

# Current nutraceuticals in the management of osteoarthritis: a review

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**Abstract:** Osteoarthritis (OA) is a progressive degenerative joint disease that has a major impact on joint function and quality of life. Nutraceuticals and dietary supplements derived from herbs have long been used in traditional medicine and there is considerable evidence that nutraceuticals may play an important role in inflammation and joint destruction in OA. We review the biological effects of some medicinal fruits and herbs – pomegranate, green tea, cat’s claw, devil’s claw, ginger, Indian olibaum, turmeric and ananas – in an attempt to understand the pivotal molecular targets involved in inflammation and the joint destruction process and to summarize their toxicities and efficacy for OA management. So far there is insufficient reliable evidence on the effectiveness of ginger, turmeric and ananas. Pomegranate and green tea only have preclinical evidence of efficacy due to the lack of clinical data. *In vivo* and clinical studies are required to understand their targets and efficacy in OA. Limited *in vitro* and *in vivo* evidence is available for cat’s claw and Indian olibaum. More extensive studies are required before long-term controlled trials of whole cat’s claw and Indian olibaum extracts, or isolated active compounds, are carried out in patients with OA to determine their long-term efficacy and safety. Devil’s claw has not been rigorously tested to determine its antiarthritic potential in *in vitro* and *in vivo* models. There is strong clinical evidence of the effectiveness of devil’s claw in pain reduction. However, high-quality clinical trials are needed to determine its effectiveness. No serious side effects have been reported for any fruits and herbs. Overall, these studies identify and support the use of nutraceuticals to provide symptomatic relief to patients with OA and to be used as adjunct therapy for OA management. More high-quality trials are needed to provide definitive answers to questions related to their efficacy and safety for OA prevention and/or treatment.

**Keywords:** cat’s claw, green tea, inflammation, osteoarthritis, pomegranate

## Introduction

Osteoarthritis (OA) is one of the most prevalent and disabling chronic diseases affecting older people. A high prevalence of OA among older people and women and the moderate to severe impact on daily life pose a significant public health problem [Malemud *et al.* 2003; Yelin, 2003]. OA involves the erosion of articular cartilage, inflammation of synovial membrane, and resorption of the underlying subchondral bone [van der Kraan and van den Berg, 2000]. These pathological changes are associated with an excessive production of proinflammatory molecules such as interleukin 1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which shift the

balance between the synthesis and degradation of matrix components resulting in progressive destruction of the joint tissue [van der Kraan and van den Berg, 2000]. Today, a cure for OA remains elusive. Nonpharmacological management includes physical therapy, aerobic exercises, muscle strengthening, weight reduction, walking aids, knee braces, footwear and insoles, electromagnets, thermal modalities and acupuncture. For OA treatment and prevention, glucosamine and chondroitin sulfate, two of the molecular building blocks found in articular cartilage, are the most commonly used dietary supplements. In randomized trials of variable quality, these compounds show efficacy in reducing symptoms,

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but neither has been shown to arrest progression of the disease or regenerate damaged cartilage [reviewed in Häuselmann, 2001; Morelli *et al.* 2003; McAlindon, 2006; Gregory *et al.* 2008]. Pharmacological management of OA has targeted symptoms of the disease rather than the underlying cause; analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) represent the mainstay of treatment [Altman, 2009]. These drugs generally decrease pain and stiffness and improve function. Although, any beneficial effects to the underlying cartilage and bone associated with the use of these drugs have not been demonstrated, they remain among the most widely prescribed drugs for OA therapy [Abramson, 2003]. Other treatment options are selective cyclooxygenase 2 (COX-2) inhibitors (rofecoxib) for pain management but these drugs are reported to be associated with gastrointestinal [Chan *et al.* 2010] and cardiovascular [Hsiao *et al.* 2009] adverse events. Matrix metalloproteinase (MMP) inhibitors have been studied for prevention of cartilage degradation but their clinical use has been limited by severe side effects [Nutti *et al.* 2009]. Intra-articular therapies like glucocorticoid and hyaluronan injections have been used for pain relief but recent observations suggest that they may accelerate cartilage breakdown [Gonzalez-Fuentes *et al.* 2010]. Basically, long-term use of available pharmacological agents to relieve OA symptoms is associated with serious adverse events and highlights the importance of developing safer alternative and prevention strategies. Such prevention and alternative/adjunct therapies could come from nutraceuticals. The term 'nutraceutical' was coined from 'nutrition' and 'pharmaceutical' in 1989 by DeFelice and was originally defined as 'a food (or part of the food) that provides medical or health benefits, including the prevention and/or treatment of a disease' [Kalra, 2003]. Zeisel distinguished whole foods from the bioactive chemical compounds derived from them and available in a nonfood matrix by using the terms 'functional foods' and 'nutraceuticals' respectively [Zeisel, 1999]. However, the term nutraceuticals has no regulatory definition and is not recognized by the US Food and Drug Administration (FDA), which uses the term 'dietary supplements' instead [Halsted, 2003]. OA as a chronic disease is a perfect paradigm of pathology of treatment, which could be addressed by nutraceuticals and dietary supplements. First, because nutraceuticals only have limited effects on their biological target and significant differences can be reached over time through a buildup

effect in which daily benefits add up and the time window for intervention is longer in chronic diseases. Second, nutraceuticals could provide a safer alternative because generally their use is devoid of adverse effects, although this is not universal. Public interest in the benefits provided by nutraceuticals such as medicinal herbs for OA is high and 47% of older adults use nonprescribed alternative medications (dietary supplements) for OA management [Ramsey *et al.* 2001]. The objective of this review is to discuss the scientific evidence supporting the efficacy of *Punica granatum* (pomegranate fruit), *Camellia sinensis* (green tea), *Uncaria tomentosa/Uncaria guianensis* (cat's claw), *Harpagophytum procumbens* (devil's claw), *Zingiber officinale* (ginger), *Boswellia serrata*, *Curcuma longa* (turmeric) and *Ananas comosus* in an attempt to understand the pivotal molecular targets involved in inflammation and the joint destruction process and to summarize their toxicities and efficacies for OA management. We have purposely not considered use of glucosamine sulphate and chondroitin sulphate because these compounds have been the main topic of numerous recent reviews [e.g. Häuselmann, 2001; Morelli *et al.* 2003; McAlindon 2006; Gregory *et al.* 2008]. For this review a literature search was performed of the Pubmed database and the scientific data with a direct link to OA were selected. We tried to include all the relevant references but the list may not be complete. If some published work is not included, the omission is unintentional.

### ***Punica granatum* (pomegranate)**

Pomegranate fruit [PF, Figure 1(A)] has been used for centuries to confer health benefits in many cultures. It is native to semitropical Asia and is now being cultivated in Afghanistan, India, China, Russia, Japan and the United States [Palaniswamy, 2003]. Modern use of PF-derived products includes treatment of AIDS [Lee and Watson, 1998], cancer [Kim *et al.* 2002], cosmetic use [Moayadi, 2004], allergic symptoms [Watanabe and Hatakoshi, 2002], cardiovascular conditions [Aviram and Dornfeld, 2003], oral hygiene [Kim and Kim, 2002] and as ophthalmic ointment [Bruijn *et al.* 2003]. Edible parts of the PF are composed of 80% juice and 20% seed [Singh *et al.* 2002b]. PF itself is a rich source of two types of polyphenolic compounds: anthocyanins (such as delphinidin, cyanidin, and pelargonidin) and hydrolyzable tannins (such as punicalin, pedunculagin, punicalagin, gallic,

A. *Punica granatum*B. *Camellia sinensis*C. *Uncaria tomentosa*D. *Uncaria guianensis*E. *Harpagophytum procumbens*F. *Zingiber officinale*G. *Boswellia serrata*H. *Curcuma longa*F. *Ananas comosus*

**Figure 1.** Medicinal fruits and herbs commonly used as dietary supplements for the treatment of osteoarthritis.

Sources: *Punica granatum*: <http://web.gccaz.edu/glendalelibrary/GLIS%20Punica%20granatum.htm>; *Camellia sinensis*: <http://www.evitamins.com/encyclopedia/assets/nutritional-supplement/green-tea/how-it-works>; *Uncaria tomentosa*: <http://www.europhyto.com/phyto-immune-defence/uncaria-tomentosa.asp>; *Uncaria guianensis*: [http://www.tradenote.net/claw\\_3/](http://www.tradenote.net/claw_3/); *Harpagophytum procumbens*: [http://www.agric.wa.gov.au/objtwr/imported\\_images/decplants/devilsclaw.gif](http://www.agric.wa.gov.au/objtwr/imported_images/decplants/devilsclaw.gif); *Zingiber officinale*: [http://medicinegardenwellness.com/shoppe/index.php?main\\_page=product\\_info&products\\_id=136](http://medicinegardenwellness.com/shoppe/index.php?main_page=product_info&products_id=136); *Boswellia serrata*: <http://www.sssbiotic.com/product/Boswellia.asp>; *Curcuma longa*: [http://realnaturals.net/real/index.php?page=shop.product\\_details&category\\_id=8&flypage=shop.flypage&product\\_id=24&option=com\\_virtuemart&Itemid=42](http://realnaturals.net/real/index.php?page=shop.product_details&category_id=8&flypage=shop.flypage&product_id=24&option=com_virtuemart&Itemid=42); *Ananas comosus*: [http://www.virboga.de/video/pics/Ananas\\_comosus\\_001802.jpg](http://www.virboga.de/video/pics/Ananas_comosus_001802.jpg)



and ellagic acid esters of glucose), which account for 92% of the antioxidant activity of the whole fruit [Singh *et al.* 2002b]. Anthocyanins are potent antioxidants, provide the brilliant color of the pomegranate juice, and their administration is reported to significantly decrease the malondialdehyde, hydroperoxide levels, lipid peroxidation and also enhance the activities of catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase in the liver [Sudheesh and Vijayalakshmi, 2005; Gil *et al.* 2000; Seeram and Nair, 2002]. Punicalagin has been shown to downregulate the expression of IL-2 from anti-CD3/anti-CD28-stimulated murine splenic CD4+ T cells and suppress mixed leukocyte reaction without exhibiting cytotoxicity to the cells via inhibition of nuclear factor of activated T cells [Lee *et al.* 2008]. This suggests that PF could be a potential candidate for the therapeutics of immune pathologies. We reported that pomegranate fruit extract (PFE)-derived bioavailable compounds suppress COX-2 enzyme activity and IL-1 $\beta$ -induced prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and nitric oxide (NO) production in OA chondrocytes [Shukla *et al.* 2008a]. We showed the inhibitory effects of PFE on IL-1 $\beta$ -induced proteoglycan breakdown in cartilage explants *in vitro* [Ahmed *et al.* 2005]. We also studied the efficacy of PFE in suppressing joint inflammation and damage using a collagen-induced arthritis mouse model. Consumption of PFE potently delayed the onset and reduced the incidence of collagen-induced arthritis in mice. Histopathology of the arthritic joints from PFE-fed mice demonstrated reduced joint infiltration by the inflammatory cells, and the destruction of bone and cartilage was alleviated with the decrease level of IL-6 [Shukla *et al.* 2008b]. Activation of mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)- $\kappa$ B is intimately associated with the increased expression of critical mediators of inflammation involved in OA pathogenesis, including the expression of IL-6 and IL-8 [Marcu *et al.* 2010; Firestein and Manning, 1999]. We recently showed that inhibition of IL-6 and IL-8 by PFE in PMACI (phorbol-12-myristate 13-acetate plus calcium ionophore A23187)-stimulated KU812 cells was mediated by inhibition of NF- $\kappa$ B, cJun-N-terminal kinases (JNKs) and the extracellular regulated kinase (ERK)-MAPK pathway [Rasheed *et al.* 2009a]. We also showed that PFE (6.25–25 mg/liter) inhibits the IL-1 $\beta$ -induced expression of MMP-1, MMP-3 and MMP-13 mRNA and proteins in OA chondrocytes, which was mediated by inhibiting the activation of p38-MAPK and JNK,

thereby reducing the available pool of activated c-Jun and activating transcription factor 2 [Ahmed *et al.* 2005]. Our recent study showed that PFE inhibits the IL-1 $\beta$ -induced activation of MKK3 and the p38 $\alpha$ -MAPK isoform and DNA binding activity of the runt-related transcription factor 2 in human chondrocytes [Rasheed *et al.* 2010]. These results provide an important insight into the molecular basis of the reported cartilage protective and arthritis inhibitory effects of pomegranate [Rasheed *et al.* 2010].

Repeated administration of high doses of PFE or its constituents ellagitannin and punicalagin to rats resulted in no toxicity in the dosages commonly used in traditional medicine systems [Cerdá *et al.* 2003]. An acute supplementation with PFE containing 330 mg of punicalagins and 22 mg of ellagic acid in 11 healthy volunteers led to the detection of ellagitannin metabolites, including ellagic acid, urolithin A, hydroxyl urolithin A, urolithin B, urolithin A glucuronide and dimethyl ellagic acid glucuronide in plasma after 2–24 h [Mertens-Talcott *et al.* 2006]. In healthy human volunteers who consumed 180 ml of a commercially available pomegranate juice containing 25 mg of ellagic acid, ellagic acid was detected at a maximum concentration of 32 ng/ml in the plasma after 1 h [Seeram *et al.* 2004]. We also showed that ellagic acid becomes bioavailable 2 h after oral ingestion of PFE [Shukla *et al.* 2008b]. Ellagic acid has been reported to inhibit the activation of NF- $\kappa$ B and the production of inflammatory mediators [Choi and Yan, 2009].

Overall, these data indicate that consumption of PF may be beneficial and of value in developing adjunct preventive and/or therapeutic approaches to the prevention and treatment of OA. However, clinical trials showing the benefit of pomegranate fruit or its extracts on inflammation and OA are lacking. Based on published evidence, further *in vivo* evaluation and clinical testing for the efficacy of PF in OA are needed [Khalifé and Zafarullah, 2011].

### ***Camellia sinensis* (green tea)**

Tea is a widely consumed beverage throughout the world and is reported to possess significant health-promoting effects (reviewed by Cabrera and colleagues and reference therein) [Cabrera *et al.* 2006]. Green tea [Figure 1(B)] contains proteins (15%), amino acids (4%), fiber (26%), other carbohydrates (7%), lipids (7%), pigments

(2%), minerals (5%), and phenolic compounds (catechins; 30%). The principal catechins found in green tea are epicatechin (6.4%), epicatechin-3-gallate (13.6%), epigallocatechin (19%) and epigallocatechin-3-gallate (EGCG; 59%), and account for 30–40% of its dry weight [Cabrera *et al.* 2006]. Green tea catechins, especially EGCG, have been reported to have antimutagenic [Cheng *et al.* 2009], anticancer [Johnson *et al.* 2010], antidiabetic [Zhang *et al.* 2010], anti-inflammatory [Danesi *et al.* 2010], antibacterial [Osterburg *et al.* 2009], antiviral [Xiao *et al.* 2008], antiobesity [Moon *et al.* 2007] and neuroprotective effects [Smith *et al.* 2010]. The strong antioxidant activity of green tea catechins has been widely demonstrated *in vitro* and *in vivo* [reviewed in Cabrera *et al.* 2003, 2006; Frei and Higdon, 2003]. Several studies have shown that EGCG blunts reactive oxygen species (ROS)-mediated cytotoxicity in human chondrocytes [Lo *et al.* 1996]. EGCG has been reported to increase the activities of catalase, superoxide dismutase, and glutathione peroxidase, which are essential components of a robust antioxidant defense system [Meng *et al.* 2001]. The potential disease-modifying effects of green tea on arthritis came to light through our study, when in a mouse model of rheumatoid arthritis (RA) induction and severity of arthritis was ameliorated by the prophylactic administration of green tea polyphenols in drinking water [Haqqi *et al.* 1999]. The anti-inflammatory and antiarthritic effects of EGCG are supported by several studies, indicating that green tea or its component EGCG can regulate the expression of cytokines, chemokines, MMPs, aggrecanase, ROS, NO, COX-2, and PGE<sub>2</sub> in cell types relevant to the pathogenesis of OA [reviewed in Singh *et al.* 2010; Akhtar and Haqqi, 2011]. We recently studied the global effect of EGCG on IL-1 $\beta$ -induced expression of cytokines and chemokines associated with OA pathogenesis in human chondrocytes. Our results suggest that the potential of EGCG in OA treatment and prevention may be related to its ability to globally suppress the IL-1 $\beta$ -induced inflammatory response in human chondrocytes [Akhtar and Haqqi, 2011]. Similarly, others have shown the inhibitory effects of EGCG on IL-1 $\beta$ , TNF $\alpha$ , IL-6, regulated upon activation normal T-cell expressed and secreted (RANTES), monocyte chemoattractant protein 1, epithelial neutrophil activating peptide-78, and growth-related oncogene  $\alpha$  expression in RA synovial fibroblasts and other cell types [Shen *et al.* 2009; Shin *et al.* 2006; Ahmed *et al.* 2006]. NF- $\kappa$ B and MAPKs are

involved in the regulation of genes important in high expression of several mediators of inflammation in OA [Marcu *et al.* 2010; Firestein and Manning, 1999]. EGCG has been reported to downregulate IL-6 expression by inducing alternative splicing of gp130 mRNA resulting in enhanced sgp130 production in RA synovial fibroblasts [Ahmed *et al.* 2008]. High levels of nitrates/nitrites have been found in the synovial fluid and serum of patients with OA [Farrell *et al.* 1992]. Studies from our laboratory have shown that EGCG inhibits NO production in IL-1 $\beta$ -stimulated human OA chondrocytes by suppressing the expression of inducible nitric oxide synthase (iNOS) mRNA, which was mediated in part by inhibition of NF- $\kappa$ B/p65 [Singh *et al.* 2002a, 2003]. COX-2 is the rate limiting enzyme in the production of PGE<sub>2</sub> and we reported that EGCG inhibited the PGE<sub>2</sub> production via inhibition of COX-2 expression in IL-1 $\beta$ -stimulated human OA chondrocytes [Ahmed *et al.* 2002]. However, Koeberle and colleagues reported that microsomal prostaglandin-E synthase 1 (mPGES-1) is a molecular target of EGCG, and inhibition of mPGES-1 is seemingly the predominant mechanism underlying suppression of cellular PGE<sub>2</sub> biosynthesis by EGCG *in vitro* [Koeberle *et al.* 2009]. Age-related accumulation of advanced glycation end products (AGEs) produced by the non-enzymatic glycation of macromolecules could be an important contributing factor for the development of OA. We recently reported that EGCG inhibited AGE-stimulated expression and production of TNF $\alpha$  and MMP-13 and this inhibitory effect was mediated at least in part via suppression of p38-MAPK, JNK, and NF- $\kappa$ B activation in human OA chondrocytes [Rasheed *et al.* 2009b]. EGCG has also been reported to inhibit the degradation of human cartilage proteoglycan and type II collagen and selectively inhibit the expression of ADAMTS-1, -4 and -5 (A Disintegrin And Metalloproteinase with Thrombospondin Motifs), which are known to cleave aggrecan [Vankemmelbeke *et al.* 2003]. Previously we showed that EGCG significantly inhibited the expression and activities of MMP-1 and MMP-13 in OA chondrocytes at physiologically achievable doses [Ahmed *et al.* 2004]. We and others have also shown that EGCG inhibits NF- $\kappa$ B activation by inhibition of proteasome activity, inhibition of I $\kappa$ B- $\alpha$  phosphorylation or inhibition of IKK- $\beta$  kinase activity in human OA chondrocytes [Singh *et al.* 2002a; Andriamanalijaona *et al.* 2005; Rasheed *et al.* 2009b]. We have also shown that EGCG selectively inhibited IL-1 $\beta$ -induced activation of

JNK, without significantly inhibiting the phosphorylation of p38-MAPK or ERK p44/ p42 in human OA chondrocytes [Singh *et al.* 2003]. Activator protein (AP)-1 transcription factor is a heterodimer of Jun and Fos proteins and plays an important role in the inflammatory response [Okamoto *et al.* 2008]. EGCG was found to inhibit the activation and DNA binding activity of AP-1 in human OA chondrocytes [Andriamanalijaona *et al.* 2005; Ahmed *et al.* 2002].

Tea consumption in general has not displayed any acute or chronic toxic effects, and in fact, it is health promoting. Schwarz and colleagues described regular tea drinkers as people with a generally healthy lifestyle [Schwarz *et al.* 1994]. However, harmful effects of 'overconsumption' of green tea cannot be ruled out and could be due to two main factors: caffeine content, and the presence of aluminum [Bruneton, 2001; Minoia *et al.* 1994]. Due to their relatively low absorption, rapid metabolism and elimination from the body, consumption of large amounts of flavonols is well tolerated by humans. At present the safe upper limit for chronic ingestion is about 1 g of flavonols/day [de Mejia *et al.* 2009]. The health benefits of tea consumption in preventing cancer have been intensively investigated [Khan and Mukhtar, 2008]. However, limited information is available about the protective effect of consumption of green tea or its bioactive components in OA. The bioavailability of EGCG or other catechins is relatively low and this may be due to the short half life, which ranges from 1.87 to 4.58 h for a 50–1600-mg dose (approximately 0.7–23 mg/kg body weight, based on 70 kg body weight) [Ullmann *et al.* 2003]. This might be overcome by repeated administration of EGCG because of its reported low toxicity and high tolerance by humans, even when given in doses as high as 1600 mg [van het Hof *et al.* 1999], which can achieve a maximum human plasma level of 7.6  $\mu\text{mol/liter}$  [Ullmann *et al.* 2003]. These studies point out that a pharmaceutically prepared formulation of green tea catechins could reach plasma levels equivalent to effective *in vitro* doses and can be used as adjunct therapy for the treatment and prevention of OA [Katiyar and Raman, 2011]. Currently, there is sufficient *in vitro* and *in vivo* data available showing the anti-inflammatory and antiarthritic potential of green tea and its constituent EGCG. Hence, more *in vivo* and clinical studies are required to evaluate its efficacy for OA.

### ***Uncaria tomentosa* and *Uncaria guianensis* (cat's claw)**

Cat's claw is a vine from the basin of the Amazon River. There are two species, *U. tomentosa* [Figure 1(C)] and *U. guianensis* [Figure 1(D)] that are traditionally used in South America for their anti-inflammatory properties. Cat's claw bark contains oxindole alkaloids (virtually absent in *U. guianensis*), polyphenols (flavonoids, proanthocyanidins, and tannins), quinovic acid  $\alpha$ -glycosides, pentacyclic alkaloids, and sterols [Ganzer *et al.* 2001]. Traditionally, the bark of cat's claw is prepared as a decoction, said to be beneficial in the treatment of arthritis, bursitis, lupus, chronic fatigue syndrome, and for stomach and intestine disorders [Foster, 1996; reviewed in Williams, 2001]. The most investigated of the active constituents in *U. tomentosa* extract for immune-modulating and anti-inflammatory effects are pentacyclic oxindole alkaloids [Williams, 2001]. However, the antioxidant and anti-inflammatory effects of the extracts of *U. tomentosa* and *U. guianensis* appear to be independent of their alkaloid content as in several assays both species of *Uncaria* were reported to be a strong free radical scavenger [Sandoval *et al.* 2000, 2002; reviewed in Rosenbaum *et al.* 2010]. We reported that *U. guianensis* in combination with *Lepidium meyenii* had chondroprotective properties in human cartilage. This action was mediated in part through upregulation of gene expression of the anabolic insulin-like growth factor 1 in IL-1 $\beta$ -stimulated chondrocytes [Miller *et al.* 2006]. Pretreatment with a hydroalcoholic extract (500  $\mu\text{g/ml}$ ) of *U. tomentosa* inhibited COX-1 and COX-2 via inhibition of the activation of NF- $\kappa$ B in Jurkat T cells [Aguilar *et al.* 2002]. *Uncaria* has been found to inhibit lipopolysaccharide (LPS)-induced iNOS gene expression, TNF $\alpha$ , PGE $_2$  and NO production, and cell death via inhibiting the activation of NF- $\kappa$ B [Sandoval-Chacón *et al.* 1998; Allen-Hall *et al.* 2010].

Recent studies support the use of *Uncaria* alone or in combination with other medicinal herbs for OA management [Piscoya *et al.* 2001; Miller *et al.* 2005; Mehta *et al.* 2007]. The available animal toxicological data did not indicate any severe toxicity by the oral intake of *Uncaria* [Piscoya *et al.* 2001; Valerio and Gonzales, 2005]. In some cases, mild nausea and diarrhea may occur upon ingestion of crude extracts [Piscoya *et al.* 2001; Santa Maria *et al.* 1997]. Several other groups have documented the safety and pharmacological profile of cat's claw in animal models and also showed that

cat's claw was non-toxic *in vitro* [Williams, 2001; Sandoval *et al.* 2002; Fetrow and Avila, 1999 and references therein]. Although in recommended dosages use of cat's claw is considered nontoxic, this aspect has not been rigorously investigated. Piscocya and colleagues evaluated the safety and side effects of *U. guianensis* extract in patients with OA of the knee [Piscocya *et al.* 2001]. Pain associated with activities of daily living was significantly reduced, however pain at rest or at night was not reduced during this 4-week trial period. In another study, a combination of a natural mineral supplement (Sierrasil, Sierra Mountain Minerals Inc., Bozeman, MT, USA) with a cat's claw extract (Vincaria, Rainforest Nutritionals Inc., Raleigh, NC, USA) showed therapeutic potential in mild to moderate knee OA [Miller *et al.* 2005]. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analog scale (VAS) scores were improved after 8 weeks compared with placebo. Rescue medication use was 28–23% lower in the herbomineral combination. Comparison of Reparagen (Rainforest Nutritionals, Inc., Raleigh, NC, USA) (1800 mg/day), a mixture of *U. guianensis* and *L. meyenii* with glucosamine sulfate (1500 mg/day) was also studied in patients with OA in a multicenter, randomized, double-blind trial. Reparagen and glucosamine sulfate produced substantial improvements in pain, stiffness and function in patients with mild to moderate OA as evidenced by improved WOMAC and VAS scores [Mehta *et al.* 2007]. More extensive studies employing animals and *in vitro* models are required before long-term controlled trials of *Uncaria* extracts (Table 1), or active compounds therein, can be initiated in a large number of human subjects to determine their long-term efficacy and safety profile.

### ***Harpagophytum procumbens* (devil's claw)**

For more than 50 years preparations of *H. procumbens* [devil's claw, Figure 1(E)] have been used in Europe for the treatment of rheumatic entities. Devil's claw is native to the southern part of the African continent and may be found in Namibia, Botswana, South Africa, Angola, Zambia, and Zimbabwe [Anonymous, 2008; Qi *et al.* 2006]. Historically, devil's claw has been used as an analgesic, for fevers and allergies, appetite stimulation, wounds and skin rashes, dyspepsia, liver and kidney disorders, as diuretic and sedative, and to treat degenerative disorders of the musculoskeletal system [Blumenthal, 1998; Stewart and Cole, 2005; Qi *et al.* 2006; Ragusa *et al.* 1984]. The

major chemical constituents of devil's claw are iridoid glycosides (primarily harpagoside, harpagide, and procumbide), sugars (mainly the tetrasaccharide, stachyose), triterpenoids (oleanolic and ursolic acid), phytosterols (primarily  $\beta$ -sitosterol), aromatic acids (caffeic, cinnamic, and chlorogenic acids), and flavonoids such as luteolin and kaempferol [Bradley, 1992]. Harpagoside, harpagide, and procumbide, found in the tubers of the plant, appear to be the most therapeutically important constituents. Whole-plant extracts appear to have a better therapeutic effect than those prepared from isolated parts [Qi *et al.* 2006]. A large body of evidence indicates that devil's claw may be an effective treatment for OA because of its pain-relieving and anti-inflammatory actions. Higher concentrations of serum oxygen-free radicals prevalent with arthritis may alter the oxidant/antioxidant balance, thus facilitating lipid peroxidation and leading to tissue damage [Jaswal *et al.* 2003]. Devil's claw extract has been shown to increase superoxide dismutase, catalase, glutathione peroxidase enzyme activities in a dose-dependent manner and a reduction in lipid peroxidation was also noted *in vivo*, which contribute to its antioxidant effects [Bhattacharya and Bhattacharya, 1998]. The flavonoids and plant phenols present in devil's claw extracts may be the constituents responsible for the observed antioxidant activity [Dugas *et al.* 2000; Sawa *et al.* 1999]. Devil's claw has been found to scavenge both superoxide and peroxy radicals [Langmead *et al.* 2002]. A recent study also showed that both root tuber extract of devil's claw and tincture are effective as free radical scavengers and inhibit LPS-induced nitrite levels in RAW 264.6 macrophages [Grant *et al.* 2009]. Significant antioxidant effects by an aqueous extract of devil's claw and by the flavonoid constituents luteolin and kaempferol have also been noted [Betancor-Fernández *et al.* 2003]. A dried aqueous extract (5 and 10 mg/kg) of devil's claw has been shown to exert a significant dose-dependent analgesic and anti-inflammatory effect in rats. However, carrageenan-induced paw edema was not affected by harpagoside, suggesting harpagoside may not have an anti-inflammatory effect at least in the doses used *in vivo* [Lanthers *et al.* 1992]. *In vitro* data also demonstrated that the active principle (sum of coactive constituents) of devil's claw inhibits not only inflammatory mediators such as iNOS and COX-2 mediated PGE<sub>2</sub> production [Fiebich *et al.* 2001; Jang *et al.* 2003; Huang *et al.* 2005] or leukotriene release [Loew *et al.* 2001] but also mediators of cartilage



**Table 1.** Summary of clinical trials on nutraceuticals and evidence of their safety and efficacy.

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
<i>Uncaria tomentosa</i> and <i>Uncaria guianensis</i> (cat's claw) [Piscoya et al. 2001]	Aqueous extract of cat's claw bark ( <i>U. guianensis</i> )	Treatment group (1 capsule 100 mg/ day). Placebo group 100 mg excipients without cat's claw	Multicenter randomized double-blind placebo-controlled trial, 4 weeks	Men with OA aged 45–75 with grade II–III of Kellgren/Lawrence classification ( <i>n</i> = 45; placebo group <i>n</i> = 15, treatment group <i>n</i> = 30)	Effective in knee OA (improvement in pain, disease indices)	No change in safety parameters and frequency of side effects (vomiting, dizziness and headache) were no different between groups
[Mehta et al. 2007]	Reparagen, a blend of two natural products – Vincaria (300 mg; <i>U. guianensis</i> ) and RNI 249 (1500 mg; <i>Lepidium meyenii</i> )	Treatment 1800 mg as two capsules twice a day. Glucosamine sulfate (1500 mg; comparator)	Multicenter randomized double-blind trial with positive control, 8 weeks	Patients with OA ( <i>n</i> = 95) men and women, Indian population >20 years of age, grade II–III of Kellgren/Lawrence classification and a baseline functional assessment of overall pain of at ≥40 mm and ≤80 mm on a 100 mm VAS score	Glucosamine (89%) and Reparagen (94%) showed substantial reduction in pain and significant benefits in WOMAC and VAS (45–62% reduction). Rescue medication use was significantly lower in the Reparagen group at each assessment period	Tolerability was excellent, no serious adverse events were noted and safety parameters were unchanged. Serum IGF-1 levels were unaltered by treatments
[Miller et al. 2005]	Sierrasil, a natural mineral product with or without Vincaria (containing <i>U. guianensis</i> extract)	High-dose Sierrasil (3 g/day), low-dose Sierrasil (2 g/day), low-dose Sierrasil (2 g/day) + Vincaria (100 mg/day) and placebo	Multicenter randomized double-blind placebo-controlled trial, 8 weeks	Patients with OA ( <i>n</i> = 107), men and women, Indian population >20 years of age, grade II–III of Kellgren/Lawrence classification and a baseline functional assessment of overall pain of at ≥50 mm on a 100 mm VAS score	Combination of Sierrasil and Vincaria was effective in relief of OA symptoms (improved physical activity, VAS pain score) and 28% reduction in rescue medication (paracetamol) was observed	Tolerability was good for all groups, no serious adverse events were noted and safety parameters remained unchanged



Table 1. (Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
[Bliddal <i>et al.</i> 2000]	<i>Zingiber officinale</i> (ginger) EV.ext-33 ginger extract	Ginger extract (170 mg). Ibuprofen (400 mg; comparator) as placebo, two capsules twice a day. Rescue medication acetaminophen 3 g/day throughout study	Randomized double-blind double-dummy placebo-controlled crossover study with a wash-out period of 1 week followed by 3 treatment periods in a randomized sequence, each of 3 weeks	Hip OA ( $n = 20$ ) and knee OA ( $n = 36$ ), aged 24–87 years, men and women (15:41)	Ranking of efficacy of three treatment periods for VAS and the Lequesne Functional Index was Ibuprofen>ginger extract>placebo. Statistically significant effect of ginger extract was only demonstrated by explorative statistical methods in the first period of treatment before crossover, while a significant difference was not observed in the study as a whole	No serious adverse events reported during the periods with active medications
[Altman and Marcussen, 2001]	EV.EXT 77 highly concentrated extract of 2 ginger species, <i>Z. officinale</i> and <i>Alpinia galanga</i>	Ginger extract (each capsule contained 255 mg of EV.EXT 77, extracted from 2,500–4,000 mg of dried ginger rhizomes and 500–1,500 mg of dried galanga rhizomes) versus placebo daily	Randomized double-blind placebo-controlled multicenter parallel-group trial, 6 weeks	Knee OA ( $n = 247$ ), moderate to severe pain, aged 45–72 years, men and women. Patients had to show OA grade II–IV of Kellgren/Lawrence classification	In 247 evaluated patients there was a reduction in knee pain on standing in ginger extract group compared with placebo (63% versus 50%). Secondary efficacy variables also showed reduction in knee pain on standing [24.5 versus 16.4 mm], reduction in knee pain after walking 50 ft (15.1 versus 8.7 mm), and reduction in the WOMAC OA index (12.9 versus 9.0 mm). Reduction in intake of rescue medication (acetaminophen) in the ginger extract group.	Good safety profile, with mostly mild GI adverse events in the ginger extract group compared with placebo group (59 patients versus 21 patients).

(Continued)

Table 1. (Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
[Kulkarni et al. 1991]	<i>Boswellia serrata</i> (Indian oilbaum) Articulin-F, herbomineral formulation containing roots of <i>Withania somnifera</i> (450 mg), the stem of <i>B. serrata</i> (100 mg), rhizomes of <i>Curcuma longa</i> (50 mg) and a zinc complex (50 mg)	Articulin-F, two capsules every 8 h	Randomized double-blind placebo-controlled crossover study, 3 months. After a 15-day wash-out period the patients were transferred to the other treatment for a further period of 3 months	Patients with OA ( $n = 42$ ) aged 48–50 years, men and women (10:32)	Treatment with the herbomineral formulation significantly altered only the severity of pain and disability score. Other parameters, including morning stiffness, Ritchie Articular Index, grip strength and joint score, showed favorable changes but were not statistically significant. Out of 42 patients, 39 preferred the herbomineral preparation, two the placebo and one was equivocal	Safety parameters were unchanged. Two patients complained of nausea, three with dermatitis and three with pain in the abdomen
[Kimmatkar et al. 2003]	<i>B. serrata</i> extract (333 mg) containing 65% organic acids or minimum 40% total boswellic acids	<i>Boswellia serrata</i> extract (300 mg/capsule). Placebo group starch powder (333 mg) three times a day	Randomized double-blind placebo-controlled crossover study, 8 weeks	Patients with knee OA ( $n = 30$ ), aged 45–72 years, men and women (12:18)	Reduced joint pain and swelling and improved the loss of function in terms of increased knee flexion, stair climbing and walking distance. No change was observed radiologically	<i>Boswellia serrata</i> was well tolerated except for minor GI complaints, including loose motions in one patient, epigastric pain and nausea in one patient.
[Sengupta et al. 2008]	5-Loxin, a novel <i>B. serrata</i> extract enriched with 30% 3-O-acetyl-11-keto-beta-boswellic acid	100 mg ( $n = 25$ ) or 250 mg ( $n = 25$ ) of 5-Loxin or a placebo ( $n = 25$ ) daily	Randomized double-blind placebo-controlled trial, 90 days	Patients with knee OA ( $n = 75$ ) aged 45–72 years, men and women. Severity was measured using VAS, WOMAC pain score and the Lequesne Functional Index	Both doses of 5-Loxin conferred significant improvements in pain and physical function scores, significant reduction in synovial fluid matrix metalloproteinase-3	Safety parameters were almost unchanged in the treatment groups compared with placebo

Table 1.(Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
[Sengupta <i>et al.</i> 2010]	BE-30 (5-Loxin; 30% 3-O-acetyl-11-keto- $\beta$ -boswellic acid) and Aflapin novel synergistic composition of O-acetyl-11-keto- $\beta$ -boswellic acid and <i>B. serrata</i> , nonvolatile oil	100 mg ( $n = 20$ ) of 5-Loxin or 100 mg ( $n = 20$ ) of Aflapin or a placebo ( $n = 20$ ) daily for 90 days	Randomized double-blind placebo-controlled trial, 90 days	Patients with moderate to mild knee OA ( $n = 60$ ) aged 40–80 years, both men and women. Severity was measured using VAS, WOMAC pain score and the Lequesne Functional Index	5-Loxin and Aflapin conferred clinically and statistically significant improvements in pain scores and physical function scores. Significant improvements in functional ability after 7 days with 100 mg Aflapin. Aflapin exhibited better efficacy compared with 5-Loxin	Safety parameters were unchanged compared with placebo group
<i>Curcuma longa</i> (turmeric)						
[Kulkarni <i>et al.</i> 1991]	Articulin-F, a herbomineral formulation containing roots of <i>W. somnifera</i> (450 mg), the stem of <i>B. serrata</i> (100 mg), rhizomes of <i>C. longa</i> (50 mg) and a zinc complex (50 mg)	Articulin-F, two capsules every 8 h	Randomized double-blind placebo-controlled crossover study, 3 months. After a 15-day wash-out period the patients were transferred to the other treatment for a further period of 3 months	Patients with OA ( $n = 42$ ), aged 48–50, men and women (10:32)	Treatment with the herbomineral formulation significantly altered only the severity of pain and disability score. Other parameters, including morning stiffness, Ritchie Articular Index, grip strength and joint score, showed favorable changes but were not statistically significant. Out of 42 patients, 39 preferred the herbomineral preparation, two the placebo and one was equivocal.	Safety parameters were unchanged. Two patients complained of nausea, three had dermatitis and three had pain in the abdomen

(Continued)

Table 1. (Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
<i>Harpagophytum procumbens</i> (devil's claw)						
[Bélaïche, 1982]	<i>Harpagophytum</i> extract (3000 mg)	<i>Harpagophytum</i> extract 3000 mg and 9000 mg/day containing herpagoside concentration of 90–270 mg/day	Observational 12–24 week study	Primary and secondary OA of knee, hip, finger and spine, men and women ( <i>n</i> = 630)	Dependent on the condition and dosage. Improvement seen 14.9–56.2% in patients at 3000 mg/day dose; and 13.9–39.08% at 9000 mg/day dose	Mild GI disturbances reported
[Lecomte and Costa, 1992]	<i>Harpagophytum</i> extract (2010 mg)	<i>Harpagophytum</i> extract (2010 mg) versus placebo group containing herpagoside concentration of 60 mg/day	Randomized double blind placebo-controlled trial, 8 weeks	Patients with OA ( <i>n</i> = 89)	Significant decrease in VAS pain score compared with placebo group after day 30 and 60. Significant improvement in mobility	No adverse effect reported. Safety profile normal
[Schmelz et al. 1997]	<i>Harpagophytum</i> extract (2500 mg)	<i>Harpagophytum</i> extract (2500 mg containing herpagoside concentration of 30 mg/day) versus placebo group	Randomized double blind placebo-controlled trial, 30 days	Patients with OA with chronic back pain and myalgia ( <i>n</i> = 100). Severity was measured using a Likert scale	<i>Harpagophytum</i> extract showed better results than placebo group. Out of all treated patients six showed strong pain and one mild pain compared with placebo, for which 32 had strong pain and nine medium pain	Safety parameters were unchanged compared with placebo group
[Rutten and Schafer, 2000]	<i>Harpagophytum</i> extract (960 mg)	<i>Harpagophytum</i> extract (960 mg/day) plus twice weekly injection	Observational 6-week study	Patients ( <i>n</i> = 99) with acute and chronic spinal disorder ( <i>n</i> = 23) and OA of knee ( <i>n</i> = 76)	68% of patients were pain free with significant reduction in symptoms	Good tolerability



Table 1. (Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
[Leblan <i>et al.</i> 2000]	<i>H. procumbens</i> extract (2610 mg)	<i>Harpagophytum</i> extract (2610 mg/day containing herpagoside concentration of 57 mg/day). Diacerhein (100–150 mg/day; comparator)	Multicenter randomized double-blind parallel-group study, 16 weeks	OA of hip and knee ( <i>n</i> = 122). Severity was measured using VAS pain score	<i>Harpagophytum</i> extract was equally effective as diacerhein	Significantly lower adverse effects in <i>Harpagophytum</i> extract treated group compared to Diacerhein. Most common adverse complications were diarrhea and flatulence.
[Chantre <i>et al.</i> 2000]	Harpadol containing cryoground powder <i>H. procumbens</i> (435 mg)	Harpadol group (6 capsules/day). Diacerhein (100 mg/day; comparator)	Randomized double-blind multicenter study, 4 months	Patients with OA of knee or hip ( <i>n</i> = 122), aged 30–79 years, had to show grade I–III on the Kellgren/Lawrence classification, a baseline functional assessment of overall pain of $\geq 50$ mm on a 100 mm VAS and a score of at least 4 on the Lequesne Functional Index	Spontaneous pain showed a significant improvement and reduction in the Lequesne Functional Index in both groups. No significant difference in efficacy between the two groups. Harpadol group used significantly less NSAIDs and antalgic drugs	The adverse effect reported was diarrhea, which was low in the Harpadol group (8.1%) compared with the diacerhein group (26.7%)
[Frerick <i>et al.</i> 2001]	<i>Harpagophytum</i> extract (960 mg)	<i>Harpagophytum</i> extract (960 mg/day containing herpagoside concentration of 30 mg/day) versus placebo group	Randomized double-blind placebo-controlled trial, 20 weeks	OA of hip ( <i>n</i> = 46). Severity was measured using WOMAC pain intensity	Significant improvement in WOMAC and stiffness scores in treatment group compared with placebo	An adverse reaction of one patient in treatment group, epigastric discomfort with suspected cholelithiasis

(Continued)

Table 1.(Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
[Chrubasik et al. 2002]	Doloteffin a proprietary <i>Harpagophytum</i> extract (60 mg tablets)	Doloteffin (60 mg) two tablets three times a day. Back group with nonspecific pain, knee OA pain group and hip OA pain group. Patients were allowed to continue with their concomitant treatments and to supplement medication with other analgesics	Observational 8-week study (post-market surveillance of the effectiveness and safety)	Total patients (n = 250) with nonspecific low back pain (n = 104) or OA pain in the knee (n = 85) or hip (n = 61). Men (30%) and women (70%). Severity was measured using Arhus Low Back Pain Index, WOMAC index	Multivariate analysis confirmed that in all groups, the generic and disease-specific outcome measures improved by week 4 and further by week 8. Hip group tended to improve more than the back group. Improvement in the knee group was less than the back group. Back patients who required NSAIDs during the 8 weeks used significantly more per patient than other two groups	About 10% of the patients suffered from minor adverse events that could possibly have been attributable to Doloteffin. Between 50% and 70% of the patients benefited from Doloteffin with few adverse effects
[Warnock et al. 2007]	<i>Harpagophytum</i> extract tablets (480 mg)	<i>Harpagophytum</i> extract tablets twice daily	Single group open study, 8 weeks	Mild to moderate rheumatic disorder having pain (rated 2-7 on 10-point scale) including patients with OA (n = 222), men (n = 82) and women (n = 140), aged 18-75 years. Effectiveness was assessed by numeric rating scales, WOMAC Index and the Algofunctional Hand Osteoarthritis Index and quality of life was measured by SF-12	Improvements in patient assessments of global pain, stiffness, function and quality of life. Reductions in mean pain scores for hand, wrist, elbow, shoulder, hip, knee and back pain. 60% of patients either reduced or stopped concomitant pain medication	No serious adverse events were reported and all were moderate GI complaints

Table 1.(Continued)

References	Product	Dose and comparator	Design and duration	Study population	Other outcome reported	Side effects
<i>Ananas comosus</i>						
[Tilwe <i>et al.</i> 2001]	Phlogenzym (contains the proteolytic enzymes bromelain, trypsin and rutin)	Bromelain (1890 mg/day). Diclofenac (100–150 mg/day; comparator)	Prospective randomized controlled single-blind study with positive control, 7 weeks	Patients with knee OA (n = 50) aged 40–75 years	Equivalence not tested. Reduction in pain, tenderness and swelling in both groups	Well tolerated, no specific adverse events reported
[Klein and Kullich, 2000]	Phlogenzym	Bromelain (540 mg/day). Diclofenac (100–150 mg/day; comparator)	Randomized double-blind trial with positive control, 4 weeks	Patients with knee OA (n = 73)	Reduction in pain indices by 80% at 4 weeks post treatment	No serious adverse events reported
[Singer <i>et al.</i> 2001]	Phlogenzym	Bromelain (540 mg/day). Diclofenac (100–150 mg/day; comparator)	Randomized double-blind controlled trial with positive control, 4 weeks	Patients with knee OA	Bromelain group showed reduction in pain score compared with diclofenac	No serious adverse events reported
[Brien <i>et al.</i> 2006]	Bromelain	Bromelain (800 mg/day) or placebo group	Randomized double-blind placebo-controlled trial, 12 weeks	Patients with moderate to severe knee OA (n = 47). Severity was measured using WOMAC and SF-36 questionnaires	No statistically significant differences were observed between groups for the primary outcome nor the WOMAC subscales or SF-36	Adverse events were generally mild in nature

GI, gastrointestinal; IGF-1, insulin-like growth factor 1; NSAID, nonsteroidal anti-inflammatory drug; OA, Osteoarthritis; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

destruction, such as TNF $\alpha$ , IL-1 $\beta$ , IL-6, MMPs, NO [Fiebich *et al.* 2001; Huang *et al.* 2005; Schulze-Tanzil *et al.* 2004a], and elastase [Boje *et al.* 2003]. Reported chondroprotective effects of devil's claw may be due to suppression of NF- $\kappa$ B activation, thereby inhibiting inflammation [Huang *et al.* 2005].

Devil's claw extract appears to be safe when used in appropriate dosages. The side effects are few, usually limited to gastrointestinal upset, dyspepsia and loss of taste; no long-term toxicities or drug-interactions are known [Vlachojannis *et al.* 2008]. Devil's claw extract exerts a peripheral analgesic effect as it has been demonstrated to decrease pain in knee and hip OA [reviewed in Ameye and Chee, 2006; Chrubasik *et al.* 2002; Chantre *et al.* 2000]. The effectiveness of certain devil's claw preparations has been tested with a daily dose of 360 mg of harpagoside (a coactive ingredient) in the treatment of painful OA of the hip, knee and nonspecific low back pain. Multivariate analysis confirmed that in all groups, both the generic and disease-specific outcome measures improved by week 4 and further by week 8 [Chrubasik *et al.* 2002]. *H. procumbens* powder was equally effective as diacerhein in reducing pain as measured using a 100 mm VAS. This study constitutes moderate evidence that 4 months' daily use of 2610 mg *H. procumbens* powder is not significantly different from 100 mg diacerhein, producing comparable improvements in pain [Leblan *et al.* 2000]. Studies on devil's claw extracts, containing 50–100 mg harpagoside daily, have shown the best results [Brien *et al.* 2006]. In a clinical study, 89 patients with OA were randomized to receive placebo or devil's claw at a total daily dose of 2010 mg/day for 8 weeks. The study identified that after 30 and 60 days of treatment, patients who received devil's claw had a significant reduction in pain ( $p = 0.018$  after 30 days and  $p = 0.012$  after 60 days of treatment) compared with placebo [Lecomte and Costa, 1992]. Effectiveness, safety and tolerability of *Harpagophytum* was studied in rheumatic disorders including OA for 8 weeks (259 patients). There were statistically significant ( $p < 0.0001$ ) improvements in patient assessment of global pain, stiffness, function and quality of life. There were also statistically significant reductions in mean pain scores for hand, wrist, elbow, shoulder, hip, knee and back pain [Warnock *et al.* 2007]. Numerous trials have been conducted using several devil's claw extracts for OA (Table 1 and rheumatism [Rutten and Schafer, 2000;

Bélaiche, 1982; Lecomte and Costa, 1992; Schmelz *et al.* 1997; Frerick *et al.* 2001; Chrubasik *et al.* 2002; Chantre *et al.* 2000; Leblan *et al.* 2000; Warnock *et al.* 2007]. Unfortunately, the results of many of the studies are of questionable value because of methodological flaws. However, devil's claw appears to be effective in the reduction of pain. More high-quality trials are needed to assess the effectiveness and efficacy of devil's claw to determine whether this is a beneficial remedy for the treatment of OA.

### **Zingiber officinale (ginger)**

Ginger, the rhizome of *Z. officinale* [Figure 1(F)], is one of the most widely used species of the ginger family (*Zingiberaceae*) and is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2,500 years in China and India for conditions such as headaches, motion sickness, nausea, vomiting, vascular conditions, cold and arthritis, and as an antimicrobial and antifungal [reviewed in White, 2007; Afzal *et al.* 2001]. Characterized in traditional Chinese medicine as spicy and hot, ginger is claimed to warm the body and treat cold extremities, improve a weak and tardy pulse, address a pale complexion, and strengthen the body after blood loss [Chang *et al.* 1995]. The major constituents of ginger include volatile oils, oleoresin (gingerol), linoleic acid and trace elements such as magnesium, phosphorus, and potassium. The pungent phenolic constituent of ginger, [6]-gingerol, inhibited LPS-induced iNOS expression and production of NO and other reactive nitrogen species in macrophages and blocked peroxynitrite-induced oxidation and nitration reactions *in vitro* [Ippoushi *et al.* 2003]. These results suggest that [6]-gingerol is a potent inhibitor of NO synthesis and also an effective protector against peroxynitrite-mediated damage. Another *in vitro* study showed that ginger extract was effective in inhibiting the production of PGE<sub>2</sub>, TNF $\alpha$ , and COX-2 expression in human synoviocytes by regulating NF- $\kappa$ B activation and degradation of its inhibitor I $\kappa$ B- $\alpha$  [Thomson *et al.* 2002]. Similarly, ginger extract decreased the IL-1 $\beta$  and LPS-induced production of NO and PGE<sub>2</sub> in OA cartilage [Shen *et al.* 2003]. It has also been reported to decrease the IL-1 $\beta$ -induced expression of TNF $\alpha$  expression and TNF $\alpha$ -induced production of COX-2 and activation of NF- $\kappa$ B in synoviocytes [Fronzoza *et al.* 2004]. Use of ginger extract also decreased carrageenan-induced edema in rats [Jana *et al.* 1999].



Ginger is on the US FDA's generally recognized as safe (GRAS) list. The British Herbal Compendium documents no adverse effects of ginger consumption [Bradley, 1990]. Ginger extract has been studied as an alternative to NSAID therapy for arthritic conditions and had moderately positive results (Table 1) [Altman and Marcussen, 2001; reviewed in Ameye and Chee, 2006]. A randomized, placebo-controlled, crossover study comparing ginger extracts and ibuprofen was performed and included 75 people with OA of the hip or knee [Bliddal *et al.* 2000]. Patients received 170 mg ginger extract, 400 mg ibuprofen, or placebo three times per day and were followed for 3 weeks. The study revealed significant improvement in symptoms for both groups before crossover; however, at the study's end there was no difference between ginger and placebo. No side effects were noted in the ginger group [Bliddal *et al.* 2000]. A randomized, double-blind, placebo-controlled trial studied the effects of ginger in the treatment of knee OA in 261 patients. During the treatment period patients ingested 255 mg of EV.EXT 77, a patented ginger and galangal, a spice that is closely related to ginger and is of the ginger extract, which contained 500–4000 mg of dried ginger rhizomes and 500–1500 mg of dried galangal rhizomes and was given twice daily. The primary endpoint of the study was pain on standing after 6 weeks. In the ginger extract group 63% versus 50% in the placebo group showed improvement ( $p < 0.048$ ). The study failed to show improvement in quality of life, decrease in the consumption of the rescue analgesic (acetaminophen). The dosage of medications used in this study was based empirically on what is typically consumed in Europe. Those receiving the ginger extract experienced more gastrointestinal side effects (116 events in 59 patients, 45%) than those who received placebo (28 events in 21 patients, 16%) [Altman and Marcussen, 2001]. While a significant number of patients experienced side effects, they were mild and mostly gastrointestinal conditions, dyspepsia, and nausea. In some studies, consumption of ginger extract was found to alleviate pain and associated symptoms in patients with OA. At present, ginger extract appears to be of limited efficacy for OA and current evidence is weak. However, these results are strong enough to advocate and support further studies using different doses and duration of treatment to assess the efficacy of ginger extract alone or in combination with other drugs for the treatment of OA.

### ***Boswellia serrata* (Indian olibaum)**

The *Boswellia* spp., which is native to India, Ethiopia, Somalia, and the Arabic peninsula, produce a gum resin that is known as olibanum (frankincense). The resin of *B. carteri* and *B. serrata* [Figure 1(G)] is used for the treatment of arthritis and other inflammatory diseases in the traditional medicine system in many countries [Safayhi and Ammon, 1997; Chevrier *et al.* 2005]. Besides their renowned anti-inflammatory activity, boswellic acids have been extensively investigated for their chemopreventive effects [Glaser *et al.* 1999; Zhao *et al.* 2003]. *B. frereana* extracts have also been reported to inhibit IL-1 $\beta$  and oncostatin M induced MMP-9 and MMP-13 expression in cartilage explants culture [Blain *et al.* 2010]. Further, boswellic acids have been reported as inhibitors of 5-lipoxygenase, the key enzyme for leukotriene biosynthesis in inflammatory disorders [Safayhi *et al.* 1992; Gupta *et al.* 1997] and human leukocyte elastase a member of serine proteases subfamily, which can hydrolyze collagen IV and elastin of the extracellular matrix [Safayhi and Ammon, 1997]. Thus, its use may be beneficial in inhibiting the progression of OA. Recently, we studied the efficacy of a herbal-leucine mix (HLM) containing *B. serrata* as one of the constituents. HLM was found to be an effective anti-inflammatory agent, as evidenced by strong inhibition of iNOS, MMP-9 and MMP-13 expression and NO production in IL-1 $\beta$ -stimulated OA chondrocytes *in vitro*. IL-1 $\beta$ -induced cartilage matrix breakdown was also inhibited by HLM, as evidenced by inhibition of glycosaminoglycan (GAG) release from human cartilage explants *in vitro*. These inhibitory effects of HLM on the inflammatory and cartilage catabolic factors were mediated by inhibiting the activation of NF- $\kappa$ B in human OA chondrocytes [Akhtar *et al.* 2011]. A novel composition of *B. serrata* extract (Aflapin, Indian Patent Application No. 2229/CHE/2008) showed anti-inflammatory and antiarthritic potential in a rat model. Aflapin showed significant protection from IL-1 $\beta$ -induced death of human primary chondrocytes, improved glycosaminoglycans production and inhibited MMP-3 production [Sengupta *et al.* 2011].

Toxicity studies of *Boswellia* in rats and primates showed no pathological changes in hematological, biochemical, or histological parameters at doses up to 1000 mg/kg and the LD50 was established at >2 g/kg [Singh and Atal, 1986]. A trial of a herbomineral formulation containing *B. serrata* as one of the components also showed significant

reduction in severity of pain and disability score in OA [Kulkarni *et al.* 1991]. A randomized clinical trial of multiplant ayurvedic drugs containing *B. serrata* demonstrated the potential efficacy and safety in the symptomatic treatment of knee OA over 32 weeks of therapy [Chopra *et al.* 2004]. A *B. serrata* extract (5-Loxin, US Patent publication no.: 2004/0073060A1) alone with O-acetyl-11-keto- $\beta$ -boswellic acid (AKBA) (Aflapin) or AKBA (30%; Loxin) alone was tested in patients with knee OA. Both treatments were effective in reducing pain and significantly improved physical functioning and stiffness scores. However, Aflapin was more effective than Loxin [Sengupta *et al.* 2010]. In a double-blind, placebo-controlled trial, *Boswellia* demonstrated a beneficial effect on knee OA [Kimmatkar *et al.* 2003]. Thirty patients were given either 1000 mg *Boswellia* daily or placebo in three divided doses for 8 weeks. Patients in the *Boswellia* group experienced a significant decrease in pain and swelling and increase in range of motion compared with placebo [Kimmatkar *et al.* 2003]. *B. serrata* extract containing 5-Loxin with 3-O-acetyl-11-keto- $\beta$ -boswellic acid (30%) inhibited the 5-lipoxygenase enzyme. A 90-day, placebo-controlled study was conducted to evaluate the efficacy and safety of 5-Loxin in the treatment of OA of the knee with 75 patients. The patients received either 100 mg ( $n = 25$ ) or 250 mg ( $n = 25$ ) of 5-Loxin daily or a placebo ( $n = 25$ ) for 90 days. Both doses of 5-Loxin conferred clinically and statistically significant improvements in pain scores and physical function scores in patients with OA. A significant reduction in synovial fluid MMP-3 was also noted. In comparison with placebo, the safety parameters were almost unchanged in the treatment groups and it was concluded that 5-Loxin reduces pain and improves physical functioning significantly in patients with OA; and it is safe for human consumption [Sengupta *et al.* 2008]. So far the *in vitro*, *in vivo* and clinical evidence (Table 1) for the effectiveness of *Boswellia* is encouraging but existing data do warrant further investigations [Moussaieff and Mechoulam, 2009].

### **Curcuma longa (turmeric)**

Turmeric is a widely used spice and coloring/flavoring agent that comes from the root of *C. longa* [Figure 1(H)] [Aggarwal and Shishodia, 2004]. Turmeric is on the GRAS substance list of the US FDA. In Ayurveda, turmeric has been used for various medicinal conditions including rhinitis, wound healing, common cold, skin

infections, liver and urinary tract diseases, and as a 'blood purifier' [Aggarwal and Shishodia, 2004; Chainani-Wu, 2003]. Turmeric was found to be effective even when given by different routes, including topical, oral or by inhalation, dependent on the intended use. The major constituent of turmeric is curcumin (diferuloylmethane), which constitutes up to 90% of total the curcuminoid content, with demethoxycurcumin and bis-demethoxycurcumin comprising the remainder [Aggarwal and Shishodia, 2004]. Curcumin has been extensively investigated due to its antitumor, antioxidant, anti-inflammatory, and analgesic properties [reviewed in Henrotin *et al.* 2010]. The anti-arthritic potential of curcumin has been widely studied *in vitro*. Curcumin was found to downregulate the catabolic and degradative effects in cartilage explants or chondrocytes stimulated with IL-1 $\beta$ , LPS, and TNF $\alpha$  and inhibited the production of MMP-3, MMP-9, and MMP-13 [Liacini *et al.* 2003; Schulze-Tanzil *et al.* 2004b; Shakibaei *et al.* 2007; Mathy-Hartert *et al.* 2009] and restored type II collagen and GAG synthesis [Shakibaei *et al.* 2005; Toegel *et al.* 2008]. In human chondrocytes, curcumin significantly inhibited MMP-3 and MMP-13 gene expression by inhibiting the JNK, AP-1 and NF- $\kappa$ B pathways [Liacini *et al.* 2002]. Other studies have shown that curcumin blocks LPS and interferon-induced production of NO and TNF $\alpha$  *in vitro* by inhibiting the activation of NF- $\kappa$ B and AP-1 [reviewed in Aggarwal and Shishodia, 2004]. Curcumin also inhibited the incorporation of arachidonic acid into membrane lipids, PGE<sub>2</sub> production, leukotriene B<sub>4</sub> and leukotriene C<sub>4</sub> synthesis, as well as the secretion of collagenase, elastase, and hyaluronidase by macrophages [Wallace, 2002].

Curcumin has also demonstrated antiapoptotic activity in chondrocytes [Shakibaei *et al.* 2005]. However, toxic effects of curcumin have been reported at high dosage (50 mM) without any beneficial effect on cartilage matrix [Toegel *et al.* 2008]. This study was performed using immortalized human OA chondrocytes, which can explain the discordance with previous studies. No clinical data are available for the effect of pure curcumin in OA. However, one study tested the clinical efficacy of a herbomineral formulation containing a component rich in curcumin in people with OA in a randomized, double-blind, placebo-controlled, crossover study [Kulkarni *et al.* 1991]. Positive results in pain management and mobility were obtained in the treated group. Use of curcumin for the

treatment of OA is of significant current research interest but more studies are needed before coming to any conclusion on its antiarthritis potential.

### **Ananas comosus**

Bromelain [Figure 1(I)] is a crude, aqueous extract obtained from the stems and immature fruits of the pineapple plant (*A. comosus* Merr, from the family of bromeliaceae), which contains a number of proteolytic enzymes. There are some *in vitro* and *in vivo* reports of antiedematous, anti-inflammatory, antithrombotic, and fibrinolytic effects of bromelain [Maurer, 2001; Brien *et al.* 2004]. Experimental evidence suggests that bromelain's action as an anti-inflammatory is mediated via decreasing levels of PGE<sub>2</sub>, thromboxane A<sub>2</sub> and through modulation of certain immune cell surface adhesion molecules, which play a role in the pathogenesis of arthritis [Hale *et al.* 2002; Kumakura *et al.* 1988]. Pretreatment of Sprague-Dawley rats with bromelains (10 mg/kg intravenously) completely prevented the potentiation of inflammation by ramipril [Caspritz *et al.* 1986]. Due to its efficacy after oral administration, its safety and lack of undesired side effects, bromelain has earned growing acceptance and compliance among patients as a phytotherapeutic drug. The majority of studies assessing bromelain for OA have been either open studies or equivalence studies designed to assess comparative effectiveness and safety against standard NSAID treatment (Table 1). The majority of the studies have methodological issues that make it difficult to draw definite conclusions. Three different preparations containing bromelain mixed with diverse enzymes have been tested in knee OA: Phlogenzym (Mucos Parma, Geretsried, Germany), which contains the proteolytic bromelain (90 mg/tablet), trypsin, and rutin; Wobenzym (Mucos Parma, Geretsried, Germany), which contains bromelain (45 mg/tablet), papain, trypsin, chymotrypsin, pancreatin, lipase, and amylase; and Wobenzym N (Mucos Parma, Geretsried, Germany), which contains bromelain (45 mg/tablet), trypsin, papain, chymotrypsin, pancreatin and rutin [reviewed in Brien *et al.* 2004]. In a double-blind, randomized, controlled trial of 73 patients with knee OA commercial proteolytic enzyme preparation (Phlogenzym) containing bromelain was compared with a dose of diclofenac (100–150 mg/day). An equivalent reduction in pain indices (80%) for the two treatments during 3 weeks of therapy and 4 weeks of follow up with few adverse reactions to either

treatment has been reported [Klein and Kullich, 2000]. In contrast, efficacy of bromelain (800 mg/day) in treating knee OA was studied in a randomized, double-blind placebo-controlled 12-week trial. No statistically significant differences were observed between groups for the primary outcome, nor the WOMAC subscales. This study suggests that bromelain is not efficacious as an adjunctive treatment of moderate to severe OA, but its limitations support the need for a follow-up study [Brien *et al.* 2006]. Two more published studies reported trials to assess the effectiveness of bromelain for knee OA [Singer *et al.* 2001; Tilwe *et al.* 2001]. These studies used 3- or 4-weeks period and doses of a standard treatment, diclofenac (150–100 mg/day); however, different doses of bromelain were tested (range from 540 to 1890 mg/day). Tilwe and colleagues compared a daily bromelain dose of 1890 mg/day (Phlogenzym) with the diclofenac comparative group [Tilwe *et al.* 2001]. Both groups showed reduced symptoms of pain, swelling and joint tenderness but the improvement was significantly better in the phlogenzym group. Singer and colleagues compared bromelain (Phlogenzym) at a dose of 540 mg/day with diclofenac [Singer *et al.* 2001]. This study demonstrated that bromelain showed significantly better improvement in both the primary outcome and summary pain scores compared with diclofenac. In conclusion, bromelain appears to have potential for the treatment of knee OA. However, there is not enough evidence to support recommending bromelain for the treatment of OA at this stage. It is important to note that there are a number of methodological issues that are common to the studies reported, including the possibility of inadequate power, duration of the study, inadequate treatment periods, inadequate or non-existent follow-up to monitor possible adverse drug reactions. Furthermore, the optimum dosage for this condition remains unclear. More trials of higher quality are needed to confirm the efficacy of bromelain in OA.

### **Conclusion**

At present, the current modalities for treating OA are symptomatic and have not been shown to block or reverse the cartilage degradation and joint destruction. This has resulted in heightened interest in the use of nutraceuticals for OA management. Many studies have been carried out to highlight the potency of several nutraceuticals and dietary supplements for the treatment of OA. Nutraceuticals offer a large variety of products

with a wide range of effects. They open new and large horizons for the treatment of degenerative joint diseases. Many nutraceuticals and dietary supplements are claimed to provide pain relief in OA and they have a great potential but there is a need for more substantial data. We have gathered studies and clinical trials of selected nutraceuticals and some results are really promising and encouraging. However, there is a need for serious, well designed, good quality clinical trials that can address most of the questions about the safety and efficacy of such fruit and plant-derived products. This could help in recommending them for OA treatment either alone or in combination with NSAIDs.

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### Conflicts of interest statement

The authors declare that there is no conflict of interest.

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