

1                   The potential for dietary factors to prevent or treat osteoarthritis

2

3 Jonathan A Green\*<sup>1</sup>, Kimberley L Hirst-Jones\*<sup>2</sup>, Rose K Davidson<sup>1</sup>, Orla Jupp<sup>1</sup>, Yongping  
4 Bao<sup>2</sup>, Alexander J MacGregor<sup>2</sup>, Simon T Donell<sup>2</sup>, Aedín Cassidy<sup>2</sup>, Ian M Clark<sup>1</sup> +

5

6 <sup>1</sup>School of Biological Sciences and <sup>2</sup>Norwich Medical School, University of East Anglia,  
7 Norwich, NR4 7TJ.

8

9 \* these authors contributed equally to this review

10

11 + corresponding author

12

13

14 Corresponding author:           Ian M Clark, PhD  
15   Professor of Musculoskeletal Biology,  
16   School of Biological Sciences,  
17   University of East Anglia,  
18   Norwich Research Park,  
19   Norwich, NR4 7TJ.  
20   United Kingdom

21

22   Tel. 01603-592760

23   Fax. 01603-592250

24   Email: [i.clark@uea.ac.uk](mailto:i.clark@uea.ac.uk)

25

26

27

28 Abstract

29 Osteoarthritis is a degenerative joint disease for which there are no disease-modifying drugs.  
30 It is a leading cause of disability in the UK. Increasing age and obesity are both major risk  
31 factors for osteoarthritis and the health and economic burden of this disease will increase in  
32 the future. Focusing on compounds from the habitual diet that may prevent the onset or  
33 slow the progression of osteoarthritis is a strategy that has been under-investigated to date.  
34 An approach that relies on dietary modification is clearly attractive in terms of risk/benefit  
35 and more likely to be implementable at the population level. However, before undertaking  
36 a full clinical trial to examine potential efficacy, detailed molecular studies are required in  
37 order to optimise the design. This review focuses on potential dietary factors that may  
38 reduce the risk or progression of osteoarthritis, including micronutrients, fatty acids,  
39 flavonoids and other phytochemicals. It therefore ignores data coming from classical  
40 inflammatory arthritides and nutraceuticals such as glucosamine and chondroitin. In  
41 conclusion, diet offers a route by which the health of the joint can be protected and  
42 osteoarthritis incidence or progression decreased. In a chronic disease, with risk factors  
43 increasing in the population and with no pharmaceutical cure, an understanding of this will  
44 be crucial.

45

46 Keywords: osteoarthritis, diet, cartilage, bioactive, polyphenol, phytochemical, flavonoid

47

48

49 Introduction:

50 Osteoarthritis (OA) is a degenerative joint disease characterised by degradation of articular  
51 cartilage, thickening of subchondral bone and osteophyte formation. Incidence and  
52 prevalence of OA has been difficult to assess, in part because of heterogeneity in definitions  
53 of the disease. A recent meta-analysis suggested that overall prevalence of OA at different  
54 anatomical sites was 23.9% (knee), 10.9% (hip) and 43.3% (hand) although only the  
55 prevalence of knee OA showed a gender difference between women and men (27.3% and  
56 21% respectively)<sup>(1)</sup>.

57

58 OA is a leading cause of disability in the UK. A recent survey<sup>(2)</sup> found 8.5 million people in  
59 the UK with osteoarthritis, with 71% of these in constant pain. There are no effective  
60 disease-modifying drugs to treat OA and drugs that relieve pain are often insufficient. Joint  
61 replacement is offered to patients at end-stage disease with 66,436 hip and 77,578 knee  
62 replacements due to OA performed in the UK in 2011<sup>(3)</sup>.

63

64 Two major risk factors for OA are increasing age, (most affected patients are >45 years of  
65 age and the greatest morbidity is seen in patients >60 years of age)<sup>(4)</sup> and increasing  
66 obesity<sup>(5)</sup>. With changing demographics, OA is an increasing public health and economic  
67 burden. The economic costs of OA in the UK are largely unknown, but direct costs have  
68 been estimated at approximately £1 billion per year. With inclusion of indirect costs,  
69 estimates from the USA range up to £8 billion per year<sup>(6)</sup>.

70

71 While the ability to slow or stop the progression of OA would have individual and population  
72 level benefits, few pharmaceutical companies maintain OA as a disease area. This is in part  
73 because there is no precedent. Further, OA generally progresses slowly, and there are no  
74 current validated biomarkers for cartilage destruction (joint space narrowing, assessed on X-  
75 ray, is the only FDA (Food and Drug Administration) approved end point in a clinical trial)<sup>(7)</sup>.  
76 Issues of toxicity, in a disease which is not life-threatening, can also make drug development  
77 problematic. It is possible to overcome at least some of these issues by selection of the  
78 patient group (where particular sub-groups are known to progress more rapidly), and by  
79 establishing the dose of drug that gives efficacy within the target tissue (i.e. cartilage)<sup>(8)</sup>.

80

81 Focusing on compounds from the habitual diet that may prevent the onset or slow the  
82 progression of OA is an alternative strategy. Since in essence, all of the population can be  
83 viewed as at risk for the development of OA in old age, an approach that relies on dietary  
84 modification is clearly more attractive in terms of risk/benefit and more likely to be  
85 implementable. However, detailed molecular studies ahead of a full clinical trial are required  
86 in order to design trials optimally that will examine potential efficacy.

87

88 There are currently limited data on the inter-relationship between diet and OA. Data come  
89 from a variety of studies: *in vitro* cell and tissue explant models, animal models,  
90 epidemiological associations, and intervention trials. There is a large variability between  
91 studies, e.g. in animal models, a dietary intake approach would be optimal in order to relate  
92 to human exposure, but some studies use intra-articular injection and/or concentrations not  
93 achievable through the diet. The intervention trials conducted to date have many different  
94 designs, number of patients, time length and outcome measures, often with too few patients  
95 and of short duration. There is a need for better quality data before dietary advice can be  
96 given. However clinical trials in osteoarthritis are expensive and it is not clear who will or  
97 should fund them.

98

99 This brief review focuses predominantly on potential dietary factors than may reduce the risk  
100 or progression of the disease. It focuses only on osteoarthritis, mainly ignoring data coming  
101 from more overtly inflammatory arthritides.

102

103 Two pertinent 'nutraceuticals' will not be discussed, but should be mentioned: glucosamine  
104 and chondroitin. Glucosamine is a sugar and precursor for glycosaminoglycan and therefore  
105 proteoglycan biosynthesis. Chondroitin is a glycosaminoglycan, a form of which is found in  
106 aggrecan, the major proteoglycan in cartilage. Hydrochloride and sulphate salts of both  
107 glucosamine and chondroitin have been extensively examined in laboratory models and  
108 clinical trials. The efficacy of these compounds remains controversial, but most recent  
109 analyses appears to indicate that high-grade preparations of chondroitin sulphate and  
110 glucosamine sulphate, may have efficacy in osteoarthritis<sup>(9-13)</sup>.

111

## 112 Micronutrients

### 113 Vitamin C

114 In prospective studies examining micronutrient intakes, the Framingham study identified a  
115 protective association between higher intake of vitamin C and the progression of  
116 radiographic knee OA<sup>(14)</sup> and a higher vitamin C intake was also be associated with lower  
117 risk of knee pain<sup>(14; 15)</sup>. However a longitudinal study showed no protective effect of vitamin  
118 C supplements on the progression of knee OA, though in multivariate analyses vitamin C  
119 supplements were beneficial in preventing the development of knee OA<sup>(16)</sup>. In healthy  
120 subjects vitamin C intake has been associated with reduced risk of bone marrow lesions on  
121 magnetic resonance imaging<sup>(17)</sup>. In these publications vitamin C has been viewed simply as  
122 an antioxidant, but it should not be forgotten that vitamin C is a co-factor enabling the proline  
123 and lysine hydroxylation essential for correct collagen biosynthesis. It also has effects on  
124 regulating the expression and translation of collagen, a major component of many  
125 connective tissues including cartilage and bone<sup>(18)</sup>. Animal model data (all from the guinea  
126 pig) are conflicting. Early studies showed that dietary ascorbate decreased pathology in  
127 surgically induced osteoarthritis<sup>(19)</sup>. In a further study additional ascorbate in the drinking  
128 water showed a protective effect on spontaneous cartilage lesions, but no effect on  
129 pathology post-surgery<sup>(20)</sup>. Most recently ascorbate supplementation increased disease  
130 severity in spontaneous osteoarthritis<sup>(21)</sup>.

131

### 132 Vitamin E

133 The Framingham study identified a weak protective association between higher intake of  
134 vitamin E and the progression of radiographic knee OA<sup>(14)</sup>. A study examining tocopherol  
135 isoforms and radiographic knee OA suggested complex associations<sup>(22)</sup> and intervention  
136 trials of vitamin E have to date been contradictory<sup>(23)</sup>. *In vitro* data in chondrocytes are  
137 sparse, but a recent study suggests that vitamin E protects against hydrogen peroxide-  
138 induced changes in extracellular matrix gene expression<sup>(24)</sup>.

139

#### 140 Vitamin D

141 Vitamin D has multiple functions in the musculoskeletal system, particularly in bone health  
142 and pathologies<sup>(25)</sup>. Many studies have explored the association between vitamin D levels  
143 and OA. Recent systematic review suggests that low serum concentrations of 25-  
144 hydroxyvitamin D are associated with increased radiographic progression of OA, but  
145 associations are weaker with symptoms of disease<sup>(26)</sup>. A recent longitudinal study  
146 demonstrated the converse, that moderate vitamin D deficiency predicts both knee and hip  
147 pain, independent of structural change<sup>(27)</sup>. However, a recent 2 year intervention trial  
148 showed no decrease in knee pain or structural change in patients with knee OA, with knee  
149 function significantly worse following vitamin D intervention<sup>(28)</sup>. Further intervention trials are  
150 ongoing<sup>(29)</sup>. Vitamin D supplementation in a rat post-surgical model of osteoarthritis showed  
151 a protective effect during the early phase of the disease, but not during the later phase<sup>(30)</sup>.  
152 However, this was scored using condyle width, an unusual method. Interestingly vitamin D  
153 receptor-deficient mice showed aggravated inflammation and cartilage damage when  
154 crossed into a TNF transgenic model<sup>(31)</sup>.

155

#### 156 Other micronutrients

157 In a Japanese population (ROAD, Research on Osteoarthritis Against Disability), low  
158 habitual vitamin K intake was the only dietary factor associated with the increased  
159 prevalence of radiographic knee OA in a cross-sectional study<sup>(32)</sup>. This supports data from  
160 US cohorts where low vitamin K was associated with OA in the hand and knee<sup>(33; 34)</sup>.  
161 However, a further study, using minimum joint space width and osteophytosis as variables  
162 showed an association of vitamins K, B1, B2, B6 and C with the former and vitamins E, K,  
163 B1, B2, niacin (B3) and B6 with the latter, both in women only<sup>(35)</sup>. Vitamin K is an essential  
164 co-factor for the formation of gamma-carboxyglutamic acid (Gla) residues, and Gla-  
165 containing proteins include osteocalcin and matrix Gla protein (MGP), both expressed in the  
166 skeleton. Vitamin K regulates mineralisation in both bone and cartilage<sup>(36)</sup>. Polymorphisms  
167 in the MGP gene have been associated with hand osteoarthritis<sup>(37)</sup>, and serum levels of

168 undercarboxylated osteocalcin maybe associated with synovitis in knee osteoarthritis<sup>(38)</sup>.  
169 Niacinamide, a form of vitamin B3, has been examined in a pilot scale clinical study of  
170 osteoarthritis and reported to show improvements at 12 weeks<sup>(39)</sup>.

171 An association between dietary magnesium intake and knee OA was demonstrated in the  
172 Johnston County Osteoarthritis Project, but this varied with ethnicity<sup>(40)</sup>. This is supported by  
173 data from the Twins UK registry where discordant twin pair analysis showed a decrease in  
174 magnesium in co-twins with OA<sup>(41)</sup>. Selenium has been implicated the osteoarthropathy of  
175 Kashin-Beck disease; meta-analysis of supplementation studies supports the benefit of  
176 supplementation in children, but highlights the low quality of methodology<sup>(42)</sup>.

177

### 178 Lipid metabolism

179 Recent studies have suggested that osteoarthritis may be part of metabolic syndrome<sup>(43)</sup>.  
180 Alterations in lipid metabolism may be key to this, with population based studies suggesting  
181 that serum cholesterol is a risk factor for osteoarthritis (reviewed in<sup>(44)</sup>). Population studies  
182 also suggest that statin use is associated with a reduction in osteoarthritis incidence and /or  
183 progression<sup>(45; 46)</sup>, but studies of pain and function in patients with osteoarthritis have shown  
184 no association<sup>(47)</sup>. This area therefore remains controversial. It has been reported that high  
185 levels of fat and fatty acids are found in osteoarthritic joint tissues and that this is associated  
186 with pathology<sup>(48; 49)</sup>. n-3 polyunsaturated fatty acids (PUFA), but not n-6 PUFA were found  
187 to be associated with specific loss of cartilage in the MOST (Multicenter Osteoarthritis Study)  
188 population of people at risk of osteoarthritis<sup>(50)</sup>. In healthy individuals, consumption of  
189 saturated fatty acids or n-6 PUFA (but not n-3 PUFA) were associated with an increased risk  
190 of bone marrow lesions<sup>(51; 52)</sup>. In animal models, a high fat diet accelerated progression of  
191 osteoarthritis<sup>(53)</sup>, whilst n-3 PUFA reduced disease<sup>(54)</sup>. Studies in isolated chondrocytes  
192 showed that n-3 PUFA inhibited IL-1 induced *MMP3*, *MMP13*, *ADAMTS4*, *ADAMTS5* and  
193 *COX2* (MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase  
194 domain with thrombospondin motifs; COX, cyclooxygenase) expression, whilst n-6 PUFA  
195 had no effect<sup>(55; 56)</sup>. A small improvement in osteoarthritis in dogs was seen with fish oil  
196 supplementation<sup>(57; 58)</sup>. Interestingly, a supplement rich in fish oil, Phytalgic, was shown to  
197 improve function and pain in osteoarthritis patients<sup>(59)</sup>, though the design of this trial has  
198 been criticised<sup>(60)</sup>.

199

### 200 Diet-derived bioactives

201 Typically, foods contain multiple bioactive compounds and these can impact upon many  
202 biological pathways<sup>(61)</sup>. Diet-derived bioactives can be classified into several groups e.g.  
203 flavonoids (and related compounds), carotenoids, plant sterols, glucosinolates and others<sup>(62)</sup>.

204

#### 205 Flavonoids

206 Flavonoids are polyphenols and include flavan-3-ols, flavonols, flavones, isoflavones,  
207 flavanones and anthocyanins. More than 6000 different flavonoids have been found and  
208 they are widely distributed in plants, with several hundred found in edible plants<sup>(63; 64)</sup>.

209

#### 210 Flavonols

211 Flavonols are found in many foods and are exemplified by quercetin, myricetin and  
212 kaempferol<sup>(64)</sup>. Quercetin and kaempferol showed no activity against IL-1-induced MMP-13  
213 levels in SW1353 chondrosarcoma cells<sup>(65)</sup>. However, Lay et al report that quercetin is able  
214 to block aggrecan loss from articular cartilage potentially via inhibition of ADAMTS4 and  
215 ADAMTS5<sup>(66)</sup> and Lee et al show that myricetin can inhibit IL-1 (interleukin-1) induction of  
216 MMP-1 from a synovial cell line<sup>(67)</sup>.

217

#### 218 Flavones

219 In fruit and vegetables, flavones are found in celery and parsley, mainly luteolin and  
220 apigenin. In the skin of citrus fruit, polymethoxylated flavones are also found e.g. tangeretin,  
221 nobiltein and sinensetin<sup>(64)</sup>. Luteolin and nobiletin have been shown to inhibit aggrecanases  
222 ADAMTS-4 and ADAMTS-5, both *in vitro*<sup>(68; 69)</sup> and *in vivo*<sup>(68)</sup>. Luteolin appears to be  
223 selective as a better ADAMTS than MMP inhibitor<sup>(69)</sup>, it also has anti-inflammatory activity  
224 which could play a role in chondroprotection<sup>(70)</sup>. Nobiletin, tangeretin and sinensetin all  
225 repress the IL-1 induction of MMP-9 in synovial cells, with nobiletin also active in  
226 chondrocytes<sup>(71)</sup>. Apigenin was shown to be a potent inhibitor of IL-1-induced MMP-13  
227 expression in SW1353 chondrosarcoma cells, potentially via AP1 and the JAK/STAT  
228 pathway, with no activity against NFkappaB<sup>(65)</sup>. It has also been shown to block IL-1-  
229 induced GAG (glycosaminoglycan) release<sup>(65)</sup> and HA (hyaluronan) release<sup>(72)</sup> from cartilage  
230 explants *in vitro*.

231

#### 232 Flavan-3-ols

233 These exist as both monomer (catechins) and polymer (proanthocyanidins) forms<sup>(64)</sup>. Green  
234 tea polyphenols were shown to be effective in a model of inflammatory arthritis<sup>(73)</sup>.  
235 Catechins from green tea (and also present in other foods including dark chocolate) can  
236 inhibit cartilage degradation *in vitro*, particularly those containing a gallate ester<sup>(74)</sup>.  
237 Epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) have been shown to be  
238 effective (submicromolar) inhibitors of ADAMTS-4 and ADAMTS-5 aggrecanase activity,  
239 indeed significantly more than their ability to inhibit MMP-1 and MMP-13 collagenase  
240 activity<sup>(75)</sup>. Other anti-inflammatory activities have been described (e.g.<sup>(76)</sup>) that suggests  
241 promise in osteoarthritis (reviewed in<sup>(77)</sup>), but no human clinical trials have been performed to  
242 date.

243 Whilst not a diet-derived bioactive, Flavocoxid, a mixture of baicalin (a flavone) from  
244 *Scutellaria baicalensis* and catechins from *Acacia catechu*, is marketed as Limbrel, a  
245 'medical food' which inhibits cyclooxygenase-2 and 5-lipoxygenase<sup>(78)</sup>. An assessment of  
246 the major catechins from *Acacia catechu* suggests that they are predominantly those  
247 described above found in green tea<sup>(79)</sup>. Small clinical trials have suggested that Limbrel  
248 shows efficacy in OA (e.g.<sup>(80)</sup>), but recently severe liver toxicity has been described in some  
249 patients<sup>(81)</sup>.

250 A grape seed proanthocyanidin extract is protective in the monosodium iodoacetate (MIA)  
251 model of osteoarthritis in the rat, showing chondroprotection and decreased pain<sup>(82)</sup>.  
252 Specifically, procyanidin B3 abrogates cartilage destruction and heterotopic cartilage  
253 formation in a surgical model of osteoarthritis in the mouse<sup>(83)</sup>. It was shown to block IL-1  
254 repression of matrix gene expression *in vitro* and also decrease iNOS (inducible nitric oxide  
255 synthase) *in vitro* and *in vivo*<sup>(83)</sup>.

256 Another mixture not derived from the diet, Pycnogenol is a pine bark extract rich in  
257 procyanidins<sup>(84)</sup>. It has been reported to inhibit NFkappaB activation and the activity of some  
258 MMPs<sup>(85; 86)</sup>. Three small clinical trials have been performed in osteoarthritis with positive  
259 outcomes reported (e.g.<sup>(87; 88)</sup>). However, a Cochrane review of Pycnogenol in chronic  
260 diseases (including osteoarthritis) stated that it was not possible to reach definite  
261 conclusions on either efficacy or safety of Pycnogenol<sup>(89)</sup>.

262

### 263 Anthocyanins

264 Anthocyanins are responsible for the red/blue pigmentation in fruits and vegetables<sup>(64)</sup>. To  
265 date most studies have been performed using fruit juices or extracts which are rich in  
266 anthocyanins. A recent clinical trial examined tart cherry juice in patients with knee



267 osteoarthritis<sup>(90)</sup>. No difference in disease scores compared to placebo was uncovered, but  
268 hsCRP (high sensitivity C-reactive protein) was significantly lowered and this was associated  
269 with decreased score<sup>(90)</sup>. Pomegranate juice or extracts, which have been reported to  
270 contain anthocyanins and many other flavonoids including flavanols, have been shown to  
271 inhibit IL-1-induced MMP expression in chondrocytes via inhibition of MAP kinases and  
272 NFkappaB<sup>(91-93)</sup>. Such extracts also show efficacy in the MIA model of osteoarthritis in  
273 mice<sup>(94)</sup>. Raspberry extract<sup>(95)</sup> and red orange extract<sup>(96)</sup> have also been reported to have  
274 some efficacy *in vitro* and *in vivo*.

275

### 276 Isoflavones

277 Isoflavones are diphenolic compounds with structural similarity to estrogens, and are  
278 consequently referred to as phytoestrogens. They are found mainly in legumes and soya is  
279 a major source of isoflavones in the diet<sup>(64)</sup>. Data in chondrocytes show that one isoflavone,  
280 genistein, reduces the production of inflammatory molecules like COX-2 and NO (nitric  
281 oxide)<sup>(97)</sup>. Extracellular matrix synthesis in cartilage may increase or decrease, potentially  
282 with increasing dose<sup>(98; 99)</sup>. In the rat inflammatory collagen-induced arthritis model, soy  
283 protein appears to be protective<sup>(100)</sup>, however, no significant effect of soy intake was  
284 measurable on osteoarthritis severity in *Cynomolgus* monkeys<sup>(101)</sup>. One human study  
285 suggested beneficial effects of soy protein supplementation on function, symptoms and  
286 biochemical markers of osteoarthritis, particularly in men<sup>(102)</sup>.

287

### 288 Flavanones

289 Flavanones are present in the diet at high concentrations only in citrus fruits including  
290 naringenin from grapefruit, hesperetin from oranges and eriodictyol from lemons<sup>(64)</sup>. No  
291 effect was seen for naringenin on IL-1-induced MMP-13 production in SW1353  
292 chondrosarcoma cells<sup>(65)</sup>. However, hesperetin, its glycoside hesperidin or its derivatives,  
293 show efficacy in inflammatory models of arthritis<sup>(103-105)</sup>. Red orange juice extract showed  
294 repression of inflammatory molecules in chondrocytes as mentioned above<sup>(96)</sup>.

295

### 296 Carotenoids

297 Beta-carotene is the most widely known carotenoid and is a precursor to vitamin A<sup>(106)</sup>.  
298 Vitamin A and its derivatives, retinoids, are known to have profound effects on cartilage and  
299 the skeleton and may contribute to osteoarthritis<sup>(107)</sup>. The Framingham study identified a

300 weak protective association between intake of  $\beta$ -carotene and the progression of  
301 radiographic knee OA<sup>(14)</sup>. A case-control study in the Johnston County Osteoarthritis Project  
302 examined the association between serum levels of several carotenoids (lutein, zeaxanthin,  
303 beta-cryptoxanthin, lycopene, alpha-carotene and beta-carotene) and osteoarthritis<sup>(108)</sup>.  
304 People with high levels of lutein or beta-cryptoxanthin were less likely to have knee  
305 osteoarthritis, whilst those with high levels of trans-beta-carotene or zeaxanthin were more  
306 likely to have knee osteoarthritis. Similarly, a cross-sectional study in a Japanese population  
307 with radiographic knee osteoarthritis examined the association between serum levels of  
308 several carotenoids (lutein, zeaxanthin, cantaxanthin, cryptoxanthin, lycopene, alpha-  
309 carotene and beta-carotene) and osteoarthritis, but found nothing significant<sup>(109)</sup>. It is worth  
310 noting that there is evidence that beta-cryptoxanthin is associated with a decreased risk of  
311 inflammatory arthritis e.g.<sup>(110)</sup>. In healthy, middle-aged people, lutein and zeaxanthin intake  
312 was associated with decreased risk of cartilage defects on MRI and beta-cryptoxanthin  
313 intake was inversely associated with tibial plateau bone area<sup>(17)</sup>.

314

#### 315 Plant sterols

316 As discussed above, there is a positive association between serum cholesterol and  
317 osteoarthritis, with statin use appearing to show efficacy in disease incidence and/or  
318 progression. Intake of plant phytosterols/stanols significantly reduce LDL cholesterol and  
319 total cholesterol in intervention trials<sup>(111; 112)</sup> and of the three phytosterols tested,  
320 (stigmasterol, sitosterol and campesterol), stigmasterol bound best to chondrocyte  
321 membranes<sup>(113)</sup>. It inhibited IL-1 induced *MMP* and *ADAMTS4* expression, though had no  
322 effect on *ADAMTS5*, potentially via its ability to inhibit NFkappaB activation<sup>(113)</sup>. Intra-  
323 articular injection of stigmasterol was shown to suppress MMP expression and reduce  
324 cartilage degradation in a rabbit anterior cruciate ligament transection (ACLT) model of  
325 osteoarthritis<sup>(114)</sup>.

326

#### 327 Glucosinolates

328 Glucosinolates are found in cruciferous vegetables and are the precursors of  
329 isothiocyanates. Broccoli is rich in glucoraphanin, and when the vegetable is chopped or  
330 chewed, it is exposed to the action of an enzyme myrosinase to yield sulforaphane, the  
331 isothiocyanate. In chondrocytes, sulforaphane was initially shown to decrease shear stress-  
332 induced apoptosis<sup>(115)</sup>. More recently it has been shown to exhibit pro-survival and anti-  
333 apoptotic activities when cell death is induced by a variety of stimuli<sup>(116)</sup>. Sulforaphane has  
334 been shown to block IL-1 and TNFalpha induction of MMP-1 and -13 expression, as well as

335 PGE2 (prostaglandin E2) and NO in chondrocytes<sup>(117)</sup> and inhibit cartilage degradation *in*  
336 *vitro*<sup>(118)</sup>. Later work showed that it was effective in inhibiting expression of ADAMTS-4 and -  
337 5, and abrogating cartilage destruction in the 'destabilisation of the medial meniscus' model  
338 of osteoarthritis in the mouse, acting as a direct inhibitor of NFkappaB<sup>(119)</sup>.

339

#### 340 Resveratrol

341 Resveratrol is a plant-derived phenol of the stilbenoid class, found at high concentrations in  
342 the skin of red grapes and in red wine. It has come to the fore as an activator of the histone  
343 deacetylase Sirt1 which has important roles in cell survival and as a mimic of caloric  
344 restriction which extends lifespan in many models<sup>(120)</sup>. Sirt1 is intimately involved in  
345 osteoarthritis with deletion of Sirt1 in mice causing more rapid development of osteoarthritis  
346 in a post-surgical model<sup>(121)</sup>. Resveratrol decreases osteoarthritis score when directly  
347 injected intraarticularly in the rabbit ACLT model of osteoarthritis<sup>(122; 123)</sup>. It is an NFkappaB  
348 inhibitor in chondrocytes and blocks inflammation and apoptosis<sup>(124-126)</sup>. It has also been  
349 shown to decrease proteolysis (e.g. MMPs and ADAMTSs) and enhance extracellular matrix  
350 synthesis<sup>(127)</sup>.

351 Interestingly, resveratrol has been shown to display synergistic effects on chondrocyte  
352 phenotype and apoptosis with curcumin (see below)<sup>(128; 129)</sup>. These compounds both inhibit  
353 NFkappaB, but are known to act via different mechanisms.

354

#### 355 Curcumin

356 Curcumin is the major curcuminoid found in the spice, turmeric. It has been shown to be an  
357 NFkappaB inhibitor<sup>(130)</sup>, and used in chondrocytes as an inhibitor of oncostatin M-, IL-1- and  
358 TNFalpha-induced signalling<sup>(131-133)</sup>. Here it was shown to inhibit JNK, AP1, STAT and  
359 MAPK signalling, to inhibit expression of key MMPs in cartilage and proposed to have  
360 potential clinical utility. Innes et al use a turmeric extract in a clinical trial of osteoarthritis in  
361 the dog, with clinical assessments showing significant improvement<sup>(134)</sup>. The anti-catabolic  
362 effects of curcumin in human articular chondrocytes were confirmed<sup>(135)</sup> and its impact  
363 extended to include anti-apoptotic activity<sup>(136)</sup>, pro-anabolic effects on matrix expression<sup>(66;</sup>  
364 <sup>136)</sup>, inhibition of COX2 expression and other inflammatory mediators<sup>(137; 138)</sup>. Efficacy was  
365 also shown in cartilage explants<sup>(66; 139)</sup> and murine models of inflammatory arthritis<sup>(140)</sup>,  
366 though not yet osteoarthritis. Curcumin itself has poor solubility and bioavailability<sup>(141)</sup>, but a  
367 curcumin-phosphatidylcholine complex (Meriva), designed to overcome this, has shown some  
368 efficacy in small-scale clinical trials<sup>(142; 143)</sup>. As discussed above, a thorough understanding

369 of mechanism of action has led to experiments showing synergy between curcumin and  
370 resveratrol<sup>(128; 129)</sup>.

371

### 372 Avocado-soybean unsaponifiables

373 Whilst not truly dietary-derived, avocado-soybean unsaponifiables (ASU), Piascledine, has  
374 been developed by Laboratoire Expanscience and is the unsaponifiable fraction of one-third  
375 avocado oil and two-third soybean oil. It is a mixture of tocopherols, plant sterols and other  
376 molecules<sup>(144)</sup>. A recent moderate sized trial of Piascledine in hip osteoarthritis (the  
377 ERADIAS study) over 3 years showed that whilst there was no significant difference in mean  
378 joint space width loss between treatment and placebo, there were significantly less  
379 progressors in the treatment group. There was no difference in clinical outcomes including  
380 pain or analgesic/NSAID (non-steroidal anti-inflammatory drug) use<sup>(145)</sup>. This was somewhat  
381 similar to an earlier smaller study examining structural modification<sup>(146)</sup>, but very different to  
382 other earlier trials, where ASU demonstrated reductions in pain, functional disability or  
383 NSAID use in patients with hip or knee osteoarthritis over 3-6 months<sup>(147-149)</sup>. In a dog ACLT  
384 model of osteoarthritis, ASU reduced disease severity and decreased MMP-13  
385 production<sup>(150)</sup>, though in an ovine model of post-meniscectomy osteoarthritis, ASU was  
386 described to have a 'subtle, but statistically significant' effect on cartilage<sup>(151)</sup>. *In vitro* data  
387 show that ASU exhibit anti-catabolic (*MMP* expression), anti-inflammatory (PGE2, NO,  
388 COX2) and pro-anabolic (type II collagen and aggrecan synthesis) in chondrocytes. It has  
389 also been shown to inhibit NFkappaB activity<sup>(152-154)</sup>. It should also be pointed out that other  
390 formulations of ASU exist and one from Nutramax has been shown to have similar *in vitro*  
391 activity in chondrocytes<sup>(155)</sup>. Data from equine chondrocytes suggests that this ASU can act  
392 synergistically with EGCG<sup>(156)</sup>. The relative merits of each preparation have been the subject  
393 of debate<sup>(144; 157; 158)</sup>.

394

### 395 Ginger

396 There have been several small clinical trials exploring the efficacy of ginger extract in the  
397 treatment of osteoarthritis. Trials using *Zingiber officinale* extract showed variable outcome  
398 and a review found that evidence for its efficacy in osteoarthritis was weak<sup>(159)</sup>. A mixture of  
399 extracts from *Zingiber officinale* and *Alpinia galangal* used in a short (6 week) study showed  
400 a significant effect in reducing clinical symptoms<sup>(160)</sup>. *In vitro* research suggests that ginger  
401 extract can decrease production of inflammatory mediators from chondrocytes<sup>(161)</sup> and  
402 synoviocytes<sup>(162)</sup>.

403

404 Sulphur-containing compounds

405 A cross-sectional study in twins demonstrated that consumption of both allium vegetables  
406 and also non-citrus fruits showed a protective association with hip osteoarthritis<sup>(163)</sup>. Further,  
407 diallyl disulphide, a compound from garlic, was shown to inhibit IL-1-induced *MMP1*, *MMP3*  
408 and *MMP13* expression<sup>(163)</sup>. Diallyl sulphide has also been shown to block expression of  
409 these enzymes and ameliorate cartilage destruction when administered intraarticularly in the  
410 rabbit ACLT model of osteoarthritis<sup>(164)</sup>.

411

412 Others

413 Interestingly, data on the progression of knee osteoarthritis, coming from the osteoarthritis  
414 initiative (OAI) showed that frequent soft drink consumption is associated with increased  
415 disease progression in men, independent of obesity<sup>(165)</sup>. This obviously requires replication.  
416 An extract of edible bird's nest (which is made from swiftlet saliva), has been shown to have  
417 anti-catabolic, anti-inflammatory and pro-anabolic activity on human osteoarthritic  
418 chondrocytes<sup>(166)</sup>. Sesamin, a lignan from sesame seeds has been reported to be  
419 chondroprotective in an explant assay, decreasing MMP expression and activation<sup>(167)</sup>. An  
420 extract of a variety of mint which overexpressed rosmarinic acid inhibits LPS-induced GAG  
421 release and inflammatory mediators from porcine cartilage explants<sup>(168)</sup>.

422

423 Conclusions

424 There are many compounds present in the habitual diet which have been shown to have  
425 activity in both laboratory models of osteoarthritis and/or human disease. Where examined,  
426 many of these compounds appear to be inhibitors of the NFkappaB pathway. This signalling  
427 pathway has been shown to play a role in the development and progression of  
428 osteoarthritis<sup>(169)</sup>. Two studies suggest that using a combination of compounds which inhibit  
429 the NFkappaB pathway via different mechanisms gives a synergistic response<sup>(128; 129)</sup>. It  
430 would thus be important to understand the mode of NFkappaB inhibition for all compounds  
431 with this activity. In order to achieve synergy, it will also be important to discover  
432 compounds which do not act via this mechanism. Since habitual dietary intakes vary widely,  
433 an understanding of food combinations which protect the joint may be key and this may also  
434 be a means to develop specific food products or offer targeted advice to reduce risk.

435 Basic science provides information on mechanisms of cartilage protection in healthy tissue  
436 and the prevention of cartilage destruction in disease. The design of randomised clinical  
437 trials in the longer term needs to include 'at risk' populations (in which incidence of OA can  
438 be used as an outcome measure), as well as patients with existing OA. This is in line with  
439 current EFSA (European Food Standards Agency) recommendations that the design of  
440 human trials must demonstrate a preventative effect on the healthy joint, separately from an  
441 impact on established OA *per se* to establish claims in both areas.

442 In summary, diet offers a route by which the health of the joint can be protected and  
443 osteoarthritis incidence or progression decreased. In a chronic disease, with risk factors  
444 increasing in the population and with no pharmaceutical cure, an understanding of this will  
445 be crucial.

446

#### 447 Acknowledgements

448 We would like to thank all members of the Clark lab present and past and our collaborators  
449 in research related to this review.

450

#### 451 Financial support

452 Research in this area in Clark laboratory is funded by the BBSRC Diet and Health Research  
453 Industry Club grant BB/I006060/1 and PhD studentships BB/J500112/1, Arthritis Research  
454 UK grant 19371, Orthopaedic Research UK grant 487 and previously Dunhill Medical Trust  
455 grant R73/0208. These funders had no role in the design, analysis or writing of this article.

456

#### 457 Conflicts of interest

458 There are no conflicts of interest

459

#### 460 Authorship

461 All authors have contributed to writing and/or critically reviewing and editing the manuscript.

462

#### 463 References:

- 464 1. Pereira D, Peleteiro B, Araujo J *et al.* (2011) The effect of osteoarthritis definition on  
465 prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage* **19**, 1270-  
466 1285.
- 467 2. OANation2012 Arthritis Care. <http://edit.arthritiscare.org.uk/LivingwithArthritis/@172527>
- 468 3. National Joint Registry 9th Annual Report.  
469 [http://www.njrcentre.org.uk/njrcentre/AbouttheNJR/Publicationsandreports/Annualreports/tab](http://www.njrcentre.org.uk/njrcentre/AbouttheNJR/Publicationsandreports/Annualreports/tabid/86/Default.aspx)  
470 [id/86/Default.aspx](http://www.njrcentre.org.uk/njrcentre/AbouttheNJR/Publicationsandreports/Annualreports/tabid/86/Default.aspx)
- 471 4. Shane Anderson A, Loeser RF (2010) Why is osteoarthritis an age-related disease? *Best*  
472 *Pract Res Clin Rheumatol* **24**, 15-26.
- 473 5. Richmond SA, Fukuchi RK, Ezzat A *et al.* (2013) Are Joint Injury, Sport Activity, Physical  
474 Activity, Obesity, or Occupational Activities Predictors for Osteoarthritis? A Systematic  
475 Review. *J Orthop Sports Phys Ther* **43**, 515-524.
- 476 6. Chen A, Gupte C, Akhtar K *et al.* (2012) The Global Economic Cost of Osteoarthritis: How  
477 the UK Compares. *Arthritis* **2012**, 698709.
- 478 7. Kraus VB (2012) Patient Evaluation and OA Study Design: OARSI/Biomarker  
479 Qualification. *HSS J* **8**, 64-65.
- 480 8. Jordan JM, Sowers MF, Messier SP *et al.* (2011) Methodologic issues in clinical trials for  
481 prevention or risk reduction in osteoarthritis. *Osteoarthritis Cartilage* **19**, 500-508.
- 482 9. Black C, Clar C, Henderson R *et al.* (2009) The clinical effectiveness of glucosamine and  
483 chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a  
484 systematic review and economic evaluation. *Health Technol Assess* **13**, 1-148.
- 485 10. Hochberg M, Chevalier X, Henrotin Y *et al.* (2013) Symptom and structure modification in  
486 osteoarthritis with pharmaceutical-grade chondroitin sulfate: what's the evidence? *Curr Med*  
487 *Res Opin* **29**, 259-267.
- 488 11. Reginster JY, Neuprez A, Lecart MP *et al.* (2012) Role of glucosamine in the treatment  
489 for osteoarthritis. *Rheumatol Int* **32**, 2959-2967.
- 490 12. Wildi LM, Martel-Pelletier J, Abram F *et al.* (2013) Assessment of cartilage changes over  
491 time in knee osteoarthritis disease-modifying osteoarthritis drug trials using semiquantitative  
492 and quantitative methods: pros and cons. *Arthritis Care Res (Hoboken)* **65**, 686-694.
- 493 13. Wu D, Huang Y, Gu Y *et al.* (2013) Efficacies of different preparations of glucosamine for  
494 the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-  
495 controlled trials. *Int J Clin Pract* **67**, 585-594.
- 496 14. McAlindon TE, Jacques P, Zhang Y *et al.* (1996) Do antioxidant micronutrients protect  
497 against the development and progression of knee osteoarthritis? *Arthritis Rheum* **39**, 648-  
498 656.
- 499 15. McAlindon TE (2006) Nutraceuticals: do they work and when should we use them? *Best*  
500 *Pract Res Clin Rheumatol* **20**, 99-115.
- 501 16. Peregoy J, Wilder FV (2011) The effects of vitamin C supplementation on incident and  
502 progressive knee osteoarthritis: a longitudinal study. *Public Health Nutr* **14**, 709-715.
- 503 17. Wang Y, Hodge AM, Wluka AE *et al.* (2007) Effect of antioxidants on knee cartilage and  
504 bone in healthy, middle-aged subjects: a cross-sectional study. *Arthritis Res Ther* **9**, R66.
- 505 18. Clark AG, Rohrbaugh AL, Otterness I *et al.* (2002) The effects of ascorbic acid on  
506 cartilage metabolism in guinea pig articular cartilage explants. *Matrix Biol* **21**, 175-184.
- 507 19. Schwartz ER, Oh WH, Leveille CR (1981) Experimentally induced osteoarthritis in  
508 guinea pigs: metabolic responses in articular cartilage to developing pathology. *Arthritis*  
509 *Rheum* **24**, 1345-1355.
- 510 20. Meacock SC, Bodmer JL, Billingham ME (1990) Experimental osteoarthritis in guinea-  
511 pigs. *J Exp Pathol (Oxford)* **71**, 279-293.
- 512 21. Kraus VB, Huebner JL, Stabler T *et al.* (2004) Ascorbic acid increases the severity of  
513 spontaneous knee osteoarthritis in a guinea pig model. *Arthritis Rheum* **50**, 1822-1831.
- 514 22. Jordan JM, De Roos AJ, Renner JB *et al.* (2004) A case-control study of serum  
515 tocopherol levels and the alpha- to gamma-tocopherol ratio in radiographic knee  
516 osteoarthritis: the Johnston County Osteoarthritis Project. *Am J Epidemiol* **159**, 968-977.

- 517 23. Canter PH, Wider B, Ernst E (2007) The antioxidant vitamins A, C, E and selenium in the  
518 treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology*  
519 (*Oxford*) **46**, 1223-1233.
- 520 24. Bhatti FU, Mehmood A, Wajid N *et al.* (2013) Vitamin E protects chondrocytes against  
521 hydrogen peroxide-induced oxidative stress in vitro. *Inflamm Res* **62**, 781-789.
- 522 25. Wolff AE, Jones AN, Hansen KE (2008) Vitamin D and musculoskeletal health. *Nat Clin*  
523 *Pract Rheumatol* **4**, 580-588.
- 524 26. Cao Y, Winzenberg T, Nguo K *et al.* (2013) Association between serum levels of 25-  
525 hydroxyvitamin D and osteoarthritis: a systematic review. *Rheumatology (Oxford)* **52**, 1323-  
526 1334.
- 527 27. Laslett LL, Quinn S, Burgess JR *et al.* (2013) Moderate vitamin D deficiency is  
528 associated with changes in knee and hip pain in older adults: a 5-year longitudinal study.  
529 *Ann Rheum Dis In Press*.
- 530 28. McAlindon T, LaValley M, Schneider E *et al.* (2013) Effect of vitamin D supplementation  
531 on progression of knee pain and cartilage volume loss in patients with symptomatic  
532 osteoarthritis: a randomized controlled trial. *JAMA* **309**, 155-162.
- 533 29. Cao Y, Jones G, Cicuttini F *et al.* (2012) Vitamin D supplementation in the management  
534 of knee osteoarthritis: study protocol for a randomized controlled trial. *Trials* **13**, 131.
- 535 30. Castillo EC, Hernandez-Cueto MA, Vega-Lopez MA *et al.* (2012) Effects of Vitamin D  
536 Supplementation during the Induction and Progression of Osteoarthritis in a Rat Model. *Evid*  
537 *Based Complement Alternat Med* **2012**, 156563.
- 538 31. Zwerina K, Baum W, Axmann R *et al.* (2011) Vitamin D receptor regulates TNF-mediated  
539 arthritis. *Ann Rheum Dis* **70**, 1122-1129.
- 540 32. Oka H, Akune T, Muraki S *et al.* (2009) Association of low dietary vitamin K intake with  
541 radiographic knee osteoarthritis in the Japanese elderly population: dietary survey in a  
542 population-based cohort of the ROAD study. *J Orthop Sci* **14**, 687-692.
- 543 33. Misra D, Booth SL, Tolstykh I *et al.* (2013) Vitamin K deficiency is associated with  
544 incident knee osteoarthritis. *Am J Med* **126**, 243-248.
- 545 34. Neogi T, Booth SL, Zhang YQ *et al.* (2006) Low vitamin K status is associated with  
546 osteoarthritis in the hand and knee. *Arthritis Rheum* **54**, 1255-1261.
- 547 35. Muraki S, Akune T, En-Yo Y *et al.* (2013) Association of dietary intake with joint space  
548 narrowing and osteophytosis at the knee in Japanese men and women: the ROAD study.  
549 *Mod Rheumatol In Press*.
- 550 36. Krueger T, Westenfeld R, Schurgers L *et al.* (2009) Coagulation meets calcification: the  
551 vitamin K system. *Int J Artif Organs* **32**, 67-74.
- 552 37. Misra D, Booth SL, Crosier MD *et al.* (2011) Matrix Gla protein polymorphism, but not  
553 concentrations, is associated with radiographic hand osteoarthritis. *J Rheumatol* **38**, 1960-  
554 1965.
- 555 38. Naito K, Watari T, Obayashi O *et al.* (2012) Relationship between serum  
556 undercarboxylated osteocalcin and hyaluronan levels in patients with bilateral knee  
557 osteoarthritis. *Int J Mol Med* **29**, 756-760.
- 558 39. Jonas WB, Rapoza CP, Blair WF (1996) The effect of niacinamide on osteoarthritis: a  
559 pilot study. *Inflamm Res* **45**, 330-334.
- 560 40. Qin B, Shi X, Samai PS *et al.* (2012) Association of dietary magnesium intake with  
561 radiographic knee osteoarthritis: results from a population-based study. *Arthritis Care Res*  
562 (*Hoboken*) **64**, 1306-1311.
- 563 41. Hunter DJ, Hart D, Snieder H *et al.* (2003) Evidence of altered bone turnover, vitamin D  
564 and calcium regulation with knee osteoarthritis in female twins. *Rheumatology (Oxford)* **42**,  
565 1311-1316.
- 566 42. Zou K, Liu G, Wu T *et al.* (2009) Selenium for preventing Kashin-Beck osteoarthropathy  
567 in children: a meta-analysis. *Osteoarthritis Cartilage* **17**, 144-151.
- 568 43. Zhuo Q, Yang W, Chen J *et al.* (2012) Metabolic syndrome meets osteoarthritis. *Nat Rev*  
569 *Rheumatol* **8**, 729-737.
- 570 44. Gkretsi V, Simopoulou T, Tsezou A (2011) Lipid metabolism and osteoarthritis: lessons  
571 from atherosclerosis. *Prog Lipid Res* **50**, 133-140.



- 572 45. Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM *et al.* (2012) Statin use is  
573 associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam  
574 study. *Ann Rheum Dis* **71**, 642-647.
- 575 46. Kadam UT, Blagojevic M, Belcher J (2013) Statin use and clinical osteoarthritis in the  
576 general population: a longitudinal study. *J Gen Intern Med* **28**, 943-949.
- 577 47. Riddle DL, Moxley G, Dumenci L (2013) Associations between statin use and changes in  
578 pain, function and structural progression: a longitudinal study of persons with knee  
579 osteoarthritis. *Ann Rheum Dis* **72**, 196-203.
- 580 48. Lippiello L, Walsh T, Fienhold M (1991) The association of lipid abnormalities with tissue  
581 pathology in human osteoarthritic articular cartilage. *Metabolism* **40**, 571-576.
- 582 49. Plumb MS, Aspden RM (2004) High levels of fat and (n-6) fatty acids in cancellous bone  
583 in osteoarthritis. *Lipids Health Dis* **3**, 12.
- 584 50. Baker KR, Matthan NR, Lichtenstein AH *et al.* (2012) Association of plasma n-6 and n-3  
585 polyunsaturated fatty acids with synovitis in the knee: the MOST study. *Osteoarthritis*  
586 *Cartilage* **20**, 382-387.
- 587 51. Wang Y, Davies-Tuck ML, Wluka AE *et al.* (2009) Dietary fatty acid intake affects the risk  
588 of developing bone marrow lesions in healthy middle-aged adults without clinical knee  
589 osteoarthritis: a prospective cohort study. *Arthritis Res Ther* **11**, R63.
- 590 52. Wang Y, Wluka AE, Hodge AM *et al.* (2008) Effect of fatty acids on bone marrow lesions  
591 and knee cartilage in healthy, middle-aged subjects without clinical knee osteoarthritis.  
592 *Osteoarthritis Cartilage* **16**, 579-583.
- 593 53. Mooney RA, Sampson ER, Lerea J *et al.* (2011) High-fat diet accelerates progression of  
594 osteoarthritis after meniscal/ligamentous injury. *Arthritis Res Ther* **13**, R198.
- 595 54. Knott L, Avery NC, Hollander AP *et al.* (2011) Regulation of osteoarthritis by omega-3 (n-  
596 3) polyunsaturated fatty acids in a naturally occurring model of disease. *Osteoarthritis*  
597 *Cartilage* **19**, 1150-1157.
- 598 55. Hurst S, Rees SG, Randerson PF *et al.* (2009) Contrasting effects of n-3 and n-6 fatty  
599 acids on cyclooxygenase-2 in model systems for arthritis. *Lipids* **44**, 889-896.
- 600 56. Zainal Z, Longman AJ, Hurst S *et al.* (2009) Relative efficacies of omega-3  
601 polyunsaturated fatty acids in reducing expression of key proteins in a model system for  
602 studying osteoarthritis. *Osteoarthritis Cartilage* **17**, 896-905.
- 603 57. Hiem-Bjorkman A, Roine J, Elo K *et al.* (2012) An un-commissioned randomized,  
604 placebo-controlled double-blind study to test the effect of deep sea fish oil as a pain reliever  
605 for dogs suffering from canine OA. *BMC Vet Res* **8**, 157.
- 606 58. Roush JK, Dodd CE, Fritsch DA *et al.* (2010) Multicenter veterinary practice assessment  
607 of the effects of omega-3 fatty acids on osteoarthritis in dogs. *J Am Vet Med Assoc* **236**, 59-  
608 66.
- 609 59. Jacquet A, Girodet PO, Pariente A *et al.* (2009) Phytalgic, a food supplement, vs placebo  
610 in patients with osteoarthritis of the knee or hip: a randomised double-blind placebo-  
611 controlled clinical trial. *Arthritis Res Ther* **11**, R192.
- 612 60. Christensen R, Bliddal H (2010) Is Phytalgic(R) a goldmine for osteoarthritis patients or  
613 is there something fishy about this nutraceutical? A summary of findings and risk-of-bias  
614 assessment. *Arthritis Res Ther* **12**, 105.
- 615 61. Ameye LG, Chee WS (2006) Osteoarthritis and nutrition. From nutraceuticals to  
616 functional foods: a systematic review of the scientific evidence. *Arthritis Res Ther* **8**, R127.
- 617 62. Denny A, Buttriss J (2007) Plant food and health: Focus on plant bioactives. **Synthesis**  
618 **Report No 4**, [http://www.ipfn.ie/download/pdf/eurofir\\_report\\_plant\\_bioactives.pdf](http://www.ipfn.ie/download/pdf/eurofir_report_plant_bioactives.pdf).
- 619 63. Falcone Ferreyra ML, Rius SP, Casati P (2012) Flavonoids: biosynthesis, biological  
620 functions, and biotechnological applications. *Front Plant Sci* **3**, 222.
- 621 64. Manach C, Scalbert A, Morand C *et al.* (2004) Polyphenols: food sources and  
622 bioavailability. *Am J Clin Nutr* **79**, 727-747.
- 623 65. Lim H, Park H, Kim HP (2011) Effects of flavonoids on matrix metalloproteinase-13  
624 expression of interleukin-1beta-treated articular chondrocytes and their cellular mechanisms:  
625 inhibition of c-Fos/AP-1 and JAK/STAT signaling pathways. *J Pharmacol Sci* **116**, 221-231.

- 626 66. Lay E, Samiric T, Handley CJ *et al.* (2012) Short- and long-term exposure of articular  
627 cartilage to curcumin or quercetin inhibits aggrecan loss. *J Nutr Biochem* **23**, 106-112.
- 628 67. Lee YS, Choi EM (2010) Myricetin inhibits IL-1 $\beta$ -induced inflammatory mediators in  
629 SW982 human synovial sarcoma cells. *Int Immunopharmacol* **10**, 812-814.
- 630 68. Imada K, Lin N, Liu C *et al.* (2008) Nobiletin, a citrus polymethoxy flavonoid, suppresses  
631 gene expression and production of aggrecanases-1 and -2 in collagen-induced arthritic mice.  
632 *Biochem Biophys Res Commun* **373**, 181-185.
- 633 69. Moncada-Pazos A, Obaya AJ, Vilorio CG *et al.* (2011) The nutraceutical flavonoid  
634 luteolin inhibits ADAMTS-4 and ADAMTS-5 aggrecanase activities. *J Mol Med (Berl)* **89**,  
635 611-619.
- 636 70. Lopez-Lazaro M (2009) Distribution and biological activities of the flavonoid luteolin. *Mini*  
637 *Rev Med Chem* **9**, 31-59.
- 638 71. Ishiwa J, Sato T, Mimaki Y *et al.* (2000) A citrus flavonoid, nobiletin, suppresses  
639 production and gene expression of matrix metalloproteinase 9/gelatinase B in rabbit synovial  
640 fibroblasts. *J Rheumatol* **27**, 20-25.
- 641 72. Durigova M, Roughley PJ, Mort JS (2008) Mechanism of proteoglycan aggregate  
642 degradation in cartilage stimulated with oncostatin M. *Osteoarthritis Cartilage* **16**, 98-104.
- 643 73. Haqqi TM, Anthony DD, Gupta S *et al.* (1999) Prevention of collagen-induced arthritis in  
644 mice by a polyphenolic fraction from green tea. *Proc Natl Acad Sci U S A* **96**, 4524-4529.
- 645 74. Adcocks C, Collin P, Buttle DJ (2002) Catechins from green tea (*Camellia sinensis*)  
646 inhibit bovine and human cartilage proteoglycan and type II collagen degradation in vitro. *J*  
647 *Nutr* **132**, 341-346.
- 648 75. Vankemmelbeke MN, Jones GC, Fowles C *et al.* (2003) Selective inhibition of ADAMTS-  
649 1, -4 and -5 by catechin gallate esters. *Eur J Biochem* **270**, 2394-2403.
- 650 76. Akhtar N, Haqqi TM (2011) Epigallocatechin-3-gallate suppresses the global interleukin-  
651 1 $\beta$ -induced inflammatory response in human chondrocytes. *Arthritis Res Ther* **13**, R93.
- 652 77. Ahmed S (2010) Green tea polyphenol epigallocatechin 3-gallate in arthritis: progress  
653 and promise. *Arthritis Res Ther* **12**, 208.
- 654 78. Burnett BP, Jia Q, Zhao Y *et al.* (2007) A medicinal extract of *Scutellaria baicalensis* and  
655 *Acacia catechu* acts as a dual inhibitor of cyclooxygenase and 5-lipoxygenase to reduce  
656 inflammation. *J Med Food* **10**, 442-451.
- 657 79. Shen D, Wu Q, Wang M *et al.* (2006) Determination of the predominant catechins in  
658 *Acacia catechu* by liquid chromatography/electrospray ionization-mass spectrometry. *J Agric*  
659 *Food Chem* **54**, 3219-3224.
- 660 80. Levy RM, Khokhlov A, Kopenkin S *et al.* (2010) Efficacy and safety of flavocoxid, a novel  
661 therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects  
662 with osteoarthritis of the knee. *Adv Ther* **27**, 731-742.
- 663 81. Chalasani N, Vuppalanchi R, Navarro V *et al.* (2012) Acute liver injury due to flavocoxid  
664 (Limbrel), a medical food for osteoarthritis: a case series. *Ann Intern Med* **156**, 857-860,  
665 W297-300.
- 666 82. Woo YJ, Joo YB, Jung YO *et al.* (2011) Grape seed proanthocyanidin extract  
667 ameliorates monosodium iodoacetate-induced osteoarthritis. *Exp Mol Med* **43**, 561-570.
- 668 83. Aini H, Ochi H, Iwata M *et al.* (2012) Procyanidin B3 prevents articular cartilage  
669 degeneration and heterotopic cartilage formation in a mouse surgical osteoarthritis model.  
670 *PLoS One* **7**, e37728.
- 671 84. D'Andrea G (2010) Pycnogenol: a blend of procyanidins with multifaceted therapeutic  
672 applications? *Fitoterapia* **81**, 724-736.
- 673 85. Grimm T, Chovanova Z, Muchova J *et al.* (2006) Inhibition of NF-kappaB activation and  
674 MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark  
675 extract (Pycnogenol). *J Inflamm (Lond)* **3**, 1.
- 676 86. Grimm T, Schafer A, Hogger P (2004) Antioxidant activity and inhibition of matrix  
677 metalloproteinases by metabolites of maritime pine bark extract (pycnogenol). *Free Radic*  
678 *Biol Med* **36**, 811-822.

679 87. Belcaro G, Cesarone MR, Errichi S *et al.* (2008) Treatment of osteoarthritis with  
680 Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs,  
681 symptoms, physical performance and vascular aspects. *Phytother Res* **22**, 518-523.  
682 88. Cisar P, Jany R, Waczulikova I *et al.* (2008) Effect of pine bark extract (Pycnogenol) on  
683 symptoms of knee osteoarthritis. *Phytother Res* **22**, 1087-1092.  
684 89. Schoonees A, Visser J, Musekiwa A *et al.* (2012) Pycnogenol((R)) for the treatment of  
685 chronic disorders. *Cochrane Database Syst Rev* **2**, CD008294.  
686 90. Schumacher HR, Pullman-Mooar S, Gupta SR *et al.* (2013) Randomized double-blind  
687 crossover study of the efficacy of a tart cherry juice blend in treatment of osteoarthritis (OA)  
688 of the knee. *Osteoarthritis Cartilage* **21**, 1035-1041.  
689 91. Ahmed S, Wang N, Hafeez BB *et al.* (2005) Punica granatum L. extract inhibits IL-1beta-  
690 induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases  
691 and NF-kappaB in human chondrocytes in vitro. *J Nutr* **135**, 2096-2102.  
692 92. Haseeb A, Chen D, Haqqi TM (2013) Delphinidin inhibits IL-1beta-induced activation of  
693 NF-kappaB by modulating the phosphorylation of IRAK-1(Ser376) in human articular  
694 chondrocytes. *Rheumatology (Oxford)* **52**, 998-1008.  
695 93. Jean-Gilles D, Li L, Vaidyanathan VG *et al.* (2013) Inhibitory effects of polyphenol  
696 punicalagin on type-II collagen degradation in vitro and inflammation in vivo. *Chem Biol*  
697 *Interact* **205**, 90-99.  
698 94. Hadipour-Jahromy M, Mozaffari-Kermani R (2010) Chondroprotective effects of  
699 pomegranate juice on monoiodoacetate-induced osteoarthritis of the knee joint of mice.  
700 *Phytother Res* **24**, 182-185.  
701 95. Jean-Gilles D, Li L, Ma H *et al.* (2012) Anti-inflammatory Effects of Polyphenolic-  
702 Enriched Red Raspberry Extract in an Antigen-Induced Arthritis Rat Model. *J Agric Food*  
703 *Chem* **60**, 5755-5762.  
704 96. Frasca G, Panico AM, Bonina F *et al.* (2010) Involvement of inducible nitric oxide  
705 synthase and cyclooxygenase-2 in the anti-inflammatory effects of a red orange extract in  
706 human chondrocytes. *Nat Prod Res* **24**, 1469-1480.  
707 97. Hooshmand S, Soung do Y, Lucas EA *et al.* (2007) Genistein reduces the production of  
708 proinflammatory molecules in human chondrocytes. *J Nutr Biochem* **18**, 609-614.  
709 98. Claassen H, Briese V, Manapov F *et al.* (2008) The phytoestrogens daidzein and  
710 genistein enhance the insulin-stimulated sulfate uptake in articular chondrocytes. *Cell Tissue*  
711 *Res* **333**, 71-79.  
712 99. Yu SB, Xing XH, Dong GY *et al.* (2012) Excess genistein suppresses the synthesis of  
713 extracellular matrix in female rat mandibular condylar cartilage. *Acta Pharmacol Sin* **33**, 918-  
714 923.  
715 100. Mohammad Shahi M, Rashidi MR, Mahboob S *et al.* (2012) Protective effect of soy  
716 protein on collagen-induced arthritis in rat. *Rheumatol Int* **32**, 2407-2414.  
717 101. Ham KD, Loeser RF, Lindgren BR *et al.* (2002) Effects of long-term estrogen  
718 replacement therapy on osteoarthritis severity in cynomolgus monkeys. *Arthritis Rheum* **46**,  
719 1956-1964.  
720 102. Arjmandi BH, Khalil DA, Lucas EA *et al.* (2004) Soy protein may alleviate osteoarthritis  
721 symptoms. *Phytomedicine* **11**, 567-575.  
722 103. Choi EM, Lee YS (2010) Effects of hesperetin on the production of inflammatory  
723 mediators in IL-1beta treated human synovial cells. *Cell Immunol* **264**, 1-3.  
724 104. Li R, Cai L, Ren DY *et al.* (2012) Therapeutic effect of 7, 3'-dimethoxy hesperetin on  
725 adjuvant arthritis in rats through inhibiting JAK2-STAT3 signal pathway. *Int*  
726 *Immunopharmacol* **14**, 157-163.  
727 105. Umar S, Kumar A, Sajad M *et al.* (2013) Hesperidin inhibits collagen-induced arthritis  
728 possibly through suppression of free radical load and reduction in neutrophil activation and  
729 infiltration. *Rheumatol Int* **33**, 657-663.  
730 106. Maiani G, Caston MJ, Catasta G *et al.* (2009) Carotenoids: actual knowledge on food  
731 sources, intakes, stability and bioavailability and their protective role in humans. *Mol Nutr*  
732 *Food Res* **53 Suppl 2**, S194-218.

733 107. Davies MR, Ribeiro LR, Downey-Jones M *et al.* (2009) Ligands for retinoic acid  
734 receptors are elevated in osteoarthritis and may contribute to pathologic processes in the  
735 osteoarthritic joint. *Arthritis Rheum* **60**, 1722-1732.

736 108. De Roos AJ, Arab L, Renner JB *et al.* (2001) Serum carotenoids and radiographic knee  
737 osteoarthritis: the Johnston County Osteoarthritis Project. *Public Health Nutr* **4**, 935-942.

738 109. Seki T, Hasegawa Y, Yamaguchi J *et al.* (2010) Association of serum carotenoids,  
739 retinol, and tocopherols with radiographic knee osteoarthritis: possible risk factors in rural  
740 Japanese inhabitants. *J Orthop Sci* **15**, 477-484.

741 110. Pattison DJ, Symmons DP, Lunt M *et al.* (2005) Dietary beta-cryptoxanthin and  
742 inflammatory polyarthritis: results from a population-based prospective study. *Am J Clin Nutr*  
743 **82**, 451-455.

744 111. Kamal-Eldin A, Moazzami A (2009) Plant sterols and stanols as cholesterol-lowering  
745 ingredients in functional foods. *Recent Pat Food Nutr Agric* **1**, 1-14.

746 112. Wu T, Fu J, Yang Y *et al.* (2009) The effects of phytosterols/stanols on blood lipid  
747 profiles: a systematic review with meta-analysis. *Asia Pac J Clin Nutr* **18**, 179-186.

748 113. Gabay O, Sanchez C, Salvat C *et al.* (2010) Stigmasterol: a phytosterol with potential  
749 anti-osteoarthritic properties. *Osteoarthritis Cartilage* **18**, 106-116.

750 114. Chen WP, Yu C, Hu PF *et al.* (2012) Stigmasterol blocks cartilage degradation in rabbit  
751 model of osteoarthritis. *Acta Biochim Pol* **59**, 537-541.

752 115. Healy ZR, Lee NH, Gao X *et al.* (2005) Divergent responses of chondrocytes and  
753 endothelial cells to shear stress: cross-talk among COX-2, the phase 2 response, and  
754 apoptosis. *Proc Natl Acad Sci U S A* **102**, 14010-14015.

755 116. Facchini A, Stanic I, Cetrullo S *et al.* (2011) Sulforaphane protects human chondrocytes  
756 against cell death induced by various stimuli. *J Cell Physiol* **226**, 1771-1779.

757 117. Kim HA, Yeo Y, Kim WU *et al.* (2009) Phase 2 enzyme inducer sulphoraphane blocks  
758 matrix metalloproteinase production in articular chondrocytes. *Rheumatology (Oxford)* **48**,  
759 932-938.

760 118. Kim HA, Yeo Y, Jung HA *et al.* (2012) Phase 2 enzyme inducer sulphoraphane blocks  
761 prostaglandin and nitric oxide synthesis in human articular chondrocytes and inhibits  
762 cartilage matrix degradation. *Rheumatology (Oxford)* **51**, 1006-1016.

763 119. Davidson RK, Jupp O, de Ferrars R *et al.* (2013) Sulforaphane represses matrix-  
764 degrading proteases and protects cartilage from destruction in vitro and in vivo. *Arthritis*  
765 *Rheum In Press*.

766 120. Lam YY, Peterson CM, Ravussin E (2013) Resveratrol vs. calorie restriction: Data from  
767 rodents to humans. *Exp Gerontol* **48**, 1018-1024.

768 121. Matsuzaki T, Matsushita T, Takayama K *et al.* (2013) Disruption of Sirt1 in  
769 chondrocytes causes accelerated progression of osteoarthritis under mechanical stress and  
770 during ageing in mice. *Ann Rheum Dis In Press*.

771 122. Elmali N, Esenkaya I, Harma A *et al.* (2005) Effect of resveratrol in experimental  
772 osteoarthritis in rabbits. *Inflamm Res* **54**, 158-162.

773 123. Wang J, Gao JS, Chen JW *et al.* (2012) Effect of resveratrol on cartilage protection and  
774 apoptosis inhibition in experimental osteoarthritis of rabbit. *Rheumatol Int* **32**, 1541-1548.

775 124. Csaki C, Keshishzadeh N, Fischer K *et al.* (2008) Regulation of inflammation signalling  
776 by resveratrol in human chondrocytes in vitro. *Biochem Pharmacol* **75**, 677-687.

777 125. Lei M, Wang JG, Xiao DM *et al.* (2012) Resveratrol inhibits interleukin 1beta-mediated  
778 inducible nitric oxide synthase expression in articular chondrocytes by activating SIRT1 and  
779 thereby suppressing nuclear factor-kappaB activity. *Eur J Pharmacol* **674**, 73-79.

780 126. Shakibaei M, Csaki C, Nebrich S *et al.* (2008) Resveratrol suppresses interleukin-  
781 1beta-induced inflammatory signaling and apoptosis in human articular chondrocytes:  
782 potential for use as a novel nutraceutical for the treatment of osteoarthritis. *Biochem*  
783 *Pharmacol* **76**, 1426-1439.

784 127. Im HJ, Li X, Chen D *et al.* (2012) Biological effects of the plant-derived polyphenol  
785 resveratrol in human articular cartilage and chondrosarcoma cells. *J Cell Physiol* **227**, 3488-  
786 3497.

787 128. Csaki C, Mobasheri A, Shakibaei M (2009) Synergistic chondroprotective effects of  
788 curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-  
789 kappaB-mediated inflammation and apoptosis. *Arthritis Res Ther* **11**, R165.

790 129. Shakibaei M, Mobasheri A, Buhrmann C (2011) Curcumin synergizes with resveratrol to  
791 stimulate the MAPK signaling pathway in human articular chondrocytes in vitro. *Genes Nutr*  
792 **6**, 171-179.

793 130. Singh S, Aggarwal BB (1995) Activation of transcription factor NF-kappa B is  
794 suppressed by curcumin (diferuloylmethane) [corrected]. *J Biol Chem* **270**, 24995-25000.

795 131. Li WQ, Dehnade F, Zafarullah M (2001) Oncostatin M-induced matrix metalloproteinase  
796 and tissue inhibitor of metalloproteinase-3 genes expression in chondrocytes requires Janus  
797 kinase/STAT signaling pathway. *J Immunol* **166**, 3491-3498.

798 132. Liacini A, Sylvester J, Li WQ *et al.* (2003) Induction of matrix metalloproteinase-13 gene  
799 expression by TNF-alpha is mediated by MAP kinases, AP-1, and NF-kappaB transcription  
800 factors in articular chondrocytes. *Exp Cell Res* **288**, 208-217.

801 133. Liacini A, Sylvester J, Li WQ *et al.* (2002) Inhibition of interleukin-1-stimulated MAP  
802 kinases, activating protein-1 (AP-1) and nuclear factor kappa B (NF-kappa B) transcription  
803 factors down-regulates matrix metalloproteinase gene expression in articular chondrocytes.  
804 *Matrix Biol* **21**, 251-262.

805 134. Innes JF, Fuller CJ, Grover ER *et al.* (2003) Randomised, double-blind, placebo-  
806 controlled parallel group study of P54FP for the treatment of dogs with osteoarthritis. *Vet*  
807 *Rec* **152**, 457-460.

808 135. Schulze-Tanzil G, Mobasheri A, Sendzik J *et al.* (2004) Effects of curcumin  
809 (diferuloylmethane) on nuclear factor kappaB signaling in interleukin-1beta-stimulated  
810 chondrocytes. *Ann N Y Acad Sci* **1030**, 578-586.

811 136. Shakibaei M, Schulze-Tanzil G, John T *et al.* (2005) Curcumin protects human  
812 chondrocytes from IL-1beta-induced inhibition of collagen type II and beta1-integrin  
813 expression and activation of caspase-3: an immunomorphological study. *Ann Anat* **187**, 487-  
814 497.

815 137. Mathy-Hartert M, Jacquemond-Collet I, Priem F *et al.* (2009) Curcumin inhibits pro-  
816 inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflamm Res*  
817 **58**, 899-908.

818 138. Shakibaei M, John T, Schulze-Tanzil G *et al.* (2007) Suppression of NF-kappaB  
819 activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix  
820 metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of  
821 osteoarthritis. *Biochem Pharmacol* **73**, 1434-1445.

822 139. Clutterbuck AL, Mobasheri A, Shakibaei M *et al.* (2009) Interleukin-1beta-induced  
823 extracellular matrix degradation and glycosaminoglycan release is inhibited by curcumin in  
824 an explant model of cartilage inflammation. *Ann N Y Acad Sci* **1171**, 428-435.

825 140. Mun SH, Kim HS, Kim JW *et al.* (2009) Oral administration of curcumin suppresses  
826 production of matrix metalloproteinase (MMP)-1 and MMP-3 to ameliorate collagen-induced  
827 arthritis: inhibition of the PKCdelta/JNK/c-Jun pathway. *J Pharmacol Sci* **111**, 13-21.

828 141. Henrotin Y, Clutterbuck AL, Allaway D *et al.* (2010) Biological actions of curcumin on  
829 articular chondrocytes. *Osteoarthritis Cartilage* **18**, 141-149.

830 142. Belcaro G, Cesarone MR, Dugall M *et al.* (2010) Efficacy and safety of Meriva(R), a  
831 curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis  
832 patients. *Altern Med Rev* **15**, 337-344.

833 143. Belcaro G, Cesarone MR, Dugall M *et al.* (2010) Product-evaluation registry of  
834 Meriva(R), a curcumin-phosphatidylcholine complex, for the complementary management of  
835 osteoarthritis. *Panminerva Med* **52**, 55-62.

836 144. Msika P, Baudouin C, Saunois A *et al.* (2008) Avocado/soybean unsaponifiables, ASU  
837 EXPANSCIENCE, are strictly different from the nutraceutical products claiming ASU  
838 appellation. *Osteoarthritis Cartilage* **16**, 1275-1276.

839 145. Maheu E, Cadet C, Marty M *et al.* (2013) Randomised, controlled trial of avocado-  
840 soybean unsaponifiable (Piascledine) effect on structure modification in hip osteoarthritis:  
841 the ERADIAS study. *Ann Rheum Dis In Press*.

842 146. Lequesne M, Maheu E, Cadet C *et al.* (2002) Structural effect of avocado/soybean  
843 unsaponifiables on joint space loss in osteoarthritis of the hip. *Arthritis Rheum* **47**, 50-58.

844 147. Appelboom T, Schuermans J, Verbruggen G *et al.* (2001) Symptoms modifying effect of  
845 avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective,  
846 placebo-controlled study. *Scand J Rheumatol* **30**, 242-247.

847 148. Blotman F, Maheu E, Wulwik A *et al.* (1997) Efficacy and safety of avocado/soybean  
848 unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A  
849 prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial.  
850 *Rev Rhum Engl Ed* **64**, 825-834.

851 149. Maheu E, Mazieres B, Valat JP *et al.* (1998) Symptomatic efficacy of avocado/soybean  
852 unsaponifiables in the treatment of osteoarthritis of the knee and hip: a prospective,  
853 randomized, double-blind, placebo-controlled, multicenter clinical trial with a six-month  
854 treatment period and a two-month followup demonstrating a persistent effect. *Arthritis*  
855 *Rheum* **41**, 81-91.

856 150. Boileau C, Martel-Pelletier J, Caron J *et al.* (2009) Protective effects of total fraction of  
857 avocado/soybean unsaponifiables on the structural changes in experimental dog  
858 osteoarthritis: inhibition of nitric oxide synthase and matrix metalloproteinase-13. *Arthritis*  
859 *Res Ther* **11**, R41.

860 151. Cake MA, Read RA, Guillou B *et al.* (2000) Modification of articular cartilage and  
861 subchondral bone pathology in an ovine meniscectomy model of osteoarthritis by avocado  
862 and soya unsaponifiables (ASU). *Osteoarthritis Cartilage* **8**, 404-411.

863 152. Gabay O, Gosset M, Levy A *et al.* (2008) Stress-induced signaling pathways in hyalin  
864 chondrocytes: inhibition by Avocado-Soybean Unsaponifiables (ASU). *Osteoarthritis*  
865 *Cartilage* **16**, 373-384.

866 153. Henrotin YE, Deberg MA, Crielaard JM *et al.* (2006) Avocado/soybean unsaponifiables  
867 prevent the inhibitory effect of osteoarthritic subchondral osteoblasts on aggrecan and type II  
868 collagen synthesis by chondrocytes. *J Rheumatol* **33**, 1668-1678.

869 154. Henrotin YE, Sanchez C, Deberg MA *et al.* (2003) Avocado/soybean unsaponifiables  
870 increase aggrecan synthesis and reduce catabolic and proinflammatory mediator production  
871 by human osteoarthritic chondrocytes. *J Rheumatol* **30**, 1825-1834.

872 155. Au RY, Al-Talib TK, Au AY *et al.* (2007) Avocado soybean unsaponifiables (ASU)  
873 suppress TNF-alpha, IL-1beta, COX-2, iNOS gene expression, and prostaglandin E2 and  
874 nitric oxide production in articular chondrocytes and monocyte/macrophages. *Osteoarthritis*  
875 *Cartilage* **15**, 1249-1255.

876 156. Heinecke LF, Grzanna MW, Au AY *et al.* (2010) Inhibition of cyclooxygenase-2  
877 expression and prostaglandin E2 production in chondrocytes by avocado soybean  
878 unsaponifiables and epigallocatechin gallate. *Osteoarthritis Cartilage* **18**, 220-227.

879 157. Frondoza CG (2008) Response to letter to editor entitled: "Avocado/soybean  
880 unsaponifiables, ASU Expanscience, are strictly different from the nutraceutical products  
881 claiming ASU appellation" (4365). *Osteoarthritis Cartilage* **16**, 1590-1591.

882 158. Henrotin Y (2008) Avocado/soybean unsaponifiable (ASU) to treat osteoarthritis: a  
883 clarification. *Osteoarthritis Cartilage* **16**, 1118-1119; author reply 1120.

884 159. Leach MJ, Kumar S (2008) The clinical effectiveness of Ginger (*Zingiber officinale*) in  
885 adults with osteoarthritis. *Int J Evid Based Healthc* **6**, 311-320.

886 160. Altman RD, Marcussen KC (2001) Effects of a ginger extract on knee pain in patients  
887 with osteoarthritis. *Arthritis Rheum* **44**, 2531-2538.

888 161. Shen CL, Hong KJ, Kim SW (2005) Comparative effects of ginger root (*Zingiber*  
889 *officinale* Rosc.) on the production of inflammatory mediators in normal and osteoarthrotic  
890 sow chondrocytes. *J Med Food* **8**, 149-153.

891 162. Ribel-Madsen S, Bartels EM, Stockmarr A *et al.* (2012) A synoviocyte model for  
892 osteoarthritis and rheumatoid arthritis: response to ibuprofen, betamethasone, and ginger  
893 extract-a cross-sectional in vitro study. *Arthritis* **2012**, 505842.

894 163. Williams FM, Skinner J, Spector TD *et al.* (2010) Dietary garlic and hip osteoarthritis:  
895 evidence of a protective effect and putative mechanism of action. *BMC Musculoskelet Disord*  
896 **11**, 280.

- 897 164. Chen WP, Tang JL, Bao JP *et al.* (2011) Effects of diallyl sulphide in chondrocyte and  
898 cartilage in experimental osteoarthritis in rabbit. *Phytother Res* **25**, 351-356.
- 899 165. Lu B, Ahmad O, Zhang FF *et al.* (2013) Soft drink intake and progression of  
900 radiographic knee osteoarthritis: data from the osteoarthritis initiative. *BMJ Open* **3**.
- 901 166. Chua KH, Lee TH, Nagandran K *et al.* (2013) Edible Bird's nest extract as a chondro-  
902 protective agent for human chondrocytes isolated from osteoarthritic knee: in vitro study.  
903 *BMC Complement Altern Med* **13**, 19.
- 904 167. Phitak T, Pothacharoen P, Settakorn J *et al.* (2012) Chondroprotective and anti-  
905 inflammatory effects of sesamin. *Phytochemistry* **80**, 77-88.
- 906 168. Pearson W, Fletcher RS, Kott LS *et al.* (2010) Protection against LPS-induced cartilage  
907 inflammation and degradation provided by a biological extract of *Mentha spicata*. *BMC*  
908 *Complement Altern Med* **10**, 19.
- 909 169. Marcu KB, Otero M, Olivotto E *et al.* (2010) NF-kappaB signaling: multiple angles to  
910 target OA. *Curr Drug Targets* **11**, 599-613.

911

912