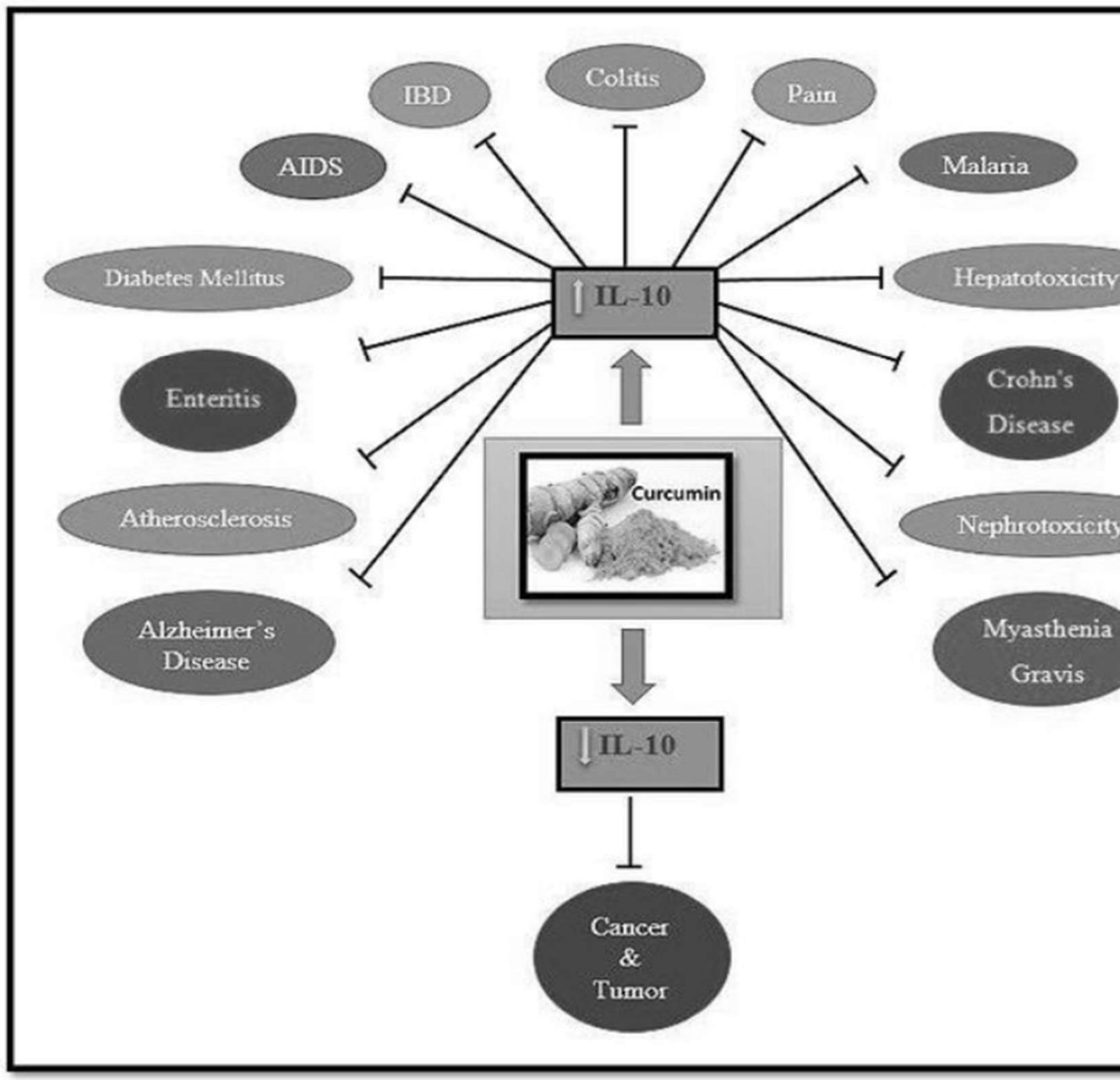


mid Mollazadeh, Arrigo F. G. Cicero, Christopher N. Blesso, Matteo Pirro, Muhammed Majeed & Amirhossein hebkar (2019) Immune modulation by umin: The role of interleukin-10, Critical views in Food Science and Nutrition, 59:1, 89-101, DOI: 10.1080/10408398.2017.1358139

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-κB promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment

Constanze Buhrmann[1], Ali Mobasheri[2], Ulrike Matis[3] and Mehdi Shakibaei*[1]

Curcumin alone does not have chondrogenic effects on MSCs, but it inhibits proinflammatory cytokines (e.g. IL-1β, Nuclear factor-κB) and support the regeneration of articular cartilage (enhanced the production of collagen type II, cartilage specific proteoglycans (CSPGs), β1-integrin, etc.

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

Animal studies show that

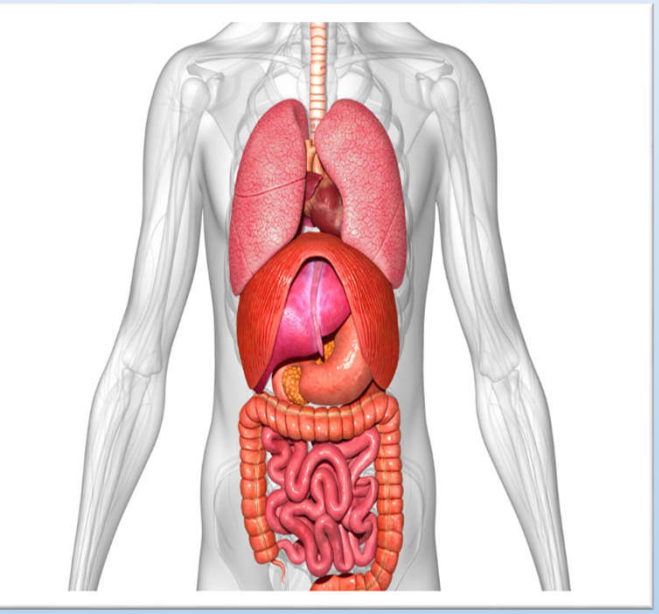
curcumin stimulated neural stem cells proliferation,

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

Curcumin Bioavailability



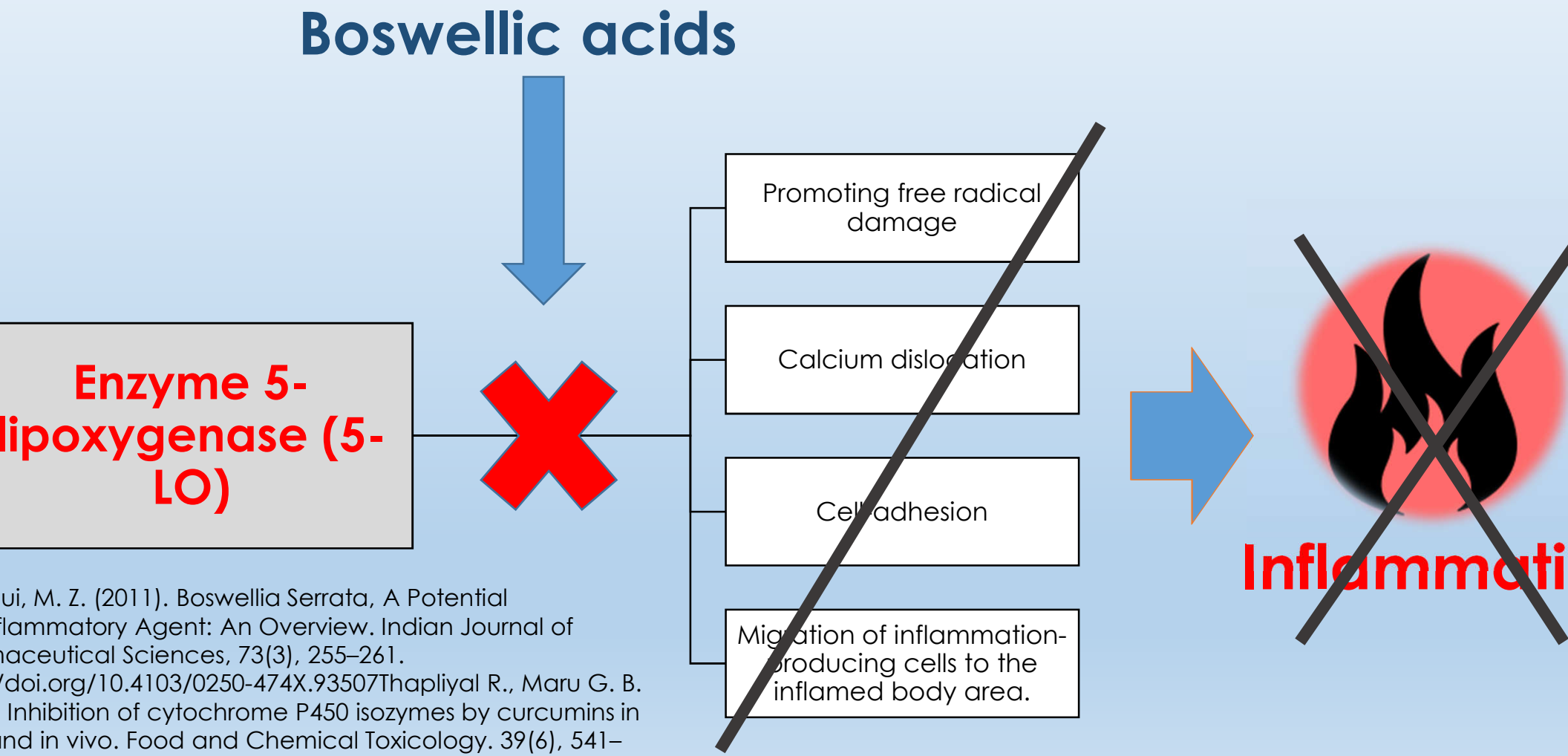
- Low bioavailability for local GI inflammatory diseases
- Higher bioavailability for systemic inflammation (e.g. joints)
- Adding piperine, the major active component of black pepper, to curcumin has been shown to increase bioavailability by 2000%

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

Boswellia Serrata

A natural and affordable agent that can reduce the inflammatory process

Boswellia Serrata



ui, M. Z. (2011). Boswellia Serrata, A Potential flammatory Agent: An Overview. Indian Journal of naceutical Sciences, 73(3), 255–261. /doi.org/10.4103/0250-474X.93507Thapliyal R., Maru G. B. Inhibition of cytochrome P450 isozymes by curcumins in nd in vivo. Food and Chemical Toxicology. 39(6), 541– oi: 10.1016/S0278-6915(00)00165-4.

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)

. Haroyan, A., Mukuchyan, V., Mkrtchyan, 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

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)

. Haroyan, A., Mukuchyan, V., Mkrtchyan, 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

Hesperidin,

a flavonoid found in citrus fruits,

inhibits secretion of pro-inflammatory cytokines IFN-γ, IL-2, IL-4 and IL-10,

and

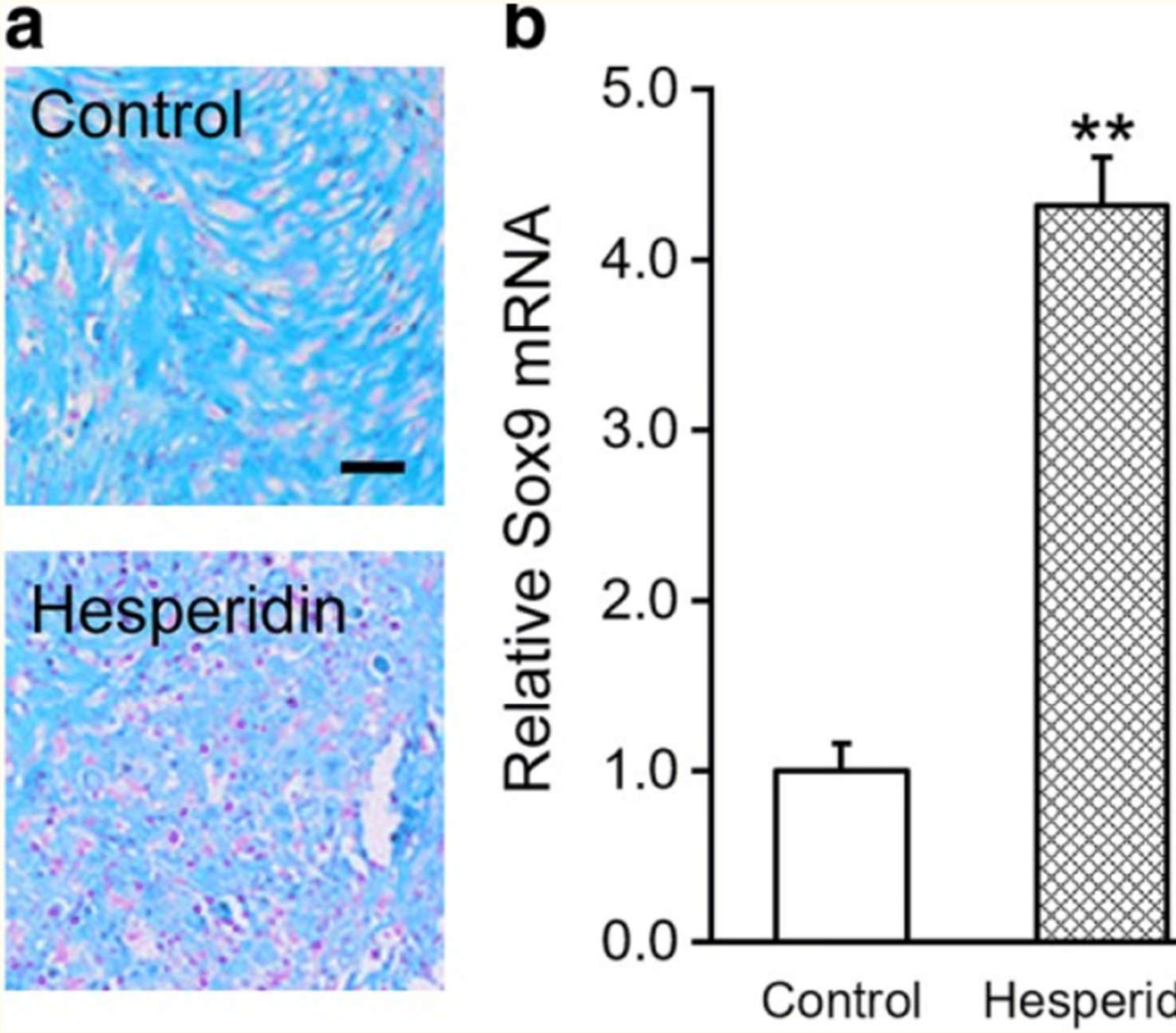
enhances the formation of cartilage by stem cells.

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

Hesperidin

peridin improves self-
ewal ability of MSCs.

At day 14 after
rentiation induction in
absence (control) or
presence of 5 μM
hesperidin.



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

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, Teglbjaerg 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.

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

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

Catherine L Hill,[1,2] Lynette M March,[3] Dawn Aitken,[4] Susan E Lester,[1] Ruth Battersby,[1] Kristin Hynes,[3] Tanya Fedorova,[3] Susanna M Proudman,[5] Michael James,[5] Leslie G Cleland,[5] Graeme Jones[3]

ing editor Tore K Kvien
itional material is
ed online only. To view
visit the journal online
dx.doi.org/10.1136/
umdis-2014-207169).

natology Unit, The
Elizabeth Hospital,
ille, South Australia
rsity of Adelaide, The
Observatory, Adelaide,

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

change in serum C reactive protein. Low-dose
oil resulted in better pain and function scores
18 and 24 months compared with high-dose
fish oil.

ed 17 December 2014
17 August 2015
ed 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

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)

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.

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

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

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 α-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 NR1C3.**

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

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

Resveratrol

Resveratrol showed **antioxidant and immunomodulatory** effects for some autoimmune diseases, such as **rheumatoid arthritis, systemic lupus** erythematosus, **psoriasis**, **inflammatory bowel diseases**, and **type 1 diabetes** mellitus.

JBC JOURNAL BIOLOGIC CHEMIST

Resveratrol reduces the inflammatory process by inhibiting proinflammatory cytokines and T-cell differentiation.

1. Oliveira, A. L. de B., Monteiro, V. V. S., Navegantes-Lima, K. C., Reis, J. F., Gomes, R. de S., Rodrigues, D. V. S., … Monteiro, M. C. (2017 Resveratrol Role in Autoimmune Disease—A Mini-Review. Nutrients, 9(12), 1306. http://doi.org/10.3390/nu9121306
2. Mobasheri, A., Shayan, P., Lueders, C., Stahlmann, R., & Shakibaei, M. (2012). Resveratrol Modulates Interleukin-1β-induced Phosphatidylinositol 3-Kinase and Nuclear Factor κB Signaling Pathways in Human Tenocytes. Journal of Biological Chemistry, 287(45), 38 38063. doi:10.1074/jbc.m112.377028 Retrieved from http://www.jbc.org/content/287/45/38050.full.html

Resveratrol Dosage

No standard dosage was found

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

Nutritional & Supplements Protocol for Nerve Regeneration

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-Mayorquín, A. E., Ortuño-Sahagún, D., & Pallàs, M. (2009). Resveratrol: An Antiaging Drug with Potential Therapeutic Applications in Treating Diseases. Pharmaceuticals (Basel, Switzerland), 2(3), 194-205.

"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.

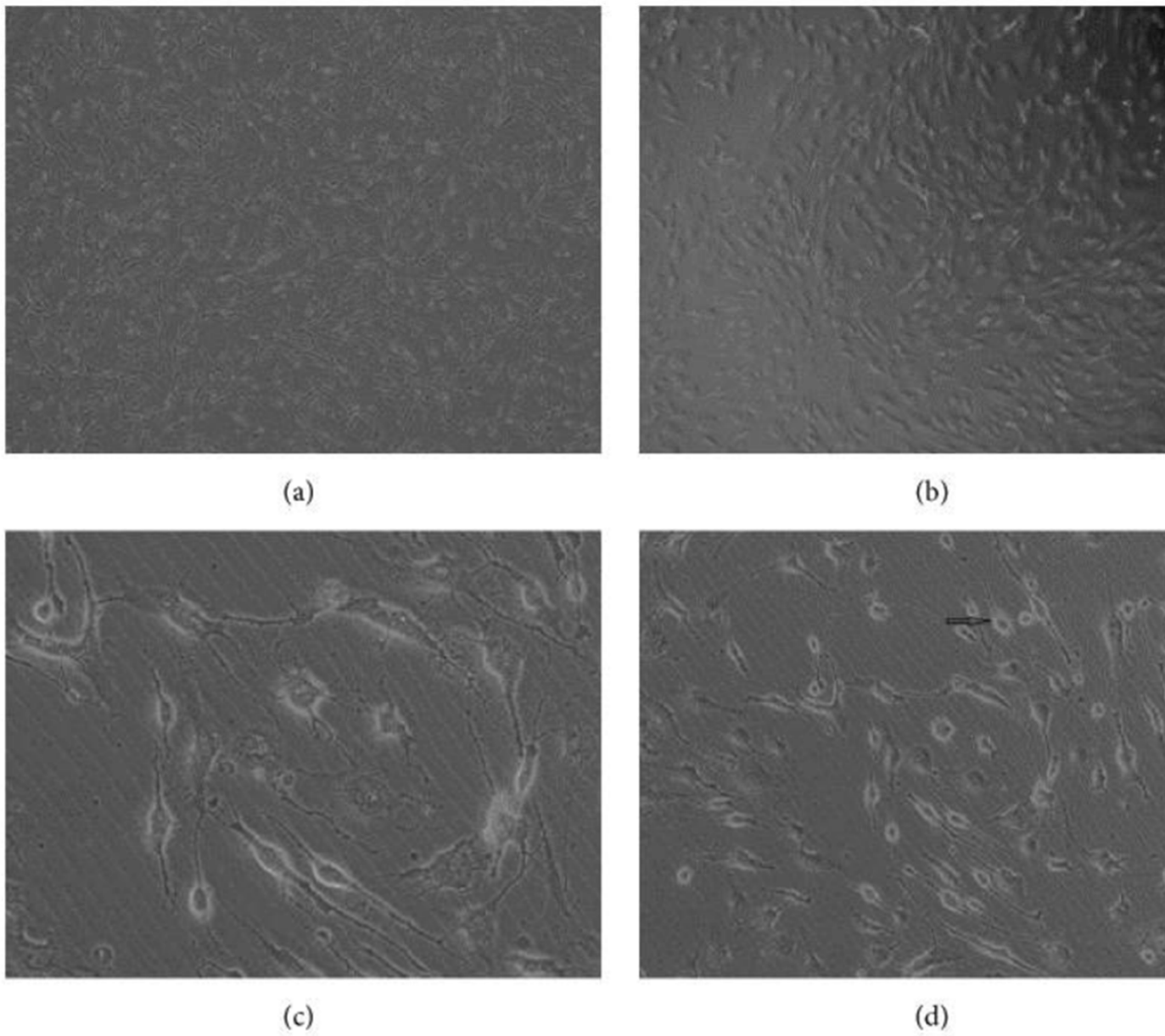
INTERNATIONAL JOURNAL OF STEM CELLS

"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.

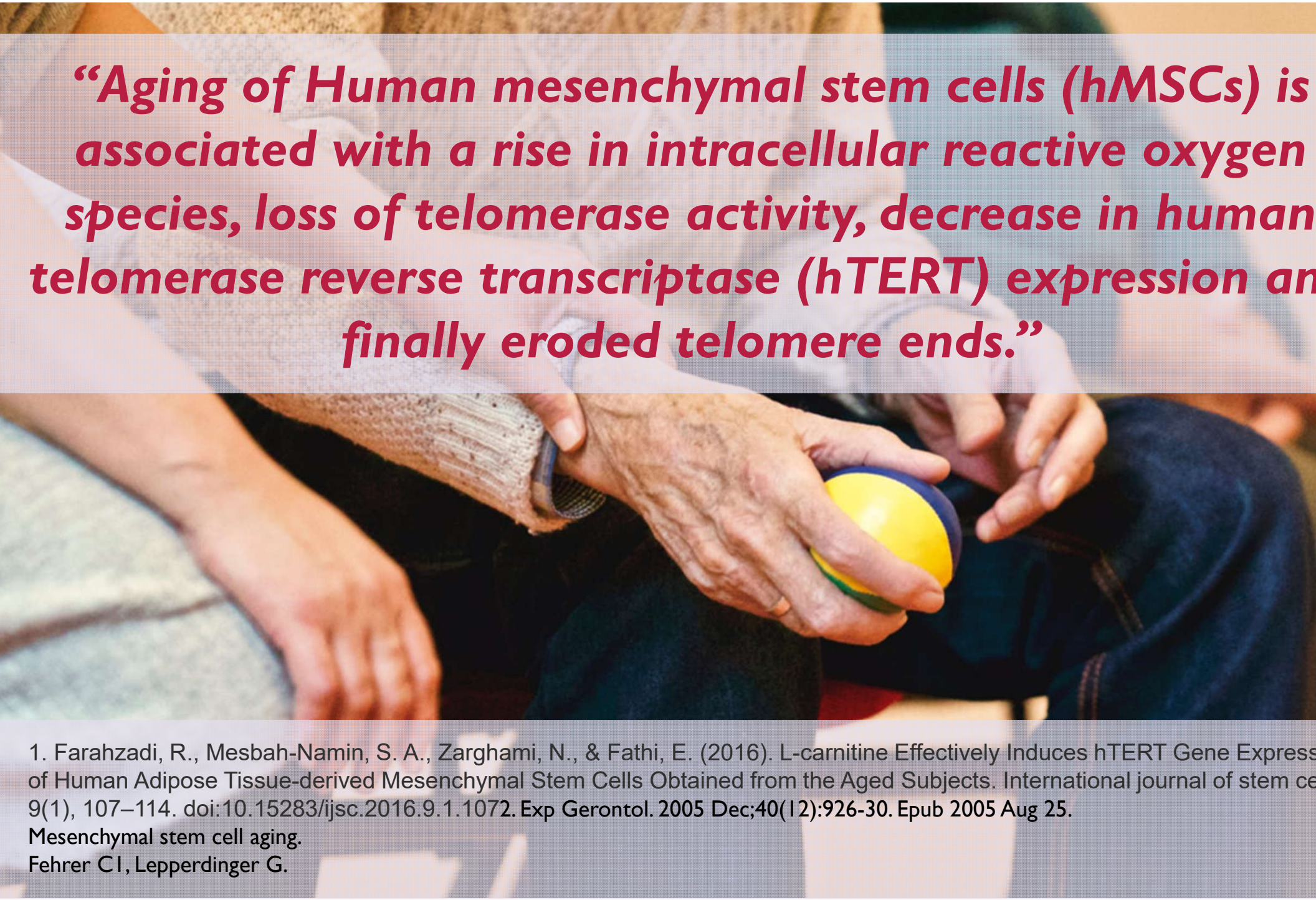
Images showing that different concentrations of resveratrol (0.0 mg/L (a), 7.5 mg/L (b), 15.0 mg/L (c), and 30.0 mg/L (d)) induce differentiation of hUC-MSCs into neuron-like cells.



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.

What's the dosage?

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



"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 an finally eroded telomere ends."

1. Farahzadi, R., Mesbah-Namin, S. A., Zarghami, N., & Fathi, E. (2016). L-carnitine Effectively Induces hTERT Gene Express of Human Adipose Tissue-derived Mesenchymal Stem Cells Obtained from the Aged Subjects. International journal of stem ce 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 C1, Lepperdinger G.

International Journal of Stem Cells Vol. 9, No. 1, 2016 http://dx.doi.org/10.15283/ijsc.2016.9.1.107

ORIGINAL ARTICLE

L-carnitine Effectively Induces *hTERT* Gene Expression of Human Adipose Tissue-derived Mesenchymal Stem Cells Obtained from the Aged Subjects

Raheleh Farahzadi[1], Seyed Alireza Mesbah-Namin[1], Nosratollah Zarghami[2,3], Ezzatollah Fathi[4]

"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

"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/β-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

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.

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.

A 24-week randomized controlled trial with 404 outpatients ≥ 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.

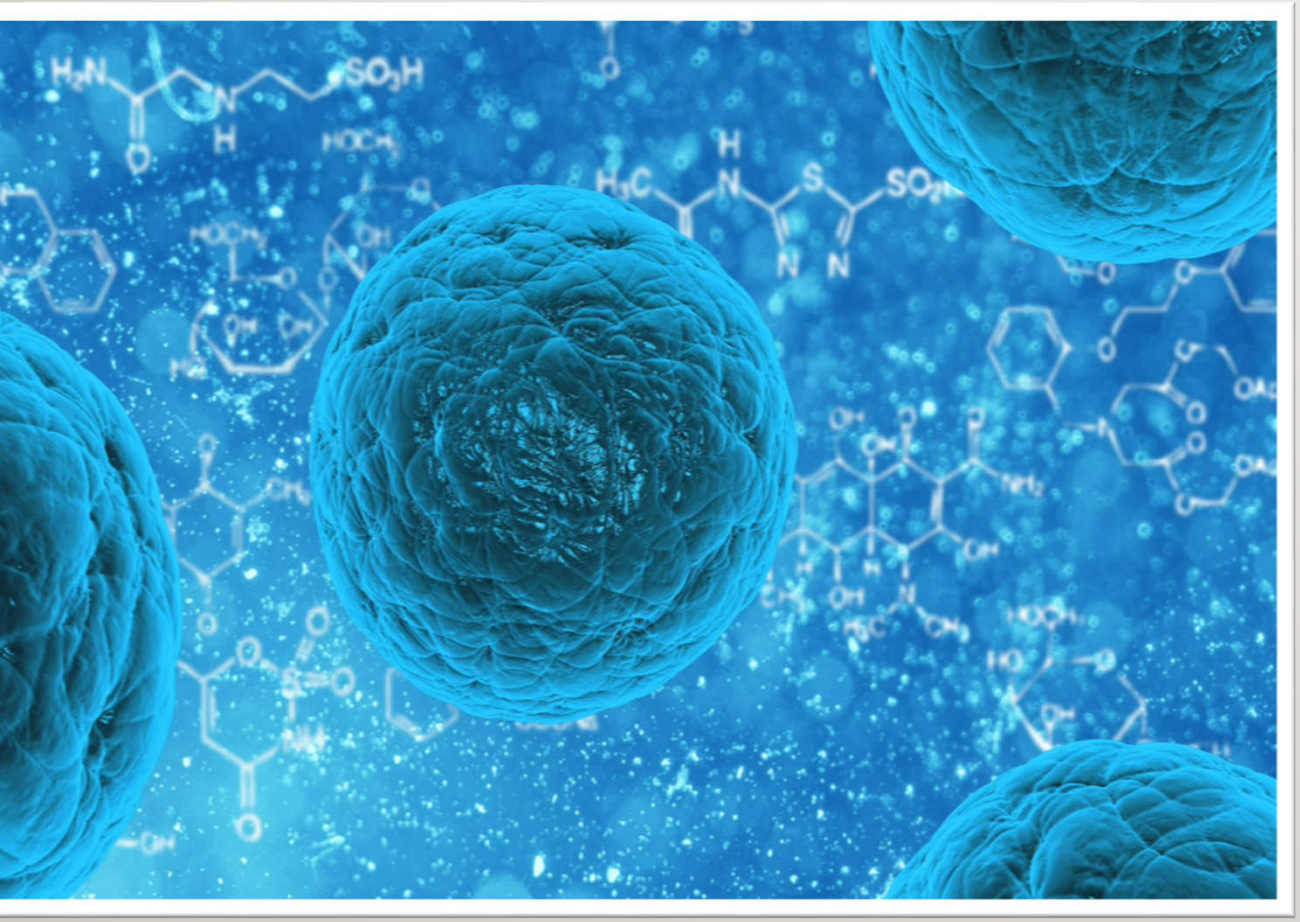
240 mg of Ginkgo Biloba once-daily improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia

Pharmacopsychiatry

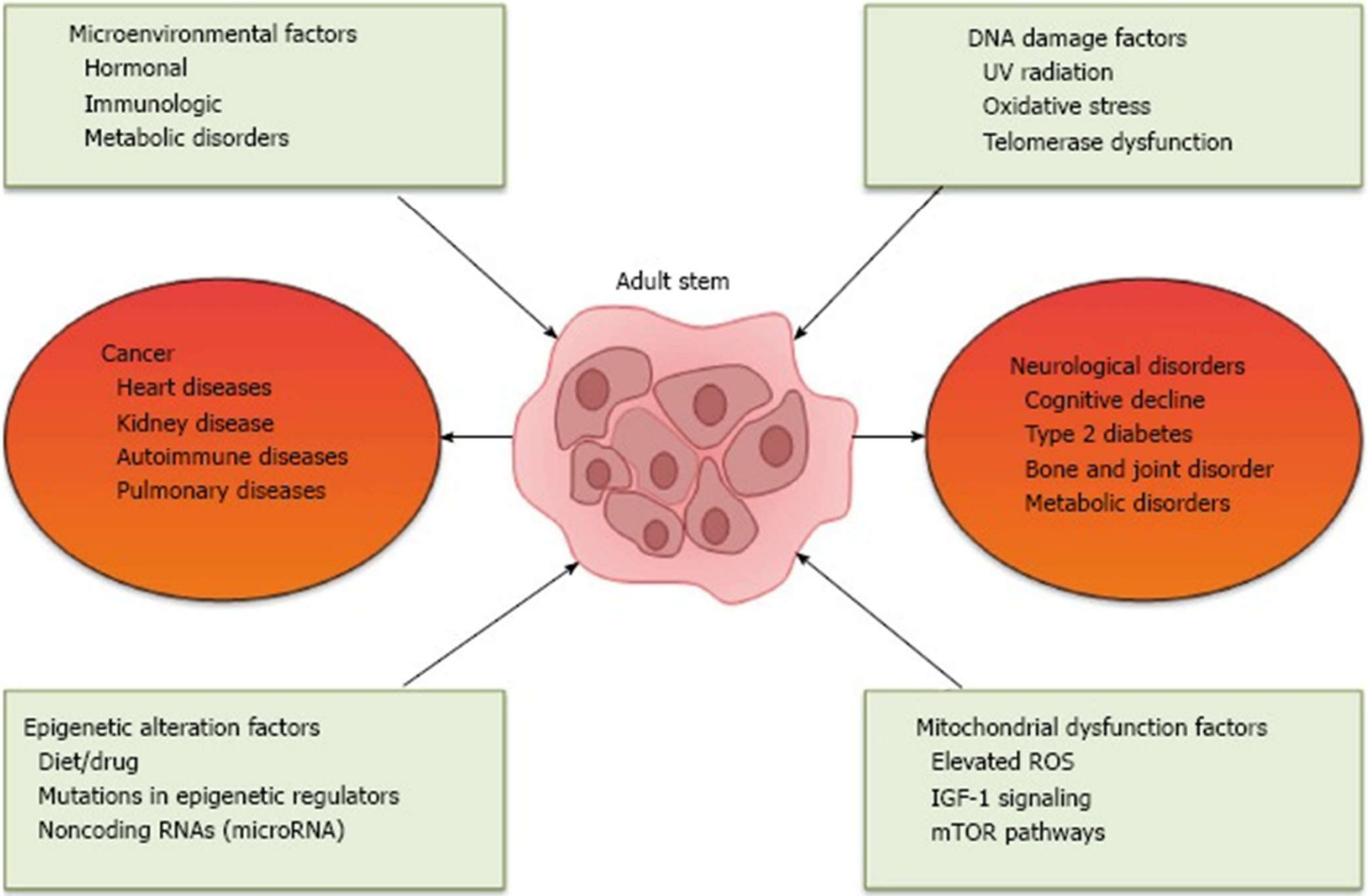
Ihl R, Tribanek M, Bachinskaya N, GOTADAY Study Group. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial.

Pharmacopsychiatry. 2012 Mar; 45(2):41-6.

Protect Stem Cells From Damage

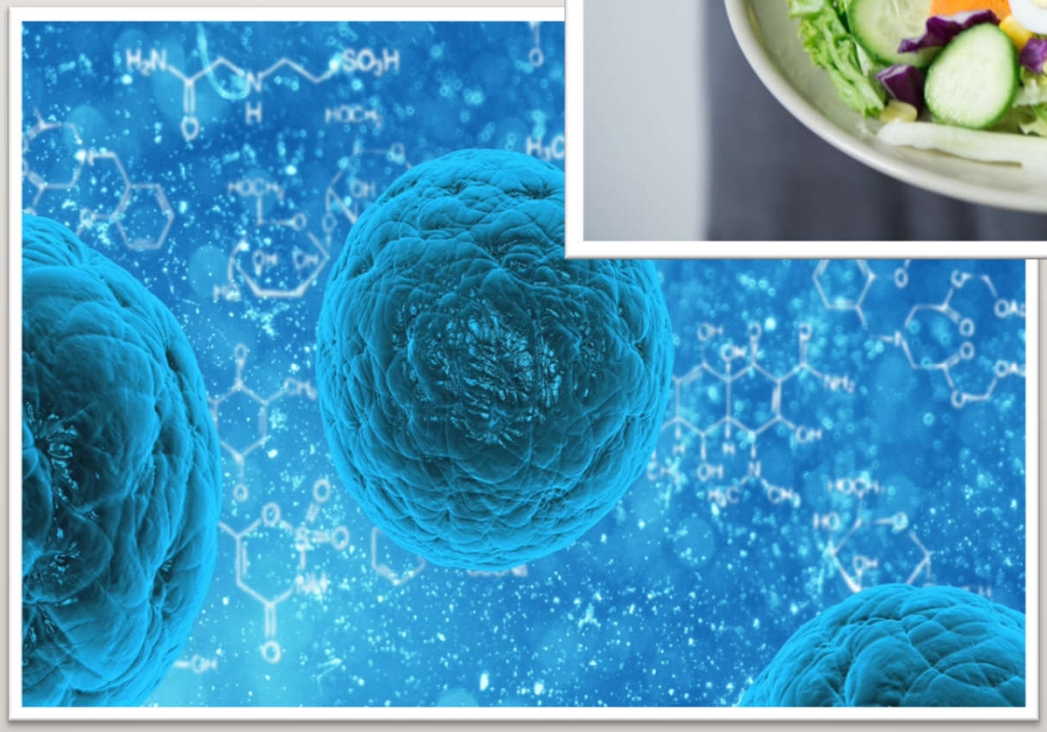


What can inhibit stem cells or reduc their ability to regenerate new tissue?



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

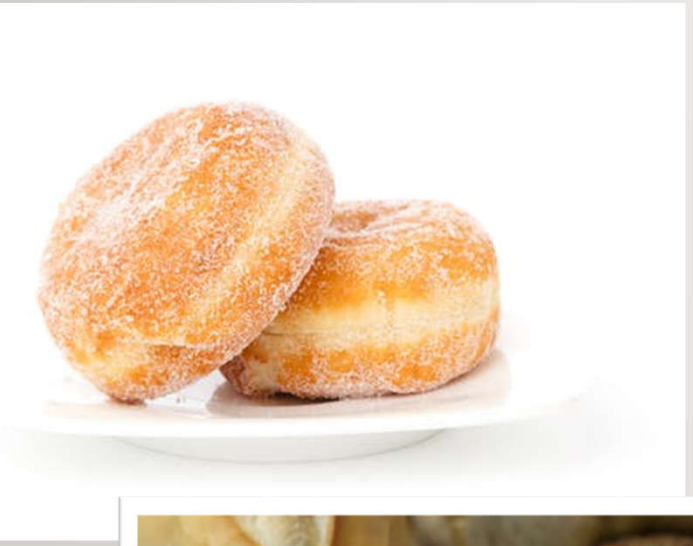
Dietary Changes to Support Stem Cells Therapy



The science of epigenetic and nutrigenetic

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

Fenech, M., El-Sohemy, 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. Journa of nutrigenetics and nutrigenomics, 4(2), 69–89. https://doi.org/10.1159/000327772



Remove Foods that Increase Inflammation:

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

"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."

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

uctose and its metabolites ectly and/or indirectly cause dative stress, chronic ammation, endothelial function, autophagy and reased intestinal permeability, l then further aggravate the tabolic syndrome with tissue l organ dysfunctions."

g, D. M., Jiao, R. Q., & Kong, L. D. (2017). Dietary Fructose: Direct or Indirect erous Factors Disturbing Tissue and n Functions. Nutrients, 9(4), 335. ://doi.org/10.3390/nu9040335

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.

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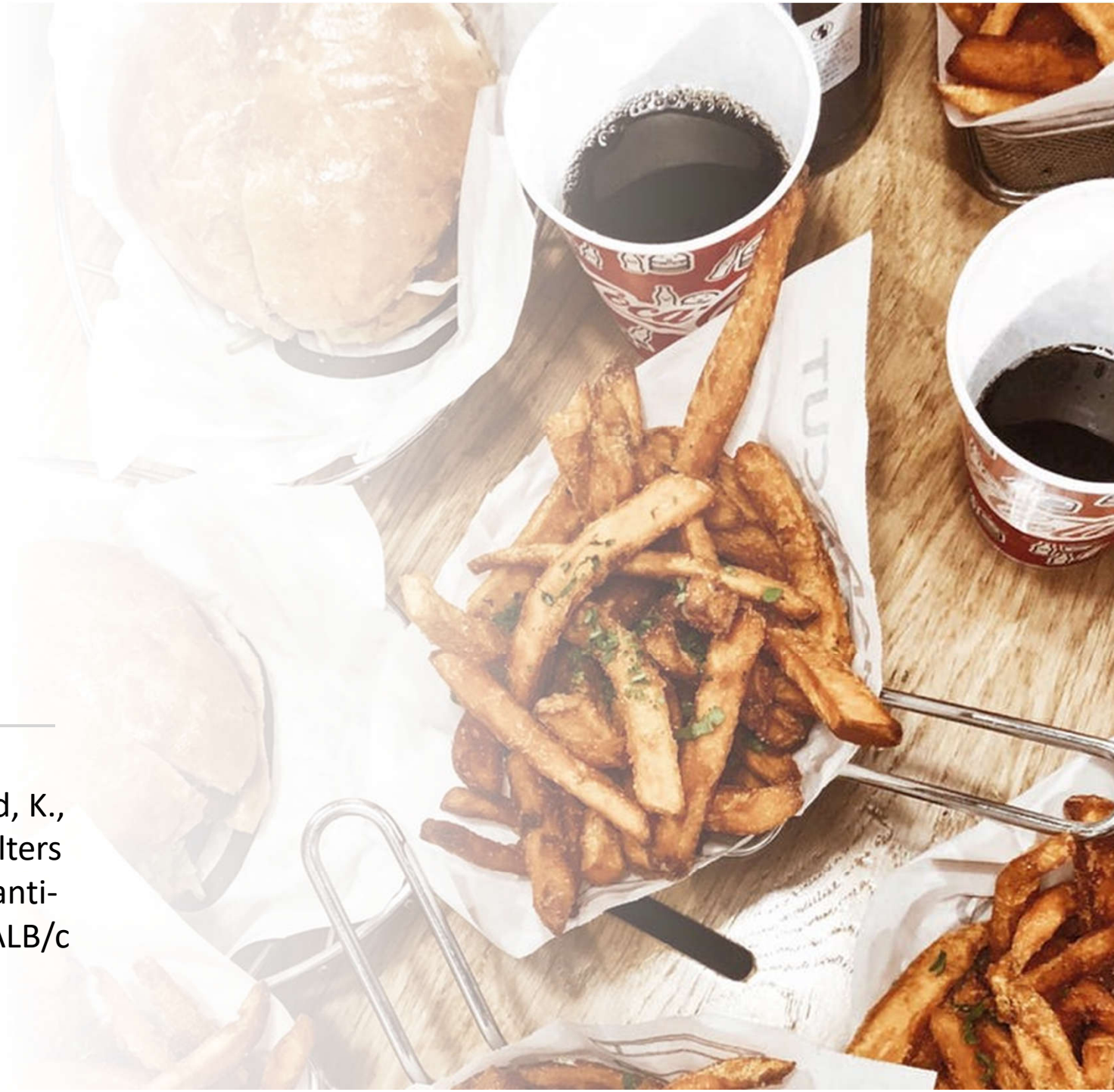


orskov, J. C., Fundova, P., Buschard, K.,
nda, D. P. (2013). Dietary gluten alters
alance of pro-inflammatory and anti-
mmatory cytokines in T cells of BALB/c
Immunology, 138(1), 23–33.
://doi.org/10.1111/imm.12007

"Gluten-containing diet increased the level of potent pro-inflammatory (IL-17, IFN-γ) cytokines, as well as of IL-2 and IL-4."

Immunology

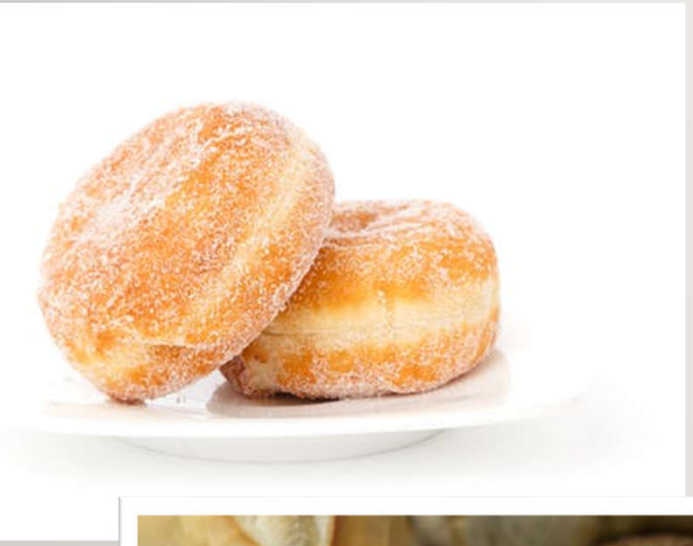
British Society for immunology

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.

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



Remove Foods that Increase Inflammation:

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


Are your patients eat pro or anti-inflammatory foods?

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

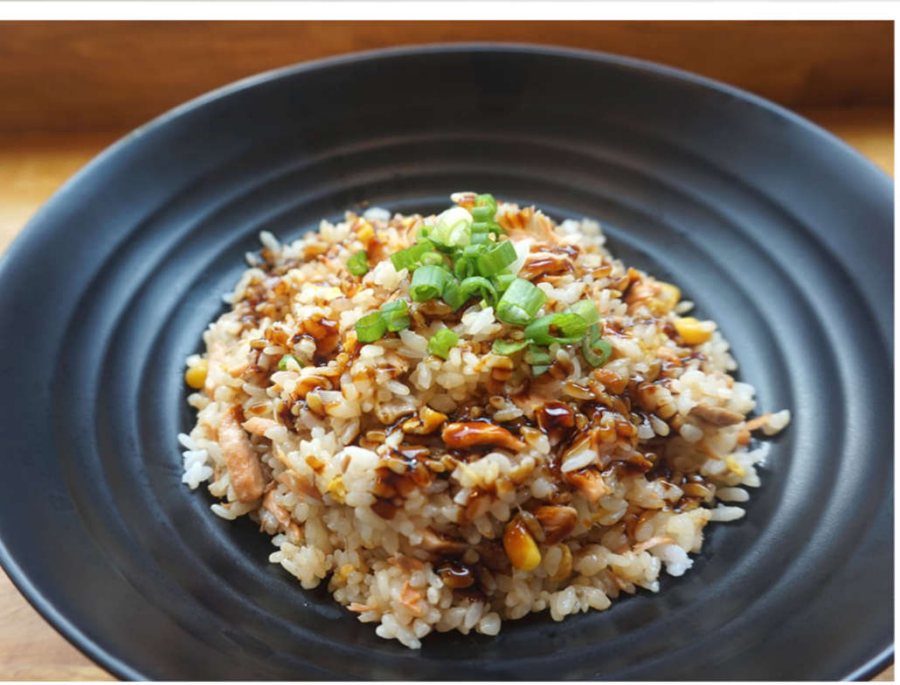
Healthy Fats: (up your intake, it fuels yo
brain and reduce inflammation)

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

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)

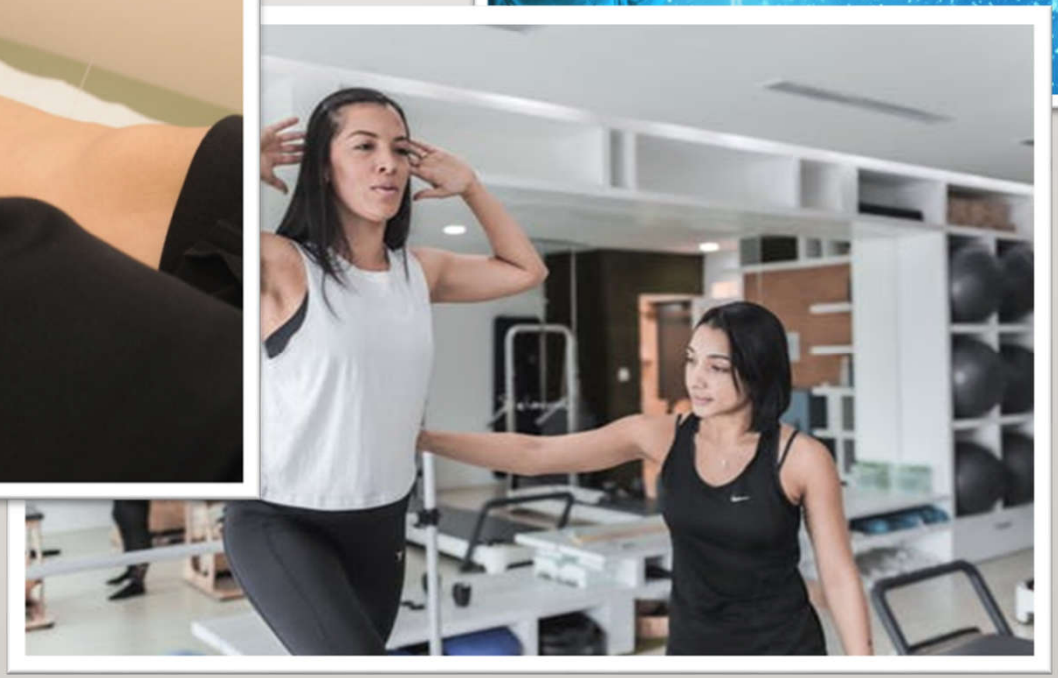
Avoid tuna fish or canned food!

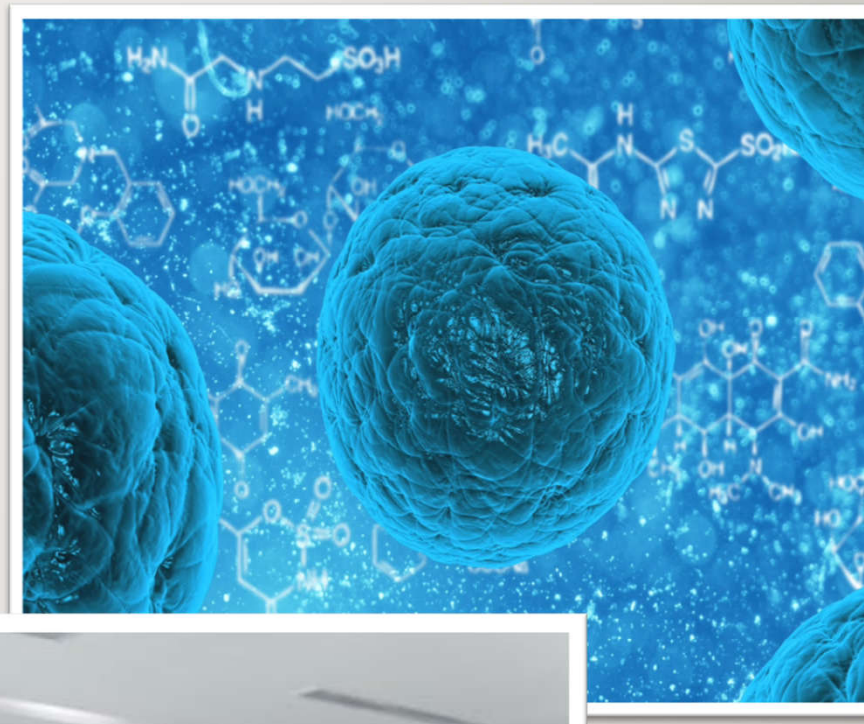


Healthy carbs: (up your intake, it fuels your brain and reduce inflammation)

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

upporting Treatments





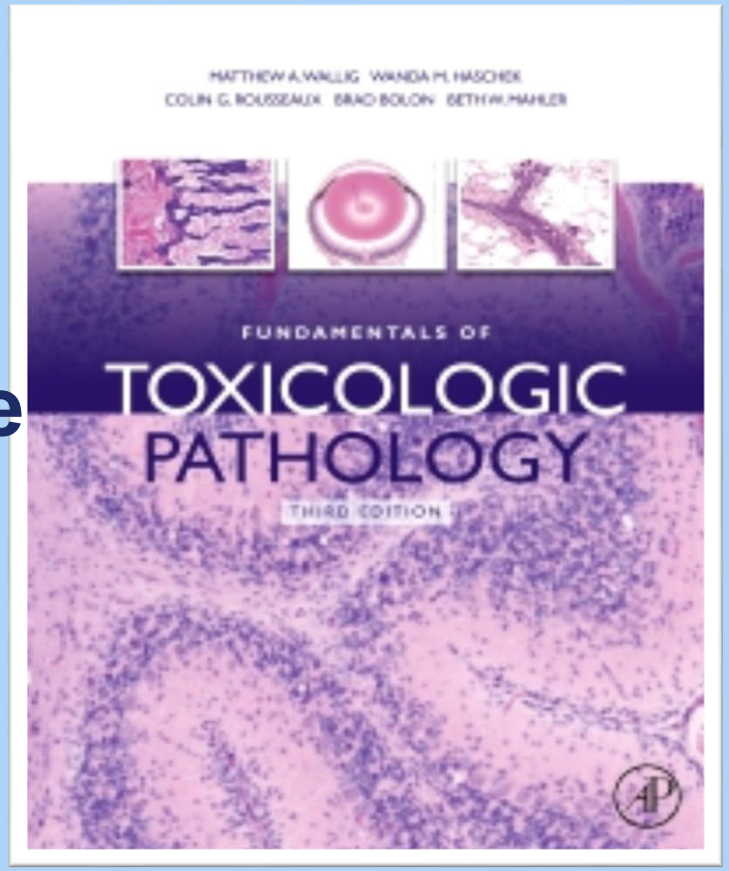
Why Our Therapies Work So Well

Acupuncture in certain points promotes the activity of stem cells and regeneration.

Jiang, S., Chen, W., Zhang, Y., Zhang, Y., Chen, A., Dai, Q., … Lin, H. (2016). Acupuncture Induces the Proliferation and Differentiation of Endogenous Neural Stem Cells in Rats with Traumatic Brain Injury. Evidence-Based Complementary and Alternative Medicine : eCAM, 2016, 2047412. http://doi.org/10.1155/2016/2047412

Why Our Therapies Work So Well

Stimulation with Electro-acupuncture can promote the activity of stem cells and regeneration.



Yan Q, Ruan J-W, Ding Y, Li W-J, Li Y, Zeng Y-S. Electro-acupuncture promotes differentiation of mesenchymal stem cells, regeneration of nerve fibers and partial functional recovery after spinal cord injury. Experimental and Toxicologic Pathology. 2011;63(1-2):151-156. doi:10.1016/j.etp.2009.11.002.

Role of Physical Therapy in OA Patien

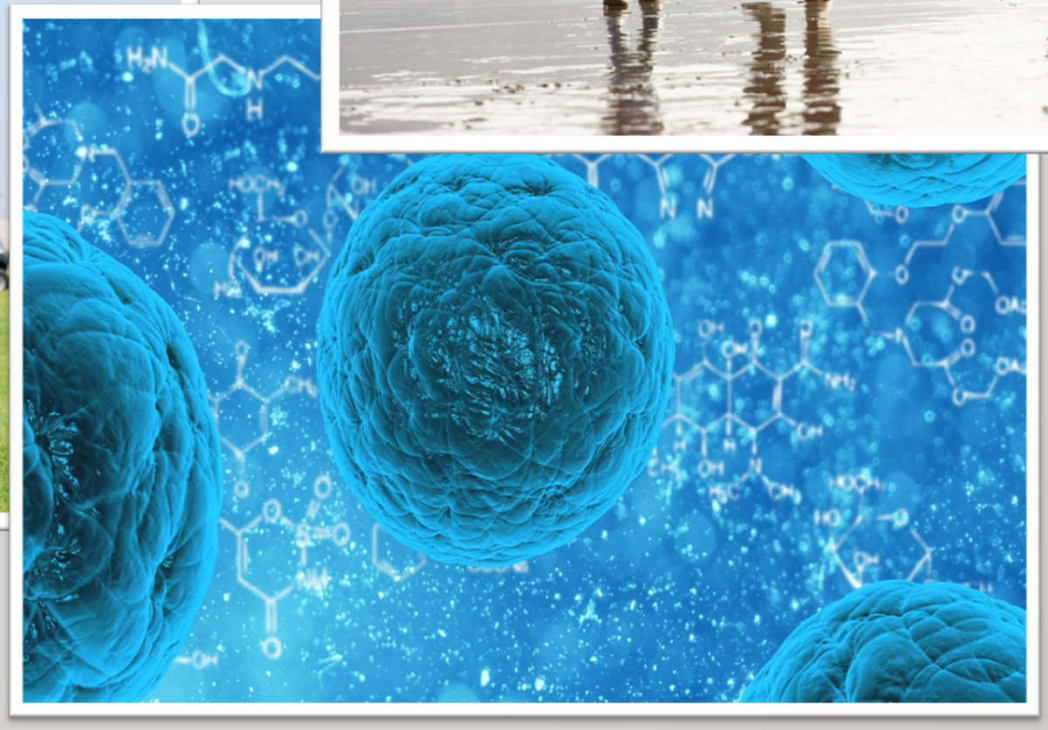
56 patients with knee OA were assigned into 2 random groups. Treatment group (NSAIDs and 10 sessions acupuncture)without exercise and treatment group with exercise for knee muscles.

Role of Physical Therapy in OA Patien

Patients with knee OA in exercise group had significant mprovement in pain, disability, walking, stair climbing, and sit u speed after 1 and 3 months, as well as 1 year follow-up.

Nejati, P., Farzinmehr, A., & Moradi-Lakeh, M. (2015). The effect of exercise therapy on knee osteoarthritis: a randomized clinical trial. Medical journal of the Islamic Republic of Iran, 29, 186.

Guidelines After Stem Cell Therapy



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.

Considerations in treatment of patients with supplements

Herbs & Supplements: Interaction with Medication

- 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

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

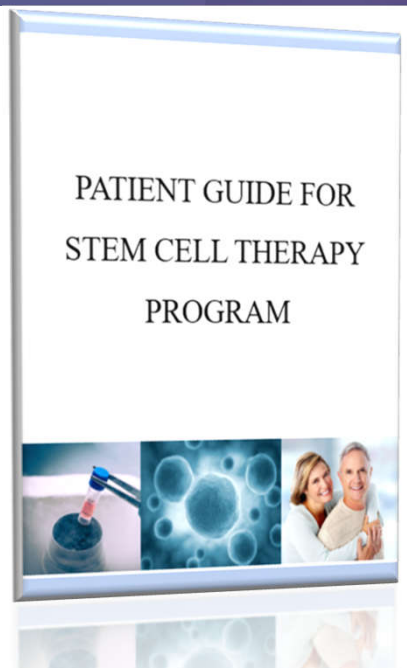
Advantages for Use of Supplements in Stem Cell Therapy

- ✓ **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.

Disadvantages for Use of Supplements in Stem Cell Therapy

- Supplements cost money
- Requires setup and inventory management (takes time)
- Refills for patients who ran out

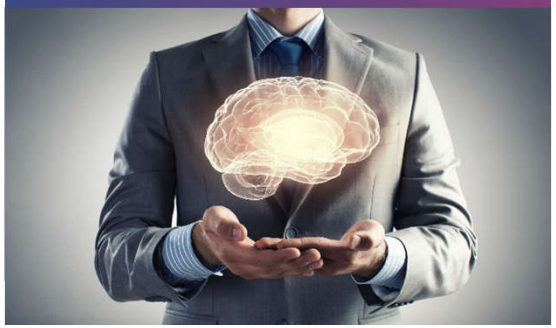
Turn-Key System to Start Your Regenerative Stem Cell Programs



STEM CELL

BRAIN & NERV SUPPORT

Key nutrients to support healthy brain function and support repair of nerve damage.



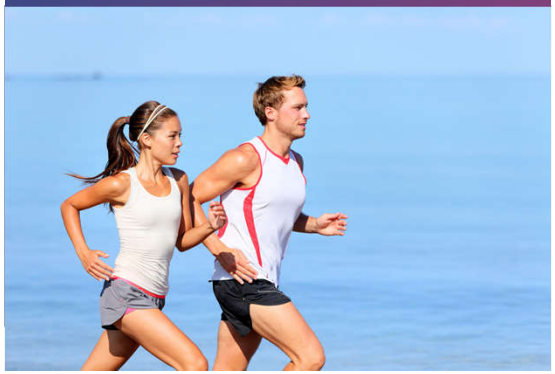
Key Nutrients

- ✓ Brain specific nutrients, such as Huperzine A, Acetyl-L-Carnitine (as acetyl-L-carnitine HCl), and sunflower-derived phosphatidylserine
- ✓ Vitamin C, bioflavonoids, Zinc, Selenium, and N-Acetyl Cysteine to increase glutathione and support antioxidants and stem cells function, as well as neural protection
- ✓ Methylated form of B vitamins to support nerve function
- ✓ Chromium to support healthy sugar levels
- ✓ Unique herbal combination: Gingko biloba and Bacopa Monnieri to support improvement in memory
- ✓ Unique formula to support healthy cortisol levels, alleviate fatigue, promote mental clarity and restful sleep: L-Theanine, Ashwagandha, and Magnolia
- ✓ Five-star certified fish oil to support brain function and nerve regeneration

*No statements or implied treatments have been evaluated or approved by the FDA. All statements provided for educational and informational purposes only.

JOINT SUPPORT

Key nutrients to support healthy brain function and support repair of nerve damage.



Key Nutrients

- ✓ Mucopolysaccharides to healthy tendons and ligaments
- ✓ Hesperidin and collagen type I and II to support cartilage repair and healthy inflammation
- ✓ Vitamin C, bioflavonoids, Zinc, and Selenium to support antioxidants and stem cells function
- ✓ Glucosamine and Chondroitin Sulfate to support formation of healthy joint structure
- ✓ Biotin, curcumin, vitamins, and Proteolytic enzymes to support healthy recovery.
- ✓ Unique formula to support healthy cortisol levels, alleviate fatigue, promote mental clarity and restful sleep: L-Theanine, Ashwagandha, and Magnolia
- ✓ Five-star certified fish oil to support healthy inflammation and regeneration

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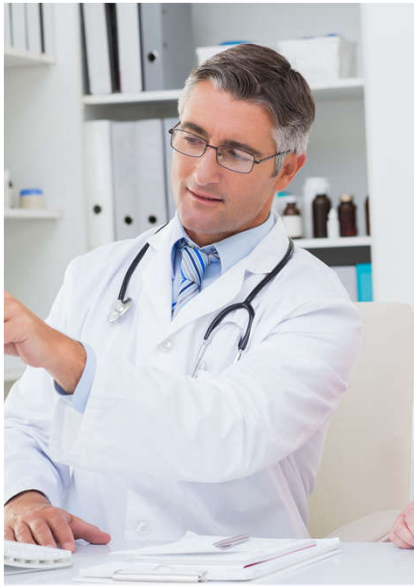
Environmental factors with epigenetic effects include behaviors, nutrition, and chemicals and industrial pollutants.



iffon C. (2018). The Impact of Nutrition and nvironmental Epigenetics on Human Health nd Disease. International journal of nolecular sciences, 19(11), 3425. ttps://doi.org/10.3390/ijms19113425

"Understanding the molecular effects of behavior, nutrients, and pollutants might be relevant for developing preventative strategies and personalized heath 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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FUNCTIONA MEDICINE

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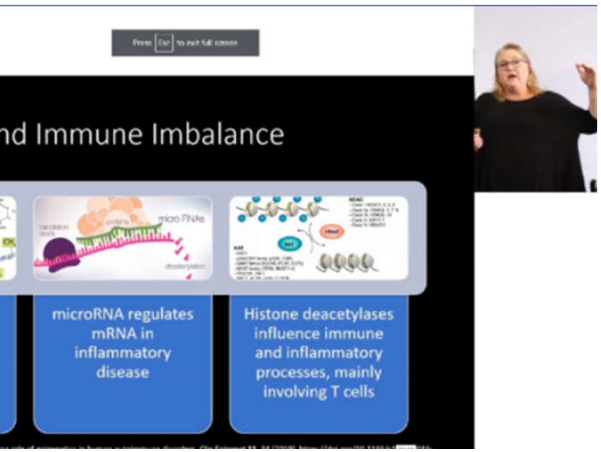
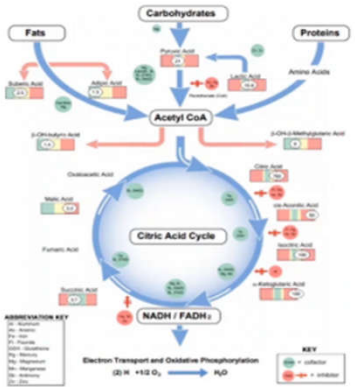
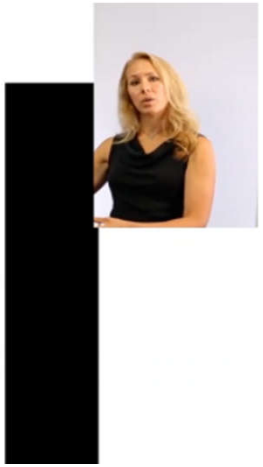
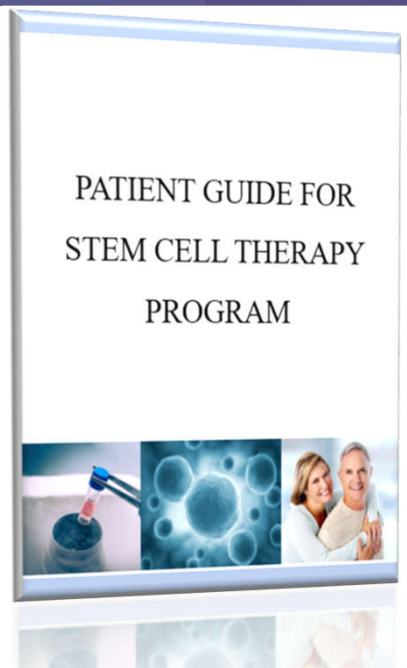






Turn-Key System to Start Your Regenerative Stem Cell Programs



STEM CELL

Supplements, Nutrition, and Lifestyle Medicine to Support Stem Cell Therapy

Thank you!

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