Abstract

Introduction

Articular cartilage is critical to the normal function of human joints. Articular cartilage provides lubrication and load bearing to permit friction-free locomotion and movement. It is a uniquely avascular, aneural, and alymphatic tissue and consists of an extensive extracellular matrix (ECM) with relatively few chondrocytes. Articular cartilage has a limited capacity to repair itself because of its avascular nature. Cartilage repair is dependent on the production of extracellular matrix by chondrocytes, and is stimulated by anabolic morphogenic proteins, such as bone morphogenetic proteins (BMPs), transforming growth factor (TGF-β), and growth factors such as insulin-like growth factor (IGF-1). Catabolic cytokines such as interleukin-1 beta (IL-1β), and tumour necrosis factor alpha (TNFα) degrade the cartilage extracellular matrix. A dynamic change in the cartilage homeostasis precedes the initiation and progression of osteoarthritis. Osteoarthritis is an unmet clinical challenge. Osteoarthritis is the most common form of arthritis and occurs in a large segment of aging individuals. There is no effective treatment for osteoarthritis, other than pain-amelioration by non-steroidal anti-inflammatory drugs. These drugs are notorious for their deleterious side effects. Therefore the drug of choice for treating osteoarthritis should be one that has anti-inflammatory properties with no side effects. Resveratrol, a component of red wine, has potent anti-inflammatory properties. In this critical review we summarize the potential actions of resveratrol in articular cartilage.

Conclusion

The anti-inflammatory effects of resveratrol have been shown in several animal model studies. Resveratrol might be the relevant compound for potential use in osteoarthritis therapy.

Introduction

Osteoarthritis (OA) is the most common form of arthritis affecting millions of people worldwide and a major cause of disability in the elderly, as well as a burden on health care resources. The aetiology of this disorder is unknown. Osteoarthritis is a chronic disease characterized by degeneration of the articular cartilage and subchondral bone affecting surrounding tissues and synovium and most commonly affects females and the weight-bearing joints such as the knee joint, especially in overweight and obese patients. Other risk factors associated with developing OA, besides obesity and overweight, are listed in table 1.

Besides the risks listed in table 1, according to a literature review other diseases associated with developing OA include cardiovascular diseases, diabetes mellitus, cancer and human immunodeficiency virus (HIV) related pulmonary tuberculosis. In a study conducted by Lees it was demonstrated that OA also affects older animals and has significant consequences for companion animal mobility and welfare.

It is well known that the current treatment of OA focuses mainly on alleviation of pain and loss of joint function. Specific medication, such as paracetamol and aspirin, is commonly used to treat the pain from OA. In more severe cases, non-steroidal anti-inflammatory (NSAID) drugs such as ibuprofen, diclofenac and naproxen may reduce both pain and inflammation.

Even though paracetamol does not reduce the inflammation, at a dose of four grams per day it can affect liver function and may cause cancer of the liver. NSAID drugs may also cause gastrointestinal discomfort, cramping, peptic ulcers and diarrhoea. In addition, diclofenac has been found to cause damage to the articular cartilage. It is well documented that no current treatment has restored injured cartilage to its original form with normal functional and structural properties.

There is a wealth of evidence showing that allogeneic or autogenic osteochondral transplants have been used to repair damaged cartilage, but these approaches have several disadvantages, including difficulty in maintaining tissue viability, the small amount of cartilage available in the body for transplantation to other sites, as well as the potential for disease transmission and the creation of a new wound at the autograft donor site.

There is therefore a dire need to detect cartilage loss before it is severe. Natural products do not have the disadvantages mentioned. This offers novel and alternative treatment opportunities for OA. The existence of traditional and complementary medicine is known to be a fertile ground source of western medicine.

Subbramaih and colleagues demonstrated that resveratrol (RSV) has a specific inhibitory factor of COX-2 and cytokine-induced NF-κB activation, therefore it might have potential in the
treatment of OA. A novel treatment for OA is with cyclooxygenase-2 (COX-2) inhibitors. Therefore, the purpose of this review is to focus on the potential role of RSV in treating OA.

**Discussion**

**Chemistry of resveratrol**

Takaoka made the key discovery enabling isolation of RSV from the roots of white hellebore in 1940. Resveratrol (3,5,4-trihydroxystilbene) is a polyphenolic phytoalexin compound found in various plants, such as grape vines, berries, peanuts, seeds and roots; the highest concentration is in the skin of red grapes (Figure 1). The structure is characterized by two double bonds and exists in two isoforms, namely trans-RSV and cis-RSV. The trans-isomer is the more stable form. Trans-to-cis isomerization is facilitated by UV light and high pH, while the reverse isomerization is facilitated by visible light, high temperature or low pH. Resveratrol was synthesized through a series of fluorinated analogues (Figure 2). Heck reaction methods were used for the synthesis of RSV. These reaction methods involved the synthesis of compounds 2-8, while compound 9 was synthesized via acetoxy analogue 7 (Table 2).

**Biological activity of resveratrol**

Scientific research of RSV has been explored over the past decade for its anti-inflammatory, anti-oxidant, anticarcinogenic and cardioprotective properties. Resveratrol might also prolong the lifespan, prevent diabetes mellitus and neurodegenerative diseases such as Alzheimer’s disease, as well as cell proliferation and apoptosis in the acute and chronic phases of OA.

In studies that were conducted in a rat model, RSV was absorbed in the duodenum as in humans.

However, most of the absorbed RSV was in the conjugated glucuronide form when compared to a small amount of unconjugated RSV and RSV sulphate. Resveratrol is distributed in all organs, among others the liver, duodenum, spleen, heart, brain, testis and kidney. Resveratrol is glucoronated in the human liver and sulphated in both the liver and duodenum.

The derivatives of RSV glucuronidation are mostly the following trans-RSV-3-O-glucuronide, trans-RSV-4-O-glucuronide and trans-RSV-3-O-sulfate.

Resveratrol demonstrates various actions and targets a large number of intracellular molecules.

**Table 1: Risk factors in associated with osteoarthritis**

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Mutations in cartilage-specific matrix proteins (usually associated with chondrodysplasias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sports injuries</td>
<td>Certain sports such as running or football put undue pressure on the knee joints. Injuries resulting in broken ligaments can lead to instability of the joint and over time to wear on the cartilage and eventually osteoarthritis</td>
</tr>
<tr>
<td>Inflammatory joint disease</td>
<td>Chronic forms of arthritis such as gout and rheumatoid arthritis</td>
</tr>
<tr>
<td>Injury to joints</td>
<td>As the result of an accident, for example car accident</td>
</tr>
</tbody>
</table>

**Figure 1:** Some of the natural sources of resveratrol.

**Figure 2:** Structure of resveratrol.
Effects of resveratrol on articular cartilage

Osteoarthritis is a chronic disease characterized by the progressive degeneration of articular cartilage, causing pain, loss of articular function and abnormal remodelling of cartilage extracellular matrix (ECM).

Articular cartilage consists of cells called chondrocytes, embedded in an ECM consisting of a macromolecular framework of collagen and proteoglycan filled with water. Chondrocytes are predominantly spherical cells, located in the matrix, which originate from mesenchymal stem cells of the bone marrow. The general opinion is that chondrocytes are essential to the maintenance of the ECM, secreting both the components of the matrix and enzymes that degrade the matrix. Chondrocytes from different cartilage zones differ in size, shape and metabolic activity but they all possess the organelles responsible for matrix synthesis, including endoplasmic reticulum and Golgi membrane. Since articular cartilage is avascular, chondrocytes obtain nutrients through diffusion. Nutrients first enter the synovial tissue, then the synovial fluid and finally the cartilage matrix.

In growth plate chondrocytes are responsible for the growth of long bones through endochondral ossification. Chondrocytes degrade ECM macromolecules, while the matrix in turn maintains a state of equilibrium between the cellular environment and the structure of cartilage. The matrix of the articular cartilage consists of two main components: the tissue fluid and the framework of structural macromolecules that gives cartilage its form and stability. The interaction of the tissue fluid with the macromolecular framework gives the tissue its mechanical properties of stiffness and resilience. Many of these molecules are proteoglycans, whereas others are non-glycosylated proteins and non-collagenous proteins.

Resveratrol has anti-inflammatory properties that regulate expression of a series of intracellular signalling proteins, cellular proliferation, inflammation and apoptosis acute and chronic phases of OA. It is well documented that pro-inflammatory cytokines such IL-1β and TNF-α up regulate the catabolic enzymes such as matrix metalloproteinases (MMPs) and cyclooxygenase-2 (COX-2) through activation of NF-kB, which leads to the degradation of cartilage, joint inflammation and pathogenesis of cartilage. The treatment of OA by COX inhibitors is well known. Although the most important therapy for the treatment of OA is pharmacologic therapy, which focuses primarily on the use of analgesics and anti-inflammatory medication for pain relief and neither targets secondary prevention and does not results in sustained improvement in pain, disability and disease progression.

A study conducted by Subbaram and colleagues showed that RSV can indeed suppresses COX-2 and the production of prostaglandin E2. In support of that, Elmali et al. demonstrated in an in vivo model that intra-articular injections of RSV had a chondroprotective effect on the cartilage in rabbit inflammatory arthritis. Therefore RSV reduces cartilage tissue destruction and may protect articular cartilage against the initiation and progression of OA. In the synoviocytes from arthritis patients, cells were treated with RSV, resulting in increased cysteine protease caspase-3 activity, cell proliferation and induction of cell apoptosis.

Resveratrol inhibits the morphological alternations of chondrocytes, suppresses IL-1β induced, suppresses NF-kB dependent proinflammatory, inhibits membrane-bound IL-1β, matrix-degrading gene products including MMPs and also mature IL-1β protein production of chondrocytes, while on the other hand, in vitro studies demonstrated that IL-1β induced inhibited chondrocyte proliferation. The authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Table 2: Fluorinated resveratrol derivatives 2-10^3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Isomer</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(E)</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>(E)</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>(E)</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>F</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>(E)</td>
<td>F</td>
<td>F</td>
<td>OCH₃</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>(E)</td>
<td>OHCH₃</td>
<td>OHCH₃</td>
<td>F</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>(E)</td>
<td>F</td>
<td>F</td>
<td>OCOCH₃</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>(E)</td>
<td>OCOCH₃</td>
<td>OCOCH₃</td>
<td>F</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>(E)</td>
<td>F</td>
<td>F</td>
<td>OH</td>
<td>81^</td>
</tr>
<tr>
<td>10</td>
<td>(E)</td>
<td>OH</td>
<td>OCOCH₃</td>
<td>F</td>
<td>76^</td>
</tr>
</tbody>
</table>

^Indicates yield of deprotection step

For citation purposes: Motaung SCKM. The potential role of resveratrol in ameliorating osteoarthritis and resultant joint damage. OA Arthritis 2013 May 01;1(2):11.
RSV had a protective effect on ovariectomized rat bone mineral density. According to the above-mentioned studies, RSV can be considered as a candidate for skeletal and bone formation molecules.

**Conclusion**

In this review we have surveyed the potential role of RSV in the future development of treatment of various types of chronic and acute OA. Even though RSV cannot be claimed to be a cure for OA, the bioactivity of this compound is alluring. Some of the recommendations for the use of RSV are:

- Inhibition of angiogenesis
- Stimulation of osteogenesis
- Modulation of cell proliferation and apoptosis
- Inhibition of metastasis
- Suppression of inflammation
- Modulation of DNA damage
- Estrogenic activity
- Modulation of xenobiotic metabolism
- Modulation of redox status

Resveratrol may reduce the side effects of non-steroidal anti-inflammatory drugs that are currently used and may thus offer new opportunities for the treatment of OA. In spite of the new exciting studies that have already been done, there is a relative lack of clinical trials. Clinical trials using RSV in early OA should enjoy very high priority.

**Acknowledgement**

I would like to thank Prof Hari Reddi from the Department of Orthopedic Surgery, School of Medicine, University of California-Davis, Sacramento, USA for his help, advice and comments on this article. This work was supported by an Emerging Grant, from Tshwane University of Technology, Tshwane, South Africa.

**Abbreviation list**

OA, Osteoarthritis; NSAID, non-steroid anti-inflammatory; HIV, human immunodeficiency virus; Cox-2, cyclooxygenase-2; MMPs, metalloproteinases; RSV, resveratrol; ECM, extracellular matrix; TNF, tumor necrosis factor; IL, interleukin; BMPs, bone morphogenetic proteins; TGF-β, transforming growth factor; IGF-1, insulin-like growth factor

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**FOR CITATION PURPOSES:** Motaung SCKM. The potential role of resveratrol in ameliorating osteoarthritis and resultant joint damage. OA Arthritis 2013 May 01;1(2):11.

Competing interests: None declared. Conflict of design: manuscripts preparation, read and approved the final manuscript.

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