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Review

Polyphenols as Potential Agents in the Management of Temporomandibular Disorders

Stefania Moccia [1], Ludovica Nucci [2], Carmela Spagnuolo [1,*], Fabrizia d'Apuzzo [2], Maria Grazia Piancino [3] and Giuseppe Minervini [2]

[1] National Research Council, Institute of Food Sciences, 83100 Avellino, Italy; stefania.moccia@isa.cnr.it
[2] Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania, Luigi Vanvitelli, 80138 Naples, Italy; ludortho@gmail.com (L.N.); fabriziadapuzzo@gmail.com (F.d.); minervinigiuseppe@hotmail.it (G.M.)
[3] Department of Surgical Sciences-Orthodontic division, Dental School, University of Turin, 10124 Turin, Italy; mpianci@gmail.com
* Correspondence: carmela.spagnuolo@isa.cnr.it; Tel.: +39-0825299-261

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Abstract: Temporomandibular disorders (TMD) consist of multifactorial musculoskeletal disorders associated with the muscles of mastication, temporomandibular joint (TMJ), and annexed structures. This clinical condition is characterized by temporomandibular pain, restricted mandibular movement, and TMJ synovial inflammation, resulting in reduced quality of life of affected people. Commonly, TMD management aims to reduce pain and inflammation by using pharmacologic therapies that show efficacy in pain relief but their long-term use is frequently associated with adverse effects. For this reason, the use of natural compounds as an effective alternative to conventional drugs appears extremely interesting. Indeed, polyphenols could represent a potential therapeutic strategy, related to their ability to modulate the inflammatory responses involved in TMD. The present work reviews the mechanisms underlying inflammation-related TMD, highlighting the potential role of polyphenols as a promising approach to develop innovative management of temporomandibular diseases.

Keywords: temporomandibular disorders; temporomandibular joint; polyphenols; anti-inflammatory; osteoarthritis

1. Introduction

Temporomandibular joint (TMJ) is a synovial joint comprising the mandibular fossa of the temporal bone and mandibular condyle. The articular disc is located between these structures and it is a hard-dense fibrous connective tissue with compressed collagen fibers lying bilaterally, allowing the functions of the stomatognathic system. The TMJ is covered with an articular capsule, which is a thick connective tissue membrane, largely divided into an outer fibrous layer and inner synovial membrane. The pathological frameworks that involve TMJ are quite heterogeneous concerning etiology, pathogenesis, and clinic events [1].

Temporomandibular disorders (TMD) encompass several clinical conditions with multifactorial etiopathogenesis involving the stomatognathic system, in particular the masticatory muscles, TMJ and the structures associated [1].

One of the main causes of TMJ pain is temporomandibular synovitis inflammation on the synovial membrane of TMJ. Temporomandibular synovitis is due to the excessive force to TMJ, which causes over-stretching and sprain of the articular capsule, articular ligament, and surrounding tissue of articular disc, or osteoarthritis (OA) of TMJ [1]. Temporomandibular joint osteoarthritis (TMJOA) is classified as a "low-inflammatory arthritic condition" and can be unilateral or bilateral, as opposed

to rheumatoid arthritis, which is a high-inflammatory condition [2]. The clinical evidence of this pathological condition occurs in 8–16% of the population with a strong preference for women [2,3]. Subversion of loads at the joint level involves a chronic trauma associated with morphological changes resulting in flattening of the articular heads. Clinical diagnosis is based on the presence of several signs and symptoms: pain (most commonly described as a deep ache) in the pre-auricular area with or without associated earache, coarse crepitus in the joint with or without clicking [4], pain in one or both joints during palpation and usually complemented with radiological evidence of arthrosis [3]. Recently, cone-beam computed tomography (CBCT) has provided a more detailed change of TMJ bone than conventional radiographic methods (tomography, Schuller's projection, spiral computed tomography, etc.), demonstrating a special advantage in TMJOA diagnosis [1]. According to the American Academy of Orofacial Pain, TMJOA is categorized into primary and secondary: (1) primary TMJOA is characterized by the absence of any distinct local or systemic factor; (2) secondary TMJOA is associated with a previous traumatic event or disease [2]. Some of the circumstances involved in TMJOA are functional overload and parafunction (like tooth grinding during sleeping), unstable occlusion (for example due to a too high restored tooth that does not interact properly with the others), or trauma (microtrauma and macrotrauma) [3,5]. TMJOA could also be a consequence of a dysfunctional articular remodeling due to a decreased adaptive capacity of the articulating structures of the joint [3]. Excessive mechanical loading on normal articular cartilage or normal mechanical loading on impaired articular cartilage is generally speculated to initiate the disruption of cartilage matrix homeostasis [1,6]. The degeneration of the structure and function of articular cartilage is accompanied by the corresponding bone changes, characterized by a defective adhesion of chondrocytes to proteins of the extracellular matrix, including fibronectin, resulting in a deficit of the tissue mechanical integrity and cartilage repair process [7–9]. Therefore, the last stage in the development and progression of TMD is represented by cartilage degradation, characterized by secondary inflammation resulting in the degenerative condition of OA [1,8]. In general, the natural course of TMJOA is favorable and can be divided into three slow progressive phases, with periods of remission and cartilage regeneration [2]. Pain is prevalent in initial phases due to the presence of synovitis and it may be associated with joint stiffness, limitation in mouth opening, increasing sensitivity to cold and damp [2]. However, the pathology of TMJOA is complex; the TMJ and its surrounding structures are involved in multifactorial processes [10]. Furthermore, the pathogenesis and underlying molecular mechanisms involved in TMJOA development remain unknown due to the limited self-healing ability of articular cartilage. TMJOA is one of the most difficult joint diseases, and currently there is no consensus treatment for complete remission. The therapeutic strategy of TMJOA mainly aims to prevent gradual destruction of cartilage and subchondral bone, inducing bone remodeling, relieving joint pain, and restoring TMJ functions [10]. The decision for surgical management of TMJOA is based on the evaluation of the individual response to non-invasive management [3]. Surgical intervention, such as joint replacement with autologous bone or an artificial joint, does not fully restore the destroyed organ, and the long-term prognosis is uncertain, with some cases requiring a second operation; however, this treatment rarely restores the destroyed joint [1]. Common clinical treatments mainly include nonsurgical options, such as psychotherapy [11], physical therapy, occlusal stabilization splints, medication, and arthrocentesis, among which inter-articular injection of drugs is a crucial and common therapy aiming to relieve pain and improve jaw function [3,10]. Sodium hyaluronate and glucocorticoid are the widely used drugs in the clinic, their strong anti-inflammatory effects are useful to relieve the pain of TMJOA patients for a long time. In recent years another promising potential therapy is the local injection of hyaluronic acid, which reduced histologic and bony morphometric measures of TMJ inflammation [12].

Currently, conventional pharmacologic interventions, such as non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, are considered the primary management for painful TMJOA, reducing TMJ-related pain and inflammatory states [13]. Generally, applied pharmacologic therapy shows efficacy in pain relief but their long-term use is frequently associated with adverse effects, such as gastrointestinal and renal toxicity, related to prolonged use [10,14]. A large number of supplements

have been tested for the treatment of TMD, but, for example, glucosamine and chondroitin have been studied with conflicting results, while others such as vitamin D and glucosamine in combination with hyaluronate, did not show any significant effect [2]. In this context, the growing need for new therapies to improve inflammatory pain have highlighted the role of natural products as a promising alternative for TMJOA, also encouraged by several scientific studies [15–17]. For example, it has been demonstrated that lectin from *Abelmoschus esculentus* was able to ameliorate the nociception in a rat model of formalin-induced TMJ inflammation [15]. The promising analgesic and anti-inflammatory role of lectin (0.001, 0.01, or 0.1 mg/kg) was mainly demonstrated through the reduction of tumor necrosis factor α (TNF-α)-levels in the TMJ tissue, in the trigeminal ganglion, and subnucleus caudalis. It was also suggested that the central antinociceptive response was mediated by the activation of the δ and κ receptors induced by *Abelmoschus esculentus* lectin in this pre-clinical model of TMJ inflammation [15]. Another encouraging study concerned the role of the bioactive compound, namely sulfated polysaccharide, isolated from the marine organism red seaweed *Solieria filiformis*. The role in reducing the TMJ inflammatory hypernociception of these compounds was assessed in a rat model [16]. Briefly, the treatment with sulfated polysaccharide (0.03, 0.3, or 3.0 mg/kg) exerted antinociceptive and anti-inflammatory effects in rat, resulting from the activation of opioid receptors in the subnucleus caudalis and reduction of pro-inflammatory mediator release in the periarticular tissue [16]. A similar study analyzed the antinociceptive effects of a polysulfated fraction from the red seaweed *Gracilaria cornea*, showing a reduction of nociception mediated by the interaction with δ/κ/μ opioid receptors in formalin-induced TMJ hypernociception rat model [17].

Moreover, the potential use of other phytochemicals to relieve pain and inflammation involved in TMD has been increasingly considered [18–21]. These natural molecules attracted scientists' interests for their ability to interfere, in mammalian cells, with several biological targets involved in inflammatory processes, oxidative stress, and tumorigenesis [22–24]. Some studies have highlighted the potentiality against TMJ inflammation of several phytochemicals, improving the clinical conditions related to inflammatory states and pain [25,26].

To make an example of the potential anti-inflammatory and analgesic effect of polyphenols, Magni et al. have shown that anthocyanin-enriched purple corn extract (53 mg/kg) reduced the development of orofacial allodynia induced by trigeminal inflammation in a TMJ inflammation rat model [21].

Phytochemical-based applications represent a promising strategy to employ in mono-treatments or association with conventional drugs. This latter hypothesis offers the possibility to obtain, from a combined treatment, a synergistic effect, increasing the therapeutic efficacy of conventional drugs and reducing the dosage and the related side effects.

2. The Role of Inflammation in TMJ

As reported above, inflammation is one of the main mechanisms involved in TMD, for this reason, the development of new innovative therapies targeting specific factors, identified in the inflammatory pathway such as specific cytokines or oxidative stress could be interesting [1].

The inflammatory signaling involved in TMJOA could be modulated by the alteration of redox-sensitive mechanism, suggesting that oxidative stress could be the critical event in the damage by reactive oxygen species (ROS) through synovial macrophages and fibroblasts activation [27,28]. Therefore, ROS and pro-inflammatory cytokines, including interleukin 1β (IL-1β), interleukin 6 (IL-6), and TNF-α are produced by synoviocytes and chondrocytes, inducing enzymes, such as cyclooxygenase-2 (COX-2) and matrix metalloproteinases (MMPs), involved in cartilage matrix degradation [8]. The progressive degradation of extracellular matrix cartilage is promoted by the release of cytokines, including IL-1β and TNF-α, which stimulate chemokines, nitric oxide (NO), prostaglandins (PG), and leukotrienes by chondrocytes [29]. Therefore, IL-1β also suppresses the expression of cartilage-specific extracellular matrix components including collagen type II and cartilage-specific proteoglycans and stimulates the de novo synthesis of catabolic enzymes such as

MMPs. The degeneration of joint cartilage is also due by apoptotic cell death of chondrocytes, promoted by IL-1β and ROS, activating caspases through the interaction with different signal transduction pathways. Among these, NF-κB (nuclear factor-κB) is involved in cellular response, inflammation, innate immunity, and arthritis [27,29,30]. This transcription factor is present in the cytoplasm in an inactive form through the interaction with a family of inhibitors, called IκBs (Inhibitor of κB). The activation of NF-κB signaling allows its nuclear translocation inducing the expression of specific target genes including cytokine and chemokine genes (TNF, IL-1, IL-2, IL-6, macrophage inflammatory protein-1, macrophage inflammatory protein-2) [31]. Another transcription factor involved in TMJ inflammatory response, that regulates the gene expression of key targets involved in several cellular processes including differentiation, proliferation, and cell death, is Activator Protein 1 (AP-1). It is associated with inflammation through the regulation of several mechanisms, including the activation of cytokine production, modulation of naive T-cell differentiation into T helper-1 or T helper-2 cells, and the suppression of glucocorticoid receptor [31]. Moreover, Mitogen-Activated Protein kinases (MAPKs), serine-threonine kinases, also mediate intracellular signaling involved in the regulation of inflammation associated with gene expression, cell survival, proliferation, inducible nitric oxide synthase (iNOS) cytokine expression, and collagenase production in synoviocytes, chondrocytes, and synovial fibroblasts, suggesting the involvement in the development of synovial injury by regulating the expression of IL-1β in synovial membranes [32–34].

3. Polyphenols as Potential Agents in TMD

Among phytochemicals, polyphenols are a heterogeneous group of about 5000 natural organic molecules, widely present in the plant kingdom. These compounds are secondary metabolites of plants, where they are involved in defense against ultraviolet radiation and foreign agents and the regulation of enzymes of cellular metabolism [35]. Their chemical structure is characterized by the presence of phenolic rings and, based on the number of phenol groups, they can be divided into different subclasses: phenolic acids, flavonoids, stilbenes, and lignans (Figure 1). Polyphenols are widely present in the human diet, including fruit and vegetables and many beverages such as wine, beer, tea, and coffee. In the last decade, increasing attention on the potential beneficial effect of polyphenols on human health has been placed, providing scientific evidence supporting that a regular intake of polyphenols can reduce the risk of the onset of chronic degenerative diseases, such as cancer, cardiovascular and neurodegenerative disorders [36,37]. Compelling evidence has reported also the role of polyphenols to improve several oral conditions, resulting as effective adjuvants in the prevention and treatment of different oral pathology conditions [38–40].

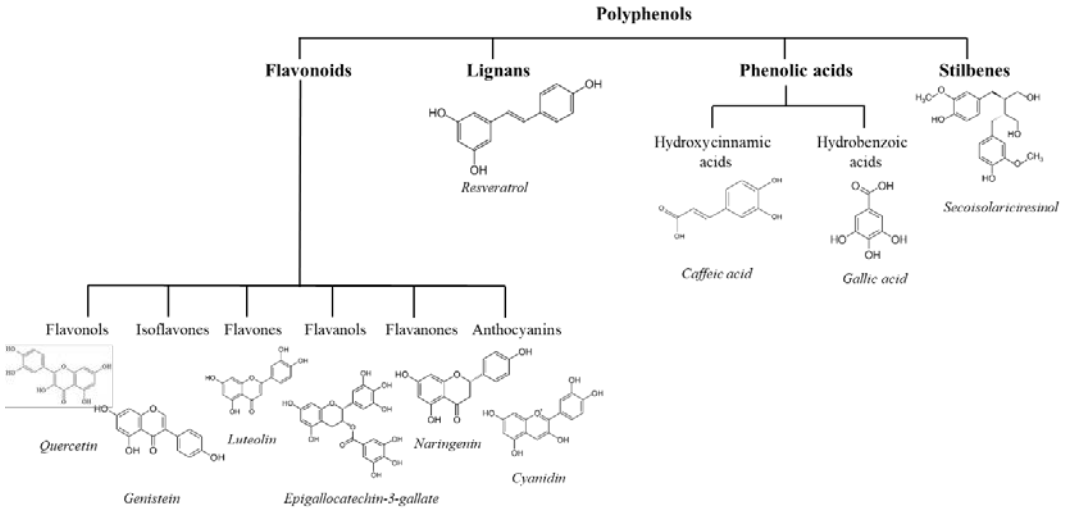

Figure 1. Chemical structures and classification of polyphenols.

3.1. Molecular Mechanisms of Polyphenols Targeting Inflammation

Polyphenols have been proposed as potential agents to improve TMJ-related inflammatory states, concerning their ability to interfere with several pathways involved in the pathogenesis of this process [18,19,41]. Indeed, the protective role of dietary polyphenols in the management and progression of OA has been incrementally supported, which is a degenerative condition affecting the TMJ [19,41]. Polyphenols could exert a potential protective effect against TMD, mainly through the modulation of chondrocytes inflammation and mitigation of cartilage destruction, resulting in the improvement of TMJ-related pain. Their modulatory activity is mediated by the interaction with important signaling pathways, including MAPKs and NF-κB, as demonstrated in fibroblast-like synoviocytes (FLS) and the murine model of Collagen-Induced Arthritis (CIA) [19,42]. Several studies have reported the reduction of pro-inflammatory cytokines, (TNF)-α, IL-6, and IL-1β and the modulation of COX-2 signaling pathway by polyphenols, such as p-coumaric acid, caffeic acid on different rat experimental models of inflammation, including monosodium urate crystal-induced inflammation in rats, formalin-induced pain in mice, and LPS-induced mechanical hyperalgesia in rats [20,43–46]. For example, the anti-inflammatory activity of polyphenol naringin has been demonstrated by an *in vitro* study, showing a reduced production of prostaglandin E2, NO, IL-6, and TNF-α in lipopolysaccharides (LPS)-induced RAW cells. This evidence is also supported by the improvement of tissue damage after treatment with naringin in a monosodium iodoacetate (MIA)-induced OA rat model [47].

Beyond the anti-inflammatory activity of polyphenols, the ability to reduce symptoms related to TMJ pathological conditions is also associated with the anti-nociceptive effect. The reduction of ROS by polyphenols, including flavonoids, is strongly involved in this mechanism since they are responsible for spinal GABA release reduction and induction of neuropathic pain [48]. The anti-nociceptive action of quercetin has been shown by a study reporting the interaction with the L-arginine/NO pathway, serotonin, and GABAergic systems [49]. As described, quercetin (10–60 mg/kg) can reduce the nociception induced by glutamate in a mouse model of chemical and thermal nociception.

Another interesting effect is the analgesic power of some compounds such as ferulic acid dimer (30 mg/kg) that in formalin-induced acute inflammatory pain mice acts through the interaction with adenosine receptors, a non-opioid mechanism, and novel pain target [50].

Here, we will focus our attention on a selection of representative molecules, namely curcumin, resveratrol, epigallocatechin3-gallate (EGCG), and on polyphenol-based extracts, whose potential protective role against TMJ degenerative condition has been described by several scientific studies. For each of them, we will summarize their putative mechanism(s) of action from *in vitro* and animal studies, and their potential applications in TMJ inflammation and TMD management will be discussed (Figure 2).

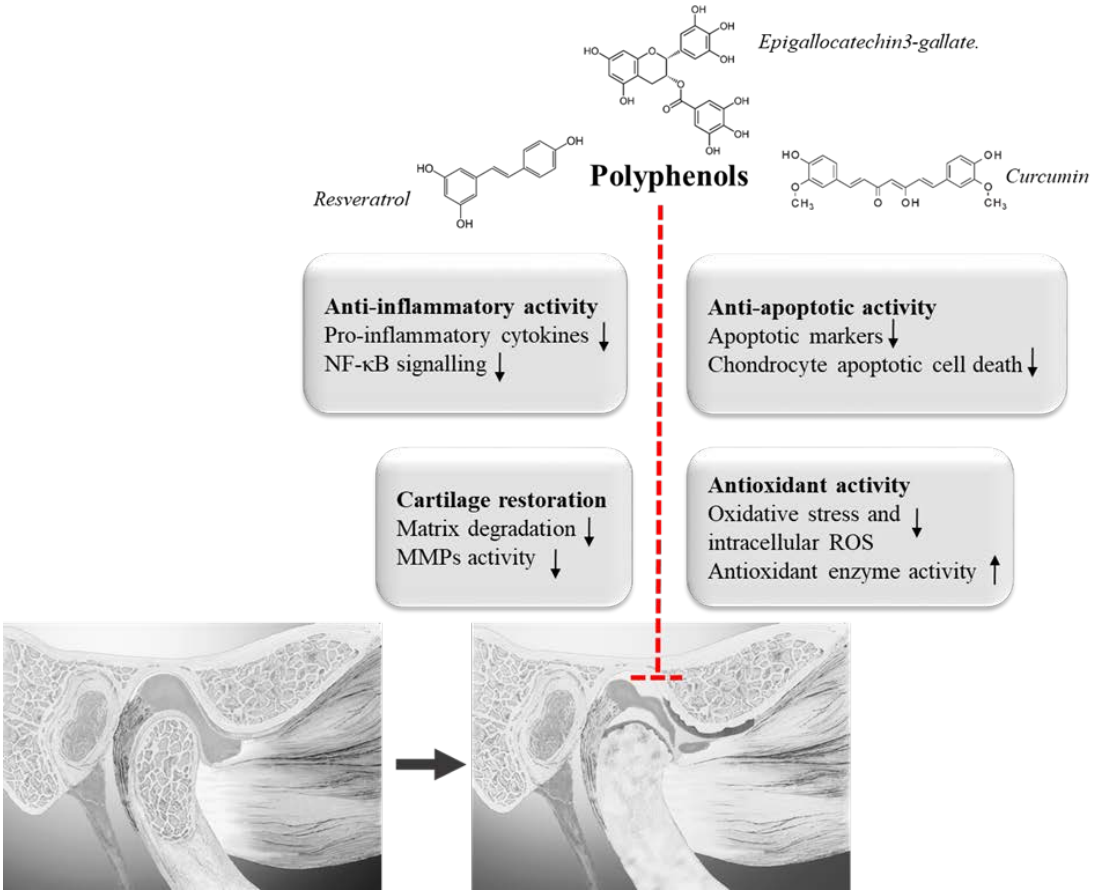

Figure 2. Suggested mechanisms triggered by polyphenols in the prevention of temporomandibular disorders (TMD).

3.1.1. Curcumin

Curcumin [1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-heptadien3,5-dione], a bright yellow-orange vegetable pigment, is a bioactive component isolated from rhizome of turmeric *Curcuma longa* [51]. The antioxidant and anti-inflammatory activities of curcumin have been widely investigated, evidencing its potential protective role in the prevention and treatment of several degenerative pathologies [52–54]. Compelling evidence has shown the role of curcumin on the extracellular matrix protein metabolism of articular chondrocytes through the modulation of inflammatory mediator production, supporting that oral or topical administration of curcumin significantly delayed the initiation and progression of OA in animal models [55,56]. The potential protective effect of curcumin in the management of OA has been explored in human synovial fibroblasts and mouse models of arthritis, reducing joint inflammation mainly through the inhibition of NF-κB activation and translocation promoted by IL-1β and PGE2 and NO production [55–61]. The reduced expression of NF-κB by curcumin has been associated with the suppression of pro-inflammatory genes and inhibition of downstream products, including COX-2, VEGF, and MMPs in chondrocytes, preventing the cartilage degradation [29,55,57,58]. It has also been shown that curcumin (5–20 μM) reduces joint inflammation by affecting cartilage remodeling and inhibiting proteoglycan synthesis, through the inhibitory effect on MMP activity, strongly involved in the destruction of cartilage [61–63].

One of the mechanisms by which curcumin promotes the protective effect against the cartilage loss is mediated by its anti-apoptotic role in chondrocyte. Enhanced apoptosis of chondrocytes is considered an important factor in the development and progression of cartilage joint degeneration. Indeed, the increase of intracellular ROS production and IL-1β which occurs during the cartilage joint degeneration, associated with mitochondrial dysfunction, stimulate the apoptotic process through

their interaction with different signal transduction pathways [29,64,65]. It has been described that curcumin (20 μM) significantly reduces the apoptosis of chondrocytes, by modulating key apoptotic biomarkers such as caspase-3 and PARP [66].

It is also worthwhile to mention the involvement of autophagy in the progression of cartilage joint damage [67,68]. Autophagy is a basal cellular mechanism of selective removal of damaged cytoplasmic components to maintain cellular homeostasis during stress conditions and it is a required process in the chondrocyte apoptosis [69]. It is not surprising that dysregulated autophagy is involved in the articular cartilage destruction and proteoglycan loss, relating to apoptotic cell death induction [67,69]. In fact, this molecule also decreases the apoptosis of chondrocytes induced by IL-1β, promoting an anti-apoptotic mechanism that involves autophagy activation by MAPK/ERK1/2 signaling pathway [70].

It has been also reported that the protective role of curcumin in the cartilage matrix degradation is mediated by the inhibition of Akt/mTOR signaling pathway, resulting in enhanced autophagy in a mouse model of OA [71]. Moreover, recent evidence reports that curcumin could modulate the Nrf2/ARE signaling pathway that is involved in the protection of cartilage damage, maintaining cartilage homeostasis, and inhibiting apoptosis in OA chondrocytes [72]. Indeed, curcumin, inhibiting inflammation, oxidative stress, and the matrix degradation of TMJ inflammatory chondrocytes promotes cartilage protection [73].

3.1.2. Resveratrol

Resveratrol (3,4′,5-trihydroxystilbene) is a phytoalexin, belonging to the polyphenol class of stilbenes and it can be found in several food sources, including grapes, berries, peanuts, red wine, dark chocolate, and tea [68,74]. Wide ranges of pharmacological properties for human health have been attributed to resveratrol, including the protection against diabetes, neurodegenerative diseases, cancer, aging, obesity, and cardiovascular diseases [75]. Based on these observations, resveratrol has been proposed as an ideal candidate in improving the TMJ inflammatory pain, by regulating the release of inflammatory cytokines and preventing the progression of cartilage damage. Accumulating evidence is going in this direction. To support this view, *in vitro* and animal model studies have focused on the role of resveratrol on OA pathogenesis. As an example, it has been demonstrated that supplementation of resveratrol (22.5 and 45 mg/kg) for 12 weeks prevents the progression of OA in C57BL/6 J mice fed a high-fat diet, by decreasing the type II collagen degradation and inhibiting the chondrocyte apoptosis [76]. The suppression of apoptosis in chondrocytes by resveratrol has also been shown in a traumatic OA-induced persistent mechanical hyperalgesia in a rat model (ACLT plus Mmx rat model), where administration of resveratrol (5 mg/kg) increases the percentage of S phase cells of the cell cycle by the increase of miR18a expression [77]. This approach has been supported by the observation that chondrocyte apoptosis in the OA rats could be associated with the expression of miR-18a, through the reduction in ATM protein kinase expression, which is the target gene of miR-18a involved in chondrocyte proliferation [77]. Moreover, the ability of resveratrol to protect articular chondrocytes is associated with the inhibitory action on MMPs expression, through a mechanism mediated by the inhibition of IL-1β-induced activation of IKB, resulting in the modulation of the NF-κB inflammatory pathway [78]. It has also been shown that improvement in cartilage degeneration could be obtained after intra-articular injection of resveratrol in an experimental model of C57BL/6 mice induced-OA. In this model, resveratrol could activate autophagy by regulating the AMPK/mTOR signaling pathway, with a consequent increase of LC3, ULK1, and Beclin1 autophagic markers, demonstrating that the promotion of chondrocyte autophagy is one of the main important mechanisms by which resveratrol exerts its chondroprotective effect [79].

An attractive hypothesis suggests the involvement of aryl hydrocarbon receptor (Ahr) in the collagen destruction, through several mechanisms related to pro-inflammatory cytokine production and bone metabolism modulation [80]. Thus, it is worthwhile to evidence that resveratrol (IC50 6 μM) is a strong AhR competitive antagonist, resulting in the inhibitory effects of AhR activation,

downregulating oxidative stress and inflammation in several preclinical models, including chondrocytes and rabbit model of OA [80,81].

The cartilage degeneration process is also induced by SIRT-1 (silent information regulator 2 type 1, also known as sirtuin 1) enzymatic activity, regulating the expression of extracellular matrix (ECM)-related protein bone homeostasis in OA and promoting mesenchymal stem cell differentiation [82]. Indeed, the increased chondrocyte apoptosis associated with cartilage breakdown in SIRT-1-deficient mice has been demonstrated, confirming the role of SIRT-1 in cartilage destruction [83]. It is not surprising that activators of SIRT-1, including resveratrol, represent an interesting strategy to counteract the progression of cartilage damage, relating to their potential application in TMJ-related OA. Accumulating evidence has supported this view, reporting that resveratrol could exert a chondroprotective role by increasing SIRT-1 protein expression in a dose-dependent manner (25 and/or 50 μM) [82].

Another attractive hypothesis is focused on the role of gut microbiota, which represents a potential target in TMJ inflammatory pain, by regulating the microglial activation involved in nociceptive response [84]. Growing evidence has reported that microglia morphology and function depend on the alteration of gut microbiota, including short-chain fatty acids (SCFAs) production, including acetic acid, propionic acid, and butyric acid, affecting the immune system and subsequently modulating the inflammatory status [84,85]. Therefore, resveratrol has been proposed as a TMJ inflammatory pain modulator, based on its ability to restore normal gut microbiota, resulting in the regulation of microglial activation and the inhibition of the release of pro-inflammatory cytokines, such as TNF-α. Indeed, it has been shown that resveratrol (40 and 80 mg/kg) significantly prevents CFA-induced TMJ inflammation in mice, reversing CFA-caused reduction and restoring the gut microbiota dysbiosis, affecting in this way the microbiota composition [84].

An interesting approach is also represented by the use of molecules in combination; for example it has been observed that, in chondrocytes, resveratrol (50 μM) in association with curcumin (50 μM) induces enhanced effects in suppressing inflammation, modulating the cytotoxic effects of IL-1β by the inhibition of the NF-κB pathway and apoptosis [29].

3.1.3. Epigallocatechin3-Gallate

EGCG is a catechin, belonging to the polyphenol family and is the most abundant catechin in green tea [86]. The health-promoting activity of EGCG has been widely described, including the protective role in cardiovascular and metabolic diseases, and anti-cancer effect [86,87]. Accumulating evidence has indicated EGCG as an anti-inflammatory agent in joints for the prevention of OA inflammation, by reducing synovial hyperplasia, cartilage degradation, and bone resorption [88]. The anti-inflammatory effect of EGCG has been widely demonstrated by *in vitro* and *in vivo* data, indicating that EGCG can regulate the expression of cytokines, chemokines, MMPs, and ROS production, NO, COX-2, and PGE2 promoting the reduced expression of pain mediators [89]. For example, it has been demonstrated that EGCG (50 mg/kg) significantly reduces the level of proinflammatory cytokines such as TNF-α and IL-17, reducing the perisynovial inflammation involved in cartilage-bone destruction in an experimental rat model of arthritis [88,90]. The role of EGCG in the suppression of inflammatory processes is mediated by the interaction with MAPK, AP-1, and JNK activation, whose inhibition leads to a reduced pro-inflammatory cytokine-induced stimulus in chondrocytes [91]. The protective effect of human chondrocytes is also indicated by the decreased production of the TNF-α, MMP-1, and MMP-13 by EGCG, mediated by the inhibition of NF-κB activation, promoting the repair of degraded cartilage matrix [92].

Analyzing the mechanisms underlying the anti-inflammatory role of EGCG, it has been shown that it (100 μM) inhibited the production of NO induced by IL-1β by interfering with the activation of NF-κB in human chondrocytes [93]. Moreover, Huang et al. have reported the ability of EGCG (50 μM) to inhibit the expression of inflammatory mediators, namely COX-2, PGE2, and IL-8, whose production was upregulated by IL-1β in human synovial fibroblasts [94].

Another mechanism by which EGCG could suppress the inflammatory response is the modulation of microRNAs (miRNAs) expression [95], whose alteration is involved in cartilage pathophysiology and OA progression [95,96]. In support of this view, it has been reported that EGCG upregulates the expression of microRNA hsa-miR-199a-3p in IL-1β-stimulated human OA chondrocytes through the inhibition of COX-2 mRNA/protein expression and PGE2 production [97]. A similar study has also demonstrated the ability of EGCG to upregulate the expression of hsa-miRNA-140-3p in human OA chondrocytes, which is a regulator of aggrecanse-2 (or ADAMTS5) expression, involved in the degradation of the cartilage matrix [95]. Finally, EGCG is also able to increase the redox-regulated transcription factor Nrf2, suppressing the inflammatory mediator production [88].

3.1.4. Polyphenol-Based Extracts against TMJ Inflammation

An attractive approach against TMJ-related inflammation is the employment of polyphenol-based extracts, which, thanks to the wide range of compounds they are made of, could be promising solutions for improvement of associated joint pain [98].

As an example, the anti-inflammatory potential of a cranberry extract, from cranberry juice, has been assessed in TMJ synovial fibroblast-like cells. In this model, the polyphenolic extract (25–100 μg/mL) significantly inhibits the production of IL-6, IL-8, and vascular endothelial growth factor (VEGF) induced by IL-1β, decreasing the inflammatory process involved in TMJ [98].

The ability of berries, such as blueberries and red raspberries, to reduce inflammation and pain has also been shown in experimental models of OA [99]. For example, the phenolic compounds of raspberry extract (15 mg/kg) significantly reduce the resorption of bone, edema, and osteophyte formation in rat models of acute inflammation and collagen-induced arthritis, resulting in the improvement of clinical signs [99]. Another study by the same authors has reported that a polyphenolic extract of blueberry, containing chlorogenic and caffeic acids, flavonoids like quercetin, myricetin, siringetin, laricitrin, isorhamnetin, and kaempferol, improves articular function and prevents articular destruction in acute inflammation and collagen-induced arthritis model of rats [100]. In this model, the blueberry extract significantly reduces edema formation by 30% after oral administration (12.5 mg/kg) for 13 days, compared to 50% reduction induced by the anti-inflammatory drug indomethacin. Other data also have provided evidence that supplementation of strawberry-based beverages (50 g/day), containing polyphenols, improved pain and inflammation in 35 obese adults with mild-to-moderate knee OA, suggesting that dietary intervention could improve the quality of life [101–103]. The anti-inflammatory effect is also described for polyphenol extract obtained from *Ribes orientale*, promoting its protective role in the attenuation of pro-inflammatory mediators, by downregulating gene expression levels of PGE2, COX-2, IL-1β, IL-6, NF-kB, and TNF-α, whereas upregulates those of IL-4 and IL-10 in an arthritic rat model [104]. Moreover, it has been reported that well-characterized curcuminoid-containing turmeric extracts, rich in curcumin, demethoxycurcumin, and bis-demethoxycurcumin, prevent joint inflammation using streptococcal cell wall (SCW)-induced arthritis, a well-described animal model of arthritis [105].

3.2. Potential Polyphenols Application in TMJ Inflammation, In Vivo Studies

Interesting data come from several *in vivo* studies that validate data reported above and support the potential preventive and therapeutic roles of polyphenols in TMJ-related inflammation.

The effect of curcumin administration on OA patients has been evaluated by several clinical studies, showing that curcumin could represent an ideal candidate in the management of pain and inflammatory state related OA [106]. Concentrations used in clinical trials are within a range of 180–2000 mg daily, in a period of treatment from 4 weeks to 8 months. For example, it has been reported that oral administration of turmeric extracts (1500 mg daily) for 4 weeks can significantly reduce pain in 367 primary knee OA patients, showing a comparable effect to ibuprofen (1200 mg daily), with a reduction of gastrointestinal side effects [107]. Significant improvement in clinical symptoms of OA in curcuminoid-treated subjects has been also shown in a randomized clinical trial in which 40 subjects

with mild-to-moderate degree knee OA received pure curcuminoids (1500 mg daily, three doses) or placebo for 6 weeks [108].

Anyway, regardless of the promising results, these data must be carefully considered because most clinical trials present limitations such as the limited number of patients and the high dosages of curcumin employed [109].

The vehicle systems used for therapeutic applications are mainly lipid nanoparticles, micelles, polymeric nanoparticles, liposomes, and emulsions. To make an example, there is evidence provided that the phytosome complex (Meriva®), composed of curcumin and phosphatidylcholine (1:2), improves oral absorption of curcumin, ameliorating symptoms and joint function in OA patients, as evaluated by Western Ontario and McMaster Universities scores [110]. It has also been shown that oral administration of curcumin-based oil-water nanoemulsions, obtained by the high-pressure homogenizing method, strongly reduces the levels of TNF-α and IL-1β in both synovial fluid and blood serum on adjuvant-induced arthritis in rats [111].

In addition, also the role of resveratrol in preventing cartilage degradation and improving pain-related inflammation has been supported by *in vivo* studies. For example, a randomized control trial has evidenced an improvement of pain gravity and a significant reduction of serum levels of the biochemical inflammation markers, such as TNF-α, IL-1β, IL-6, after resveratrol administration (500 mg daily) to patients with knee OA [112]. The interesting results obtained in patients with mild to moderate radiological evidence of knee OA should also be highlighted, where resveratrol (500 mg daily) was used as an adjuvant in association to meloxicam therapy (15 mg daily) for 90 days and patients had improved pain, compared to the placebo [112]. The anti-arthritic effect of EGCG-glucosamine-casein-based nanoparticles has also been evaluated (1:2:8, w/w/w) on rats, resulting in histopathological changes in the joint cartilage with reduced inflammatory cell infiltration, synovial hyperplasia, and cartilage destruction [113].

The major challenge in the application of polyphenols is their poor absorption and low systemic bioavailability after oral intake, mainly related to their poor water solubility and high metabolism and clearance rate. These limitations must be critically considered, indicating the bio-transformation of polyphenols that occur during their uptake across the gastrointestinal system, liver, and finally in the peripheral tissue cells. Hence, following the oral intake, these compounds become substrates of phase I and phase II enzymes and are conjugated to methyl and sulfate groups and glucuronic acid in the small intestine and liver [114]. Further transformations are performed by the intestinal microflora enzymes leading to the formation of phenolic acids that undergo liver metabolism. These chemical changes modify the polyphenol structures and could alter their biological effects. For this reason, several formulation strategies and delivery techniques have been developed and applied to overcome this limitation and improve oral bioavailability [115]. This goal can be achieved by the use of nanoparticle-based delivery systems, which represent an attractive approach to ameliorate the stability, increase the half-life, promoting a controlled and sustained release and improving the bioavailability of bioactive compounds [116]. Microencapsulation and nanoencapsulation techniques can improve the functional properties of polyphenols, emphasizing the use of eco-compatible and biocompatible processes, by using green methodologies to support the environmental sustainability [117].

In detail, environmentally friendly nanocarriers are made up of polysaccharide and protein-based delivery systems, providing a physical barrier that protects and stabilizes bioactive molecules, such as polyphenols [117].

For example, polysaccharide-based hydrogel particles are very promising carriers, loading different functional compounds, including polyphenols, with poor solubility, allowing oral or topical applications [118]. Polyphenol, including resveratrol, curcumin, and EGCG are commonly encapsulated to obtain polyphenol-loaded microparticles and nanoparticles that can be employed in novel formulation for TMJ-management studies.

4. Alternative Therapies for TMD Management

TMD are several heterogeneous disorders affecting the masticatory muscles and TMJ and related structures, which leads to a reduction in masticatory mobility and orofacial pain [119]. As reported above, the symptomatic management of TMD often requires the use of pharmacological therapies, which include the administration of local drugs, including intra-articular injections, and systemic ones, such as NSAIDs and analgesics [3,120]. The first group includes the techniques of infiltration of drugs into TMJ, using minimally invasive approaches based on arthroscopy. Currently, arthroscopy has been overcome by arthrocentesis techniques representing the washing of the upper articular cavity, which involves the use of needles for the passage of the physiological solution [3,120]. Over the years, the invasive approach to TMJ therapy has significantly reduced, both for a better understanding of the functional mechanisms of the stomatognathic system, and promising and encouraging innovative applications. The management of temporomandibular disorders should be conducted through conservative and reversible actions including counseling, physiotherapy, and cognitive-behavioral approaches [121,122]. Currently, it is known that psychological and psycho-social impact factors contribute to the development and progression of TMD [92,123]. In this regard, it has been observed by numerous studies that psychological factors including stress, anxiety, and tension are closely related to the onset of headache, orofacial and TMJ-related pain, resulting in the chronic pain of TMJ which leads to distress, depression, and somatization [124]. One of the key questions regards the impact of chronic orofacial pain of TMJ on the quality of life of subjects, making psychic support crucial, including placebo therapies that can improve TMD pain management and may be responsible for 10–75% of pain relief [125] and also counseling approach [121]. The term counseling is used for a series of practices relating to the psychological sphere and properly means to “come to help”, “to support”, since TMJ-pain leads to a biopsychosocial limitation [121]. The inclusion of a psychological approach in the management of TMD may be reasonable and should be included in any therapeutic approach considering the strong psychological characteristic of the disorder. However, there is partial evidence derived from a limited number of controlled and randomized well-designed clinical trials and also the lack of definition of criteria and methods promoting a multidisciplinary therapeutic approach of TMD.

Moreover, several strategies for TMJOA management have been developed to prevent the progressive degradation of articular cartilage, promoting TMJ function and reducing the TMJ-related pain. Hence, the development of tissue engineering strategies represents a booming field of research, achieving the restoration of degraded cartilage and subchondral bone lesions. An emerging role of stem cells in TMD has been highlighted for their ability to regenerate TMJ, including mesenchymal stem cells in the progressive degeneration of articular disc displacement [126–128]. Mesenchymal stem cells are multipotent stem cells assigned to repair skeletal tissues such as cartilage, bone, and bone marrow and could represent a valid alternative in TMJOA, as supported by several studies [126–128]. Tissue engineering investigations explored the employment of several scaffold materials, including biocompatible polymers, namely polyglycolic acid (PGA), polylactic acid (PLA), and also, natural biopolymers, such as fibrin and chitosan, which were applied as biocompatible materials in TMJ cartilage engineering [128]. Biologic scaffold materials based on extracellular matrix (ECM), including decellularized urinary bladder matrix (UBM) were also successfully considered for their remodeling properties and biocompatible mechanical behavior in cartilage regeneration [129]. Combined innovative biomaterial design strategies and stem cell-based therapies can represent a concrete valid alternative to the management of TMJOA and further investigations could be required to validate the therapeutic intervention in clinical studies.

5. Conclusions

Analyzing the data reported above, it clearly emerges that polyphenols could be promising agents for several pathological conditions converging in OA. The clinical condition of OA refers to similar aspects in all affecting articular districts, including the knee and TMJ, resulting in the chronic

degenerative alteration of the articular cartilage, characterized by inflammation and pain, rigidity, and loss of functionality.

Hence, TMJOA represents one of the most common TMD, leading to progressive degeneration of the articular cartilage and alterations of the subchondral bone, associated with the release of pro-inflammatory mediators [119]. This clinical condition recognizes a multifactorial pathogenesis, whose symptoms are frequently related to orofacial pain, reduction of mandibular motility, and pain in the execution of normal movements [119]. However, TMJOA therapy is still controversial today especially when the severity of the disease is not such as to justify aggressive interventions, such as intra-articular infiltrations.

In this scenario, an interesting approach that is being increasingly explored is the use of alternative therapies, including the application of natural molecules in association with conventional therapies promoting a reduction of drug dosage and relative side effects with additive and/or synergistic effects.

Hence, we propose the potential use of polyphenols, whose biological activities are widely reported by scientific studies, critically analyzing how selected polyphenols, namely resveratrol, curcumin, and EGCG can modulate the processes underlying TMJOA.

Here, we reviewed the results of several studies largely based on the anti-arthritic capacity of polyphenols, suggesting the possibility that they can improve the inflammatory process interacting with several key pathways also involved in TMJ-related pain. In particular, it is worthwhile to highlight that the pleiotropic feature of these compounds is probably responsible for the described biological activities. Polyphenols, including flavonoids, could protect against TMD mainly through the modulation of chondrocytes inflammation and mitigation of cartilage destruction, resulting in the improvement of TMJ-related pain. Hence, we present evidence that polyphenols, such as curcumin, resveratrol, and EGCG could improve cartilage restoration, directly or indirectly interacting with several pathways associated to inflammation-promoting TMJ management (Figure 2). Focusing on the potential TMJ anti-inflammatory properties of polyphenols, several lines of evidence support this view. Interestingly, Ma et al. [84] have suggested resveratrol as a promising strategy to develop a novel therapeutic approach for TMD pain considering that it could alleviate TMJ-related inflammation, recovering disturbed gut microbiota. Similarly, others have reported that curcumin inhibits inflammation, oxidative stress, and matrix degradation of chondrocytes through the Nrf2/ARE signaling pathway in TMJ inflammation [73]. The role of EGCG in suppression inflammation by reducing synovial hyperplasia, cartilage degradation, and bone resorption has been also evidenced [88]. Data on different polyphenolic extracts also showed a potential role against TMJ-inflammation. These results offer several insights such as the possibility to find new compounds with strong biological effects and /or to exploit the well-known synergistic effects of polyphenolic extracts, due to the presence in them of different molecules belonging to different sub-families. Future studies will be fundamental to understand and therefore make the most of this potential.

Moreover, the use of these natural compounds in association with conventional drugs appears particularly interesting, aiming to enhance the response and reduce doses and the side effects. However, because of the several difficulties related to the small number of experimental and clinical studies, referred to TMJ-related conditions, the concept that the modulation of inflammation and oxidative stress induced by polyphenols could have beneficial effects (alone or as adjuvant) remains just an attractive hypothesis.

Anyway, the potential therapeutic applications of polyphenols must be stressed considering both strengthens and weaknesses, these latter related mainly to their limited bioavailability and bio-transformation, challenged by the heterogeneity of human gut microbiota. To overcome these limitations, innovative formulation strategies have been developed improving the delivery techniques, including nanoparticle-based delivery systems, micelles, polymeric nanoparticles, and liposomes.

Additionally, interesting studies have evaluated the intra-articular injections of polyphenols in the protection of articular cartilage indicating a promising therapeutic approach against cartilage

collagen degradation [130]. In particular, a significant role in protecting the cartilage from damage was associated with EGCG treatment in CIA rat models [130].

In this context, considering that another problem for TMD treatment concerns the limited accessibility of the TMJ, which makes it difficult to treat by injection, the assumption of new controlled release nutraceutical products could be extremely interesting.

In conclusion, the overview obtained in this review confirms that polyphenols, acting probably modulating several processes associated with oxidative stress and inflammation, could be suggested as potential innovative TMD-management agents. Actually, there is growing interest of scientists for the ability of natural compounds to interact with several mechanisms involved in pathological conditions, increasingly directing research to validate further studies.

The challenge for the future will concern the design of appropriate studies aimed at validating the better understanding of molecular mechanisms in TMJ triggered by polyphenols in order to develop future clinical studies and concretely consider their application in TMOA prevention and/or treatment. The discussion presented here has been addressed to the development of a future study to prove that naturally occurring flavonoids can improve TMJ-related conditions.

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Abbreviations

TMD	Temporomandibular disorders
TMJ	Temporomandibular joint
OA	Osteoarthritis
TMJOA	Temporomandibular joint Osteoarthritis
EGCG	Epigallocatechin3-gallate
CBCT	Cone-beam computed tomography
NSAIDs	Non-steroidal anti-inflammatory drugs
Nrf2	Nuclear factor erythroid 2-like 2
ROS	Reactive Oxygen Species
TNF-α	Tumor necrosis factor α
IL-1β	Interleukin 1β
IL-6	Interleukin 6
PG	Prostaglandins
MMPs	Matrix metalloproteinases
JNK	C-Jun N-terminal kinase
COX-2	Cyclooxygenase-2
NO	Nitric oxide
NF-κB	Nuclear factor-κB
MAPK	Mitogen-Activated Protein kinase
AP-1	Activator protine-1
LPS	Lipopolysaccharides
VEGF	Vascular endothelial growth factor

SCFAs	Short-chain fatty acids
SIRT-1	Sirtuin 1
FLS	Fibroblast-like synoviocytes
CIA	Murine model of Collagen-Induced Arthritis
PGA	Polyglycolic acid
PLA	Polylactic acid
ECM	Extracellular matrix
UBM	Decellularized urinary bladder matrix
Ahr	Aryl hydrocarbon receptor

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