Rheumatology and Orthopedic Medicine

open access text

Mini Review

Natural products as potential therapeutics for the temporomandibular joint arthritis: a mini review

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Abstract

Temporomandibular joint arthritis reduces quality of life and its genesis is poorly understood. Conventional therapy involves systemic analgesic and anti-inflammatory medication but side-effects are the reasons why we aim to develop alternative approaches. Natural products are of great relevance and here we review some phenolic and polysaccharide rich compounds which have shown positive results in animal models of TMJ arthritis.

Introduction

Temporomandibular (TMJ) joint disorders consist of a group of clinical conditions that lead to painful states, limiting daily activities and reducing quality of life. Among the many types of TMJ disorders, TMJ arthritis is a clinical condition that possesses inflammatory components. However, the mechanisms underlying its pathogenesis is poorly understood which justifies the choice of conservative and reversible therapies such as systemic medication with analgesics and non-steroidal anti-inflammatory drugs (NSAIDS) as a first choice for pain management [1-3].

Albeit drug therapy is widely recommended to modulate pain and inflammatory states, it is relevant to consider the possibilities of side-effects that may arise as a consequence of it. This scenario opens avenues for the search of novel therapeutics that are capable of offering the same pharmacological effects but with a less addictive or toxic profile. Thus, natural occurring products emerge as potential tools for developing drugs just as efficient as the conventional ones. However, the possibility of reducing side-effects becomes a prominent feature of natural products in the management of inflammatory diseases [3]. Here, we aim to discuss the possibilities of use of natural products to treat temporomandibular joint arthritis.

Literature review

Attempting to validate the use of natural products, many studies have reported the effects of different potential therapeutics on experimental models of TMJ arthritis. Abbey et al., 2007 reported the beneficial effects of a *Theobroma cacao* bean extract enriched for polyphenols on an *in vivo* model of TMJ inflammation as well as trigeminal ganglia cultures. Their results suggested that the natural product tested could repress stimulated calcitonin gene-related peptide (CGRP) by a mechanism that could have the involvement of calcium channel activity blockade [4].

Claiming the underutilization of natural products to treat inflammatory conditions, Cady et al., 2010 investigated the effects of grape seed extract on neurons and glia in trigeminal ganglia and trigeminal nucleus caudalis in response to persistent temporomandibular joint inflammation. In response to grape seed extract, basal expression of mitogen-activated protein kinase phosphatase 1 was elevated in neurons and glia in trigeminal ganglia and trigeminal nucleus caudalis, and expression of the glutamate aspartate transporter was increased in spinal glia. Rats on a normal diet injected with adjuvant exhibited greater basal levels of phosphorylated-p38 in trigeminal ganglia neurons and spinal neurons and microglia.

However, adjuvant-stimulated levels of phosphorylated-p38, OX-42, and glial fibrillary acidic protein were significantly repressed in extract treated animals. Furthermore, grape seed extract suppressed basal expression of the neuropeptide calcitonin gene-related peptide in spinal neurons. These results provided evidence that grape seed extract may be beneficial as a natural therapeutic option for temporomandibular joint disorders by suppressing development of peripheral and central sensitization [5].

Using a zymosan-induced TMJ model of arthritis, Rivanor et al., 2014 investigated the analgesic and anti-inflammatory effects of a seaweed lectin from *Caulerpa cupressoides* on zymosan-induced TMJ arthritis. It reduced mechanical threshold, inhibited leukocyte influx into the TMJ, and decreased TNF-α and IL-1β in the TMJ, revealing a valuable alternative therapeutic of TMJ inflammatory conditions [6].

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Key words: *TMJ arthritis, inflammation, natural products*

Received: December 16, 2016; **Accepted:** January 13, 2017; **Published:** January 17, 2017

Val et al., 2014 investigated the efficacy and the sub-chronic toxicity of *Tephrosia toxicaria* Pers. It partially reversed the head withdrawal threshold, the number of cells, myeloperoxidase activity and the inflammatory cell influx in the synovial membrane. TMJ immunohistochemical analyses treated with *T. toxicaria* showed increased heme oxygenase-1 expression. *T. toxicaria* did not produce any signs of toxicity and effectively decreased zymosan-induced TMJ inflammatory hypernociception dependent upon the heme oxygenase-1 pathway integrity [7].

Freitas et al., 2016 evaluated the *Abelmoschus esculentus* lectin efficacy and the mechanism of action through which it exerts anti-inflammatory activity. It increased inflammatory nociceptive threshold, reduced leukocyte influx along with MPO activity, leukocyte influx into the synovial membrane, and Evans Blue extravasation. It promoted HO-1 overexpression while decreased TNF-α and IL-1β expression in the TMJ tissue and trigeminal ganglion [8]. These natural products showed analgesic and anti-inflammatory activity, promoting new perspectives for drug design and development of novel therapeutics.

So far, we can find many studies on the potential use of natural products to tackle pain and inflammation, but there are limitations of use regarding these novel therapeutics. The major one would be determining what component of a raw extract plays a role in reducing painful and inflammatory conditions. Secondly, seasons can also affect the synthesis patterns of those phytochemicals present in plants or marine organisms, leading to differences in composition along the year. Finally, the synthesis of such bioactive products is very little in nature, so that tiny amounts are yielded.

Thus, it could be very illogical to promote the use of natural products in the medical research having known such disadvantages. However, these drawbacks could be easily overcome by biochemical isolation of identification of active substances from raw extracts, carrying out pharmacological studies of mechanisms of actions or even structure-activity relationship studies, as well as toxicological profile assessment. Once a structure has been defined along with its mechanisms of action and toxicological profile, it is possible to perform its synthesis in the laboratory, changing some functional groups to maximize affinity to receptors, lipophilic profile, and pharmacokinetic parameters. This is exactly the border between the the naturally-occurring compounds and the synthetic ones. It is the point at which we are going to intervene to make possible the design of novel therapeutics based on a natural carbon structure, which will enable the pharmaceutical research to create new alternatives to the already existing drugs and maximize the arsenal of therapeutic agents against TMJ arthritis.

Conclusion

Natural products offer a novel method for preventing and treating inflammatory diseases and are potential tools for TMJ arthritis management. These naturally occurring products could be of great clinical relevance, as well as could serve as pharmacological scaffold once their molecular structures were determined and may be reproduced. Thus, providing drugs with similar activity with less adverse effects once they were studied further, bringing on medicinal benefits of the natural products to treat TMJ arthritis.

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