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Nutraceuticals-A New Approach in the treatment of Arthritis

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Abstract

Arthritis is a common disease in which the end-point results in joint replacement surgery. This article reviews the use of nutraceuticals as alternative treatments for pathological manifestations of arthritic disease. There is some evidence for beneficial effects of nutraceuticals, such as green tea, herbal extracts, chondroitin sulphate and glucosamine. However, in most cases, there is little scientific evidence at the cellular and molecular levels to explain their mechanisms of action.

KEYWORDS -

Introduction

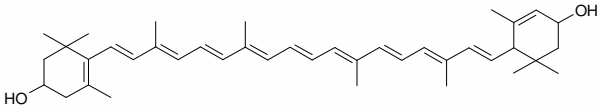
Inflammatory diseases including different types of rheumatic diseases are a major cause of morbidity of the working force throughout world. This has been called the 'King of Human Miseries' (1). Although rheumatism is one of the oldest known diseases of the mankind and affects a large percentage of population globally, no substantial progress was seen till the synthesis of aspirin in 1899 by the German Company Bayer, the hint of which also was obtained from a plant, the Willow bark (*Salix alba*) used world wide in folk medicine for the relief of aches, fever and rheumatic pain (2).

At present, pharmacological treatments for arthritic disease are generally palliative and antisymptomatic and none is effective at treating the underlying pathology. Hence, such treatments are incapable of affecting the progression of the disease. Therefore, over the time, there has arisen a need for alternative therapies to treat the painful symptoms of arthritis, and possibly slow disease progression. Recently, the use of nutraceuticals as 'self-help' therapies for sufferers of arthritis has become popular (3).

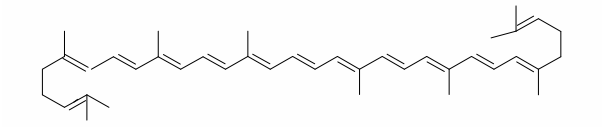
Nutraceuticals are in their formative years, but make no mistake, the nutraceutical boom is coming and it will be worth billions to the companies who define it. In a recent report, Data monitor placed the market at more than $16.7 billion (divided into the $8.8 billion functional foods segment and the $7.9 billion dietary supplement market). The optimistic Dr. Stephen DeFelice, Chairman of the Foundation for Innovation in Medicine, strongly believes nutraceuticals are worth $250 billion right now. Business Communications Corp., reports that ingredients for nutraceuticals are worth $1.2 billion. Clearly, the future is bright – and profitable -- for companies that develop successful nutraceuticals (4).

Lutein is a natural carotenoid that offers protection against age-related macular degeneration (AMD), the leading cause of adult blindness in the western world. Unfortunately, there is no cure or medicine available, but science advises that six mg per day of lutein may help to protect against AMD (4).

Lycopene offers tremendous nutraceutical opportunities. A study at Harvard by Dr. Giovannucci over a six year period involving 48,000 males produced outstanding results. The men with the diets highest in lycopene experienced a 45 percent reduction in prostate cancer (4).



LUTEIN



LYCOPENE

However, it is important to identify whether or not these nutraceutical therapies have any scientific basis, so that, in the future, similar properties can be exploited for drug discovery development in the treatment of degenerative joint diseases. This review describes the current scientific evidence supporting the use of nutraceuticals as therapeutic agents in the treatment of degenerative joint disease.

Nutraceuticals for the treatment of arthritic disease

Green tea extracts

One of the constituents of green tea is polyphenolic

compound termed catechins. The most abundant catechin in green tea is (−)-epigallocatechin 3-gallate (EGCG), but (−)-epigallocatechin, (−)-epicatechin 3-gallate (ECG) and (−)-epicatechin are also present. The most widely recognized properties of the green tea catechins are their antioxidant activities (5). Benefits of green tea have been recognized in cardiovascular disease (6, 7) and cancer (8). More recently, the benefits of the catechins extracted from green tea have been recognized in models of arthritic disease. Studies by Haqqi *et al*. (9) reported prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. More recently (10), *in vitro* models of cartilage degradation were used to study the effects of the individual catechins extracted from green tea. In this study, using a bovine *in vitro* model of cartilage degradation, it was shown that EGCG and ECG inhibit IL-1-induced proteoglycan release and type II collagen degradation in cartilage explants (10). Similarly, in a human *in vitro* model of cartilage degradation, EGCG suppressed IL-1β-induced iNOS (inducible nitric oxide synthase) mRNA and protein expression and production of nitric oxide, concomitant with attenuated activation of the transcription factor NF-κB (11). A recent study (12) has shown that the catechin gallate esters found in green tea potently inhibit the aggrecan-degrading activity of the aggrecanases ADAMTS-1, -4 and -5. Interestingly, the concentrations needed for aggrecanase inhibition were two orders of magnitude lower than those needed to inhibit either collagenase or another cell-surface enzyme involved in cytokine release, ADAM-10. Thus, these extracts of green tea appear to show a preferential inhibition of certain members of the ADAMTS group of proteolytic enzymes, the aggrecanases. It is not known whether or not these components of green tea are inhibiting these matrix proteases at the protein and/or gene expression level. From the above studies, molecular evidence appears to be emerging explaining why catechins extracted from green tea that exhibit both anti-inflammatory and chondroprotective effects might be beneficial to arthritis sufferers. However, further studies are required to determine whether or not oral consumption of green tea can lead to sufficiently high concentrations of catechins within the joint to mimic the effects that were observed in the *in vitro* studies.

Asian herbal remedies

For probably thousands of years, herbal extracts have been used to treat a wide variety of diseases manifested in the human population of Asia (6). The mechanisms by which these substances relieve symptoms of such diseases have been the subject of recent studies. Tao *et al*. (13) recently reported the beneficial effects of *Tripterygium wilfordii* Hook F in a clinical trial using patients with rheumatoid arthritis in which an ethanol-ethyl acetate extract of the plant suppressed symptoms of rheumatoid arthritis when compared with a placebo control. Recently, the beneficial effects of compound SKI 306X (a mixture of extracts from *Clematis mandshurica*, *Tricosanthes kirilowii* and *Prunella vulgaris*) were reported in an animal model of osteoarthritis and an *in vitro* model of arthritic disease (14). SKI 306X inhibited IL-1-induced proteoglycan degradation in rabbit articular cartilage explants; the same extract resulted in decreased lesions in a collagen-induced osteoarthritis model in rabbits. Extracts of these plants have traditionally been used in Chinese medicine to treat inflammatory conditions. However, the above and other studies indicate that there might be a scientific basis for the beneficial effects observed in arthritic diseases, although the complex nature of such extracts and their variability has thus far precluded elucidation of the active ingredients and their specific mechanisms of action.

Glucosamine and/or chondroitin sulphate

Nutraceuticals such as glucosamine and chondroitin sulphate are often used either separately or in combination for the treatment of arthritic ailments (15). The safety profile of these nutraceuticals has been recently reviewed (16). An analysis of marketed products indicated that the amounts of glucosamine and chondroitin sulphate present in the products sold often fell short of those declared on the label (17). These discrepancies very likely contribute to the confusion underlying the potential benefits of these nutraceuticals in treating arthritic disease. Nonetheless, the molecular basis underlying the benefits of using either glucosamine or chondroitin sulphate has not yet been determined. Glucosamine occurs naturally in the body and is one of the basic sugar components used in the synthesis of repeating disaccharide units that constitute all of the glycosaminoglycans (GAG) found on proteoglycans in articular cartilage (e.g. chondroitin sulphate, dermatan sulphate, keratan sulphate, heparan sulphate and also hyaluronan). Earlier in 1971, the effects of glucosamine on articular cartilage were established (18). More recently, several studies (15–29) have been carried out to investigate the effects of glucosamine and its derivatives on cartilage metabolism and its degradation in *in vitro* models, animal models of cartilage degradation and clinical studies. However, collectively, the studies investigating the effects of glucosamine have provided a wide range of variable results. There is also significant confusion for the best source of glucosamine. Review of the numerous research papers showed effects of several different forms of glucosamine on cartilage metabolism which includes sulphate esters of glucosamine (23), versus the hydrochloric (21, 23) and sulphuric (25–27) acid salts of glucosamine. It is likely that specific glucosamine salts have little overall effect upon outcome due to dissociation either in the gut (for *in vivo* studies) or in tissue culture media (for *in*

vitro investigations). Glucosamine sulphate was the preferred derivative used in a recent clinical trial (26); however, this decision is very difficult to reconcile given that the only difference between glucosamine hydrochloride and glucosamine sulphate is the acid (hydrochloric acid versus sulphuric acid, respectively) that was used to hydrolyse the chitin starting material (lobster, crab or prawn shells are common sources of the chitin used to produce glucosamine salts). Clearly, the acid salt ion (chloride or sulphate) will make no difference once the nutraceutical reaches the stomach where the endogenous stomach hydrochloric acid will make both of these glucosamine derivatives to glucosamine hydrochloride. Recent studies have investigated the molecular mechanisms of how glucosamine might exert its effects on cartilage metabolism. Gouze *et al*. (22) and Largo *et al*. (28) showed that glucosamine can inhibit the IL-1-induced activation of the transcription factor NF-κB. Ilic *et al*. In recent studies (29) investigated the effects of long-term exposure to both glucosamine and mannosamine on prevention of articular cartilage proteoglycan degradation. Inhibition of proteoglycan degradation was demonstrated at high concentrations of both glucosamine and mannosamine (≥5 mM). It was also shown that these effects were not acting directly on the soluble degradative enzyme 'aggrecanase' itself but more likely on some intracellular signalling molecule, as suggested by some workers (22, 28). Further studies are needed to find the effect of oral glucosamine in cartilage metabolism within the joint. In all *in vitro* studies (15–29), the glucosamine was added at supraphysiological concentrations to show any 'chondroprotective' effects on cartilage metabolism. Thus, it is hard to reconcile how such levels could be attained in either plasma or tissues *in vivo* after oral consumption of these nutraceuticals. The above examples emphasize some of the variabilities seen in glucosamine studies and are likely to be due to the different culture conditions used, the source of the cartilage used, the source of the glucosamine and its derivatives, and the concentration of glucosamine added. The outcomes of clinical trials exploring the efficacy of both glucosamine and chondroitin sulphate in the treatment of osteoarthritis performed over the past 22 years have been chronologically reviewed (30–32). The goal of these reviews was to assess both the potential symptom-modifying (e.g. pain and function outcomes) and structure-modifying (e.g. change in joint space narrowing) activities of glucosamine and chondroitin sulphate in alleviating symptoms of osteoarthritis of the knee using outcome-oriented meta-analysis of these randomized clinical trials. The general 'take-home' message from these reviews is that glucosamine ingestion has shown efficacy in both narrowing joint space and some symptom modifying parameters. However, although chondroitin sulphate ingestion showed similar symptom-modifying effects, the structure-modifying benefits still need to be confirmed. These clinical findings, clearly demonstrate that there is a need for more basic research aimed at elucidating the cellular and molecular mechanisms involved with these two interesting nutraceuticals.

Conclusions

At present, there are no pharmaceutical-based treatments that have been proven to slow the progression of cartilage destruction seen in arthritic disease. Current treatments targeting inflammatory aspects of the disease are expensive and there are long waiting lists for joint replacement surgery. Therefore, there has been continued interest in alternative therapies such as; the use of nutraceuticals in the treatment of arthritic disease that include green tea extracts, glucosamine and extracts from herbal plants (used in Asian medicine). Current research into these nutraceuticals indicates that they might alleviate the inflammation and tissue degradation experienced in arthritic disease. However, further studies and additional clinical trials are needed to elucidate how these molecules actually modulate cartilage cellular metabolism in a chondroprotective manner. Once the molecular mechanisms of inhibiting inflammation and degradation by nutraceuticals have been elucidated, their beneficial properties might further be exploited with the development of new drug targets to treat the inflammatory symptoms of arthritis as well as to potentially slow the progression of cartilage matrix degeneration in the pathogenesis of the disease.

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