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Clinical Monitor by Kerry Bone

Longevity Research Breaks New Ground for Garlic

In intriguing and unexpected research, an international team of scientists led by the Harvard School of Public Health claim to have found a unifying pathway which explains the benefits of dietary restriction (DR) on longevity.[1] Using various *in vivo* and *in vitro* experimental models, they found increased endogenous hydrogen sulfide (H_2S) production was an important consequence of DR that was also necessary for the longevity effect. Specifically, the researchers found the restriction of two key sulfur amino acids (methionine and cysteine) which automatically accompanies DR resulted in increased H_2S production. They also demonstrated the increased H_2S conferred the longevity benefits, including protection against ischaemia and other cytoprotective (cellular protective) effects. At the mechanistic level, sulfur amino acid restriction increased expression of the trans-sulfuration pathway enzyme cystathionine gamma-lyase (CGL). Upregulation of CGL leads to increased production of H_2S.

This is consistent with the hormesis and longevity theory of David Sinclair, in which low-level stressors promote adaptive changes resulting in stress resistance. In this instance the H_2S functions as the adaptive response to the stress of sulfur amino acid deprivation. At a tissue level the authors hypothesise that increased H_2S will result in a number of benefits including vasodilatory effects (a known activity of H_2S as a gaseous messenger like nitric oxide), prevention of cell damage under stress via sulfhydration of key proteins, and antioxidant effects.

Allium sativum

While describing their discovery as a unifying mechanism, the authors do concede that their finding: "in no way rules out other dietary triggers or downstream mechanisms of DR benefits". This of course leaves room for the other key longevity/hormetic pathways discussed in previous issues, including Nrf2 and SIRT1 (sirtuins).

The authors concluded: "H_2S was in vogue for centuries past as a cure-all before being viewed as a poisonous toxin with little or no acceptable level of exposure. Recently, H_2S has re-emerged as a potential therapeutic agent addressing numerous health issues ... Here, we identified DR as a trigger of increased endogenous H_2S production, and H_2S as a molecular mediator of pleiotropic DR benefits including longevity and stress resistance. These findings have broad implications for our basic understanding of DR and its potential clinical applications."

The Harvard team notes that the use of exogenous H_2S as a DR mimetic is appealing, but remains challenging due to the short half-life of the gas and risks of toxicity at high levels. However, there is already an option here with garlic (*Allium sativum*).

In 2007 a group of US scientists revealed that garlic-derived organic polysulfides (formed from allicin) act as H_2S donors.[2] The implications of this finding were highlighted in *e-Monitor* No. 21, May 2008, but basically the discovery provided a link between the cardiovascular benefits of garlic and its sulfur-containing molecules. The Harvard research above suggests that garlic can now be reaffirmed as a major longevity herb, supported by the robust foundation of a critical mechanism of action as a DR mimetic.

Comment

Since 2007, interest in the H_2S-generating properties of garlic has been slowly increasing. For example, two 2014 reviews attributed this factor as a key mechanism behind the antihypertensive effects of garlic bioactives.[3,4] Another review in 2011 noted: "it has been proven that the garlic ingredients ... act as hydrogen sulfide donors or mediators ...".[5]

In contrast, biomedical interest in H_2S has exploded, with more than 20% of research papers on this topic published in the past 5 years. The initial work by Kimura and co-workers in 1996 suggesting H_2S is a biologically relevant signalling molecule has been followed by numerous studies demonstrating an effect of this gas on virtually every organ system and tissue in the body.[6] Aside from the new finding above of increased healthspan by mimicking calorie or dietary restriction, upregulation of H_2S is implicated in neuroprotection, blood pressure control, erectile function, arterial health, antiplatelet effects and cardioprotection to name a few.[7,8]

The discovery of the link between dietary restriction and H_2S production is likely to add an exciting new chapter in our understanding of garlic. Regular intake of garlic via the diet (preferably raw) or as a herbal product now has serious credibility as part of an antiageing protocol.

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Ginger is Proving to be Clinically Effective for A Variety of Painful, Inflammatory Disorders

Ginger (*Zingiber officinale*), either alone or in combination, has lately been investigated in clinical trials as a treatment for a number of painful conditions, ranging from migraine headaches to osteoarthritis and dysmenorrhoea. In a double blind, randomised clinical trial, 100 patients who suffered acute migraines without aura were randomly allocated to receive either ginger powder (250 mg) or sumatriptan (50 mg).[1] Trial participants were instructed to take just a single dose upon headache onset. The time of headache onset, its severity, the time interval from headache onset to taking the treatment, and a self-assessment of response (visual analogue score, VAS) for five subsequent migraine attacks were recorded by the patients.

The frequency distribution of mean headache severity at 2 hours after treatment demonstrated similar efficacy for the sumatriptan and ginger groups ($p = 0.116$). Comparing mean headache severity before and 2 hours after treatment revealed a 4.7 unit reduction (according to VAS) in the sumatriptan group ($p < 0.0001$ versus baseline) and a 4.6 unit reduction in the ginger group ($p < 0.0001$). In this study, 70% of sumatriptan-treated and 64% of ginger-treated patients showed favourable relief (≥ 90% decrease in headache severity) at 2 hours following treatment.

Side effects from sumatriptan included dizziness, sedation, vertigo and heartburn. The only reported clinical adverse effect of ginger was dyspepsia. Side effect rates were 20% for sumatriptan versus 4% for ginger ($p = 0.028$). Eighty-eight percent of sumatriptan users and 72% of ginger recipients were inclined to continue their randomly assigned treatment for the abortion of migraine attacks.

A systematic literature search in bibliographic databases was carried out to assess the clinical efficacy and safety of oral ginger for the treatment of osteoarthritis (OA).[2] Inclusion criteria were randomised controlled trials (RCTs) comparing ginger with placebo in OA patients aged 18 years or more. Major outcomes looked for were reductions in pain and disability. Withdrawals due to adverse events were noted. The efficacy effect size was estimated using Hedges' standardised mean difference (SMD), and safety using the risk ratio (RR).

Of 122 retrieved references, 117 were discarded, leaving five trials (593 patients) for meta-analyses. The majority reported relevant randomisation procedures and blinding, but applied an inadequate intention-to-treat (ITT) analysis. Following ginger intake, a statistically significant pain reduction SMD of -0.30 ($p = 0.005$) with a low degree of inconsistency among trials, and a statistically significant reduction in disability SMD of -0.22 ($p = 0.01$) were seen, both in favour of ginger. Patients given ginger were more than twice

as likely to discontinue treatment compared to placebo (p = 0.04). Four of the trials used various extracts of ginger and the fifth tested a ginger extract in combination with *Alpinia galanga*. Daily doses ranged from 500 to 1000 mg/day (given these were of extract, this indicates fairly high doses). The SMD of -0.30 for ginger compared with placebo corresponds to an effect size for pain which is only slightly above the critical threshold limit for a relevant SMD in OA, but it is comparable, although a little higher, to the SMD of -0.21 seen with paracetamol. Compared to the effect of NSAIDs, the SMD for ginger indicates an effect size in the middle of the NSAID range of -0.17 to -0.66, all when compared to placebo.

The authors concluded that ginger was modestly efficacious and reasonably safe for the treatment of OA. They judged the evidence to be of moderate quality, based on the small number of treatments and inadequate ITT analysis.

Adding to previous studies investigating the efficacy of ginger in the treatment of primary dysmenorrhoea are two further trials: one comparing dried ginger, zinc sulfate and placebo and the other comparing dried ginger with mefenamic acid. The first trial enrolled 150 high school students who were randomly allocated into one of the three treatment groups: ginger (750 mg/day), zinc sulfate (660 mg/day, elemental zinc 267 mg/day) or placebo.[3] All participants took the medications for four days, starting from the day before menstruation to the third day after, for two cycles. Severity of pain was assessed every 24 hours using the visual analogue scale. Compared with placebo, the girls taking ginger and zinc sulfate reported more reduction in pain ($p < 0.05$). Both active treatments had similar positive effects on pain and comparable mild side effects.

One hundred and twenty-two female students with moderate to severe primary dysmenorrhoea were randomly allocated to receive ginger or mefenamic in the other controlled clinical trial.[4] The mefenamic group received 250 mg capsules every 8 hours, and the ginger group received 250 mg capsules every 6 hours from the onset of menstruation until pain relief over two consecutive cycles. (The content of the capsules was not defined, although the authors cite an earlier trial that used the same brand of ginger capsules for the treatment of primary dysmenorrhoea (see *e-Monitor* No. 26, May 2009). The capsules contained ginger powder.) The intensity of pain was again assessed using the visual analogue scale. After treatment, pain intensity in the mefenamic and ginger groups were 39.01 ± 17.77 and 43.49 ± 19.99, respectively, in the first month, and 33.75 ± 17.71 and 38.19 ± 20.47, respectively, in the second month ($p > 0.05$). The severity of dysmenorrhoea, pain duration, cycle duration and bleeding volume were not significantly different between groups during the study. Menstruation days were slightly more in the ginger group in the first ($p = 0.01$) and second cycle ($p = 0.04$), and there was a trend to slightly increased bleeding for ginger. Repeated measurement showed a significant difference in pain intensity within each group over time, but not between groups. The author suggested ginger is as effective as mefenamic acid for pain relief in primary dysmenorrhoea.

Zingiber officinale

Comment

Despite the suggestion from the above trial that ginger might increase menstrual bleeding, there is now clinical trial evidence to suggest that it might actually be an effective treatment for heavy menstrual bleeding (HMB). Ninety-two young women with HMB received either dried ginger (750 mg/day) or placebo capsules over three cycles.[5] Treatment was started the day before menstrual bleeding and continued until the third day of the period (that is, for four consecutive days). Menstrual blood loss decreased by an average of 46.6% on the ginger group, compared to just 2.1% in the placebo group ($p < 0.001$ between groups). There was no difference in adverse events between the two groups. These striking results need to be repeated in other trials, but possibly herald a significant new addition to ginger's clinical repertoire.

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Extending Boswellia's Clinical Repertoire

Current clinical research indicates that the therapeutic range of *Boswellia serrata* goes well beyond its use in osteoarthritis and inflammatory bowel disease.[1] Now recent publications are credibly extending its repertoire even further. The surprising findings in two recent trials that Boswellia improved blood glucose, lipids and metabolic parameters in patients with type 2 diabetes has already been reviewed (see *e-Monitor* No. 50, May 2014).[2,3]

Now there is a suggestion that Boswellia is relevant in other pain management, either because of its anti-inflammatory activity, or perhaps by a different mechanism.[4] Twelve healthy volunteers were randomised to receive either a single oral dose of Boswellia (250 mg, presumably of extract) or a matching placebo using a crossover design. Pain was assessed at baseline and at hourly intervals after the medication by applying a mechanical force to the nail bed of the index finger. The single dose of Boswellia significantly increased both the pain threshold force (force at which pain is registered) and time, as well as both the pain tolerance force (maximum force that can be tolerated) and time, compared to both baseline and the placebo. These differences were in evidence at most of the tested times, namely one, two and three hours after the herb's administration.

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Boswellia serrata

Comment

The discovery that Boswellia can influence metabolic parameters and blood sugar levels in patients with type 2 diabetes is a fascinating finding that deserves more investigation and validation. It is potentially a very useful link, because current research is demonstrating that type 2 diabetes (T2D) and osteoarthritis (OA) tend to be comorbid. Hence, diabetic patients taking Boswellia to manage their osteoarthritis might receive a bonus benefit in terms of their diabetes outcomes.

Recent research on the association between T2D and OA has revealed some interesting insights. One epidemiological study found that younger adults and older women with OA have increased risks of developing diabetes.[5] Another found a biological link between bone loss at the subchondral bone plate in knee OA and T2D, suggesting that T2D accelerates OA pathology.[6] Along these lines, bone mineralisation was elevated and less heterogeneous in adults with OA and T2D, compared to a control group with just OA.[7] This is suggestive of deleterious effects of T2D on the biomechanical properties of bone, with potentially a higher fracture risk. Another study suggested musculoskeletal disorders were a typical finding among patients with T2D, with obesity and accumulation of abnormally glycosylated by-products proposed as potential pathogenic mediators of these connective tissue abnormalities. Specifically, the researchers found a strong association of OA involving even non-weight bearing joints in patients with T2D, ruling out mechanical factors due to obesity and indicating that a common pathophysiological mechanism connected these two clinical conditions.[8]

Nigella Improves Blood Lipids and Metabolic Syndrome

The clinical evidence for the role of *Nigella sativa* seed in the management of blood glucose and lipids (and hence in metabolic syndrome) is accumulating (for example, see *e-Monitor* No. 44, November 2012). In a recent Malaysian study, Nigella was evaluated for its effects among a group of menopausal women exhibiting some of the signs of metabolic syndrome (dyslipidaemia with slightly elevated blood pressure and blood glucose, average BMI around 28).[1] In this randomised trial, hyperlipidaemic menopausal women were assigned to treatment (n = 19) or placebo groups (n = 18) and given Nigella seed (1 g per day) or placebo for two months. At baseline, blood samples were taken and then at one month intervals thereafter until one month after the end of the study. Results showed that Nigella significantly improved the blood lipid profile of these menopausal women (decreased total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and increased high-density lipoprotein (HDL) cholesterol) compared to the placebo treatment over two months of intervention. One month after cessation of treatment, lipid profiles in the Nigella-treated group tended to change towards the pre-treatment levels.

The reduction in LDL cholesterol in the Nigella group was 26.7%, a significant change compared to both baseline ($p < 0.05$) and the placebo group ($p < 0.05$). Although the differences in blood pressures were not significant between the Nigella and placebo groups, the herb produced better results. Significant changes were observed with fasting blood glucose for Nigella (versus placebo, $p < 0.05$), which lowered this parameter by 21% after two months of treatment.

A second trial from Iran investigated the effects of Nigella and aerobic training on lipid profile and maximum oxygen consumption (VO_2 max) in sedentary, overweight women.[2] In this randomised, double blind, controlled trial, 20 sedentary women were divided into two groups and assigned to Nigella supplementation (2 g of seed per day) or a placebo for 8 weeks. Both groups also participated in an aerobic training program (3 times/week). Blood lipids and VO_2 max were determined at baseline and at the end of 8 weeks. Compared to baseline, Nigella plus exercise significantly lowered total cholesterol (TC, $p < 0.01$), triglycerides ($p < 0.001$), low-density lipoprotein (LDL) cholesterol ($p < 0.001$) and body mass index ($p < 0.01$), and increased high density lipoprotein (HDL) cholesterol and VO2 max ($p < 0.01$). The aerobic training program plus placebo lowered TC ($p < 0.001$) and LDL cholesterol ($p < 0.01$) and increased VO2 max ($p < 0.01$).

Compared to exercise alone, Nigella plus exercise significantly lowered LDL cholesterol and raised HDL cholesterol ($p = 0.01$). The authors suggested a synergistic effect between Nigella and aerobic training (although it was more likely to have been just additive).

Comment

Both trials involved small patient numbers, so their results are preliminary in nature. However, the positive outcomes are consistent with previous trials, including positive effects for Nigella on blood lipids, blood pressure and fasting blood glucose in patients with type 2 diabetes or exhibiting signs of metabolic syndrome.

The mechanism of action of Nigella in these disorders is not known, although a range of possible effects have been reviewed for Nigella and its key constituent thymoquinone.4 However, an interesting recent discovery is that a group of indazole-type alkaloids in Nigella exhibited antihyperglycaemic effects in vitro via AMPK activation. AMPK (5′ adenosine monophosphate-activated protein kinase) is a key enzyme involved in cellular energy homeostasis. It acts as a master metabolic switch, stimulating catabolic (energy producing) pathways, resulting in increased fatty and glucose oxidation. Agents that activate AMPK lower insulin resistance, blood glucose and blood lipids, and this is entirely consistent with the observed clinical activity of Nigella.

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