HEALTH BENEFITS OF GREEN TEA AND GREEN TEA CATECHINS WITH AN OVERVIEW ON THEIR CHONDROPROTECTIVE EFFECTS: A REVIEW

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ABSTRACT

Green tea is one of the most widely consumed beverages in the world and considered as a medicine since ancient times with significant rises in the scientific researches were seen. The purpose of this paper was to review the literature about the role of green tea and EGCG in regeneration of the articular cartilage using the published works in the medical and dental literature which were mostly related to the subject, and published between 2002 and 2020.

This review showed that green tea extract or EGCG can slowing the cartilage breakdown by inhibiting the proteoglycan and type II collagen breakdown, production of PGE-2, iNOS, COX-2, gelatinolytic activity of MMP-2, ADAMTS-1, -4 and -5 aggrecan-degrading activity, activities of MMP-1, MMP-3, and MMP-8, IL-1β-activated MAPK, NF-kappaB, and AP-1 that signaling pathway, advance glycation end products induced expression of TNF-α and MMP-13, the activation of c-Jun N-JNK-MAPK.

Green tea can promote chondrocyte growth, proliferation, and enhance the secretion and synthesis of the cartilage extracellular matrix by upregulating expression levels of aggrecan, collagen II and Sox9 gene, improving the level of COMP, HA, IL-6, and TNF-α, and causes reduction of ROS and NO radicals in chondrocytes and enhanced pro- and activated MMP-2 binding to TIMP-2. It also can reduce the elevated gene expression of the MMP regulator Cbp/p300 interacting transactivator 2, CRP, and ESR, swollen and tender joints count, and modified Stanford HAQ score.

Keywords: Green tea, EGCG, Chondrocyte, Extracellular matrix.

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INTRODUCTION

Types of tea

Tea is the second most consumed beverages in the world next to the water and consumed more than any other drink around the world. In all over the world millions of people are consumed more than three billion cups of tea per day. Each year, the tea leaves are produced in about 2.5 million tons, and about 20% of the products are green tea, which is mainly consumed in Asia, Europe, United States and some parts of North Africa. Tea young leaves and terminal buds are picked from the Camellia sinensis bushes two times/year during spring and early summer. There are four basic forms of manufactured tea, the white tea, oolong tea,
black tea, and green tea. Although all of them come from the same plant, the differences occur in the harvesting and processing. The oolong tea is partially fermented, while the black tea is fully fermented (1).

The white tea is manufactured from the young leaves and new growth buds, which are steamed in order to inactivate the polyphenol oxidation and then dried. Oolong tea is incompletely oxidized product, and accounts for only 2% of tea consumption around the world. Although less popular, oolong tea still has different benefits. Black tea result from the over-oxidation of tea leaves during the manufacture of oolong tea. The tea leaves are crushed into a small pieces which allow the polyphenol oxidase to catalyze the oxidation, and causing polymerization of catechins with formation of the theaflavins and the thearubigins. To prevent fermentation, a freshly harvested tea leaves are immediately steamed, yielding a dry, stable product of green tea. The steaming process will destroy the enzymes which are responsible for breaking down the color pigments in the leaves and during subsequent rolling and drying, the green tea can maintain its green color, and the green tea polyphenols are preserved by these processes. Different factors affect the composition of green tea and its leaves like the season, age of plant, climate, and the type horticultural practices (2). It was reported that all tea types can contaminated with Ochratoxin A (OTA); so tea safety level determination is important for both imported and consumed tea before marketing (3).

**Green tea**

**Chemical composition**

Catechins, the polyphenolic flavonoids are attributed to most of the beneficial effects of green tea, and account for about 40% of the dry weight of green tea, and include the epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). EGCG is considered as the most bioactive component of green tea and representing about 50–80% of the total catechin content. The other constituents as a percentage from the dry weight are: Proteins (15–20%), amino acids like teanine, glutamic acid, tryptophan, serine, glycine, aspartic acid, valine, leucine, tyrosine, threonine, lysine and arginine, (1–4%), carbohydrates like pectins, cellulose, fructose, glucose, sucrose (5–7%), and minerals like Mg, Zn, Ca, Cr, Mn, Fe, Cu, Mo, Se, Na, P, Co, Sr, Ni, K, F, and Al (5%) (2).

The other constituents are vitamins like Thiamine (B1), Riboflavin (B2) Niacin (B3), Vitamin B6, Vitamin E, and Vitamin C; Pigments as chlorophyll and carotenoids; Sterols as stigmasterol; Lipids as linoleic and a-linolenic acids; Xanthine bases like caffeine and theophylline; Volatile compounds such as aldehydes, alcohols, esters, lactones, hydrocarbons, etc. The chlorogenic, gallic acid, caffeine, theaflavins, theanine, and quercetin are the other constituents. Figure-1 shows the chemical structures of catechins in green tea (3).
Absorption, distribution, and elimination

Green tea catechins oral bioavailability was low in rats and other rodents and ranging from 2% to 13%. The low metabolism rate in the gastrointestinal fluid and presystemic hepatic elimination may be the cause. The maximum plasma concentration levels of the free catechins were lower in the fed state compared to the fasted one. It was found that in fasting condition, 800mg of EGCG had more than five folds higher maximum plasma concentration of EGCG in comparison with a fed state. The highest concentration of EGCG was found in the large intestine, whereas the highest concentration of EGC was in the bladder. The kidney, prostate, and lung also showed significant EGCG and EGC concentrations. The liver, heart, spleen, and thyroid showed lowest concentrations of tea catechins. Over 90% of the total urinary EGC and EC was excreted within 8 h in the urine.

Pharmacological action of green tea

Green tea with its constituent has recently attracted significant attention for its health benefits for its different types of disorders. The pharmacological actions include:

**Anti-hypertensive:** Elevated blood pressure is considered as a common disorder. EGCG can induce endothelium-dependent vasodilatation, and in patients with myocardial diseases, green tea was found to be a good therapeutic agent to prevent cardiac remodeling.

**Anti-diabetic activity:** This activity including enhancing insulin action, ameliorating insulin resistance, activating insulin signaling pathway, protecting islet β-cells, scavenging free radicals, and decreasing inflammation. It can also prevent the diabetes-related tissue dysfunctions attributable to oxidation. The water extract of green tea can reduce the blood glucose in mice. The daily consumption of a high concentration of green tea can significantly reduce the blood glucose levels. The hepatic glucose production regulation was decreased also by EGCG. Others found that, the stimulated insulin secretion was enhanced by EGCG in diabetic animals.

**Anti-microbial activity:** It was showed that the green tea extract cause inhibitory effect against Proteus mirabilis and Streptococcus pyogenes, methicillin-susceptible and methicillin-resistant *Staphylococcus*.
The influenza virus replication in cell culture can also be inhibited significantly by EGCG and ECG. The antifungal effects of amphotericin B can be enhanced by EGCG allowing the use of a lower doses of the antymycotics drugs.

Anti-cancer activity: It was found that the consumption of high levels of green tea per day was associated with a reduced incidence of malignancy and higher age of cancer onset, less transformation of the lesion from the premalignant to malignant status, less prevalence and recurrence rate, and less can inhibit the development and metastasis of prostate cancer. The tumor growth inhibitory effects green tea polyphenols were nearly 250 times less effective than doxorubicin in human cancer cell. Therefore, they are mostly used for cancer prevention than as for cancer treatment.

Several studies have reported that polyphenols can induce apoptosis and inhibit the cell growth in different types of malignancies, through activation of cyclin D1, and caspase-3, activation of Caspase-9, stabilization of p53 in cells, or decrease the Bcl-2 expression with an increase in Bax expression, or suppress the proliferation of cancer cells, and a significant reduction in the tumor volume.

Cosmetics: It was reported that tea plant and its extracts can be used as anti-ageing treatment, skin and hair care. Its constituents are also effective to enhance the skin microcirculation and to protect skin against harmful effects of ultraviolet irradiation. Due to its anti-inflammatory, antioxidiant, anti-hyaluronidase, hair-strengthening, and photoprotective and sealing blood vessels properties.

Weight control: Several researchers studied the anti-obesity effect of green tea. The weight of intraperitoneal adipose tissues was significantly decreased in mice, after consumption of diets containing green tea. These anti-obesity effects of green tea are by its potential to increase the fat oxidation.

Anti-cariogenic effects: The bactericidal effect of catechins was seen against Escherichia coli, Streptococcus salivarius, Streptococcus mutans, and Lactobacillus acidophilus. The EGCG causes damage to the cytoplasmic membrane of the bacteria by the generation of hydrogen peroxide. EGCG can also prevent acid production by cariogenic bacteria via inhibition of lactate dehydrogenase, and increases the oral cavity pH.

Periodontal Health: The wide range of its antibacterial effects against gram positive and gram-negative microorganisms is considered as a useful antiplaque agent. It can keep the plaque pH at about neutral and prevent the colony growth. It was found that a seven days application of green tea mouthwash had comparable anti-plaque effect similar to that with chlorhexidine. Catechins can also protect the gingival epithelium against the invasion by Porphyromonas gingivalis, so catechins can play important role in prevention from periodontal disease.

Bone metabolism: It was also observed that green tea extracts showed positive effects on the proliferation and activity of bone cells. Green tea bioactive components appear to promote bone formation by decreasing ROS, TNF-α, COX-2, and by increasing osteoblast activity and survival, resulting in enhanced mineralization, and suppress bone resorption by inhibiting osteoclast formation via increasing osteoclast apoptosis that results in suppressing osteoclastogenesis.
Prevent joint destruction process

Types of articular cartilage: In general, different types of cartilage occur at a specific anatomical location. The hyaline cartilage includes articular cartilage, nasal cartilage, costal cartilage, and many laryngeal and tracheobronchial cartilages. The elastic cartilage is found in the epiglottis, and at the attachment of the vocal cords to the larynx and also part of the external ear. The fibrocartilage is fibrous and forms the annuli of intervertebral discs in the spine, the menisci of the knee and certain joints, the plates connecting the opposing surfaces of bones like pubic symphysis, glenoid and acetabular labra, at the bone attachment sites of tendons and ligaments, and in articular discs (17).

Articular cartilage composition: About 65 to 80% of wet weight of the articular cartilage is formed by water, and about 80% being in the superficial zone and 65% in the deep zones. This allows a load dependent deformation of the cartilage during pressure. The collagen forms about 10–20% of wet weight of the articular cartilage, and about 90-95% is type II collagen which provides a tensile strength to the articular cartilage (17).

Proteoglycans form about 10–20% wet weight and provides the compressive strength to the cartilage and maintains the fluid and electrolyte balance in the articular cartilage. These are produced inside the chondrocytes and then secreted in the matrix. The subunits of proteoglycans are called as glycosaminoglycans (GAGs) with a main two types, the chondroitin sulphate and the keratin sulphate. These GAGs are bound to a protein core to form aggrecan molecule. The link protein stabilizes this chain with the hyaluronic acid (HA) chain to form the bottle brush-like structure of the GAG molecule. Figure-2 shows the proteoglycan aggregate macromolecule. The chondrocytes cells are sparse and highly specialized cells and forming about 1–5% of volume and spread within the matrix. It synthesizes the matrix components and regulate its metabolism (18).

Figure 2: Diagram shows the proteoglycan aggregate macromolecule, the glycosaminoglycan side-chains and the sulfated molecules. The sulfate groups are highly negatively charged and cause the aggrecan to spread out (17).

Articular cartilage diseases: Condylar cartilage diseases are numerous and a number of factors including inflammation and oxidative stress are believed to play a role in the development of chronic joint diseases. Osteoarthritis (OA) is the common joint disorder and occurs when the cartilages between the two joints are
wears down so the bones rub together resulting in swelling and pain\cite{19}. Rheumatoid arthritis (RA) is autoimmune disease that leads to varying degrees of joints disability with inflammation of the joints and surrounding tissues. Fluoroquinolone like ciprofloxacin has a chondrotoxic effect in growing condylar cartilage and contraindicated for children and adolescents and during pregnancy and nursing due to the potential for joint cartilage lesions \cite{20}.

**Attenuation of the catabolic activity of the condylar cartilage by EGCG or green tea extract:** The chondroprotective effects of EGCG or green tea extract on attenuating the catabolic activity of the condylar cartilage have been established in several in vivo and in vitro studies. Table-1 shows summary of all these studies.

**Table 1:** Summaries shows the chondro-protective effect of EGCG or green tea extract by antioxidant mechanism or other potential mechanisms.

<table>
<thead>
<tr>
<th>Experimental material</th>
<th>Compound</th>
<th>Observed effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human non-diseased, osteoarthritic and rheumatoid cartilage cell cultures.</td>
<td>EGCG</td>
<td>Inhibiting proteoglycan and type II collagen breakdown prophylactic for arthritis and may benefit the arthritis patient by reducing inflammation and slowing cartilage breakdown.</td>
<td>(21)</td>
</tr>
<tr>
<td>Human chondrocytes derived from OA cartilage.</td>
<td>EGCG</td>
<td>Inhibition in the production of PGE-2, iNOS and COX-2</td>
<td>(22)</td>
</tr>
<tr>
<td>Human chondrocytes were derived from OA cartilage</td>
<td>EGCG</td>
<td>Inhibits the IL-1β-induced production of NO in human chondrocytes by interfering with the activation of NF-kappa B</td>
<td>(23)</td>
</tr>
<tr>
<td>Human recombinant MMP-2 and Type I collagen</td>
<td>EGCG</td>
<td>Formation of a reversible complex with MMP-2, resulting in the inhibition of gelatinolytic activity of MMP-2, and enhanced pro- and activated MMP-2 binding to TIMP-2</td>
<td>(24)</td>
</tr>
<tr>
<td>Human chondrocytes.</td>
<td>EGCG</td>
<td>Inhibiting IL-1β-induced catabolic effects in OA chondrocytes that are dependent on c-Jun JNK.</td>
<td>(25)</td>
</tr>
<tr>
<td>Human ADAMTS clones and aggrecan purified from bovine nasal cartilage</td>
<td>EGCG</td>
<td>Inhibition of ADAMTS-1, -4 and -5aggrecan-degrading activity.</td>
<td>(26)</td>
</tr>
<tr>
<td>Human chondrocytes</td>
<td>EGCG</td>
<td>Inhibited the expression and activities of MMP-1 and MMP-13 in OA chondrocytes at physiologically achievable doses</td>
<td>(22)</td>
</tr>
<tr>
<td>Articular cultured chondrocytes</td>
<td>EGCG</td>
<td>Inhibited the IL-1β-activated MAPK, NF-kappaB, and AP-1 that signaling pathway.</td>
<td>(27)</td>
</tr>
<tr>
<td>Human chondrocytes were derived from OA cartilage</td>
<td>EGCG</td>
<td>Inhibited advance glycation end products induced expression of TNF-α and MMP-13 in human OA chondrocytes.</td>
<td>(20)</td>
</tr>
<tr>
<td>Cytokine-activated equine chondrocytes.</td>
<td>EGCG</td>
<td>Inhibited COX-2 expression and PGE-2 production in activated chondrocytes.</td>
<td>(28)</td>
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</table>
### Table 1 (Continued):

<table>
<thead>
<tr>
<th>Conditions</th>
<th>EGCG</th>
<th>Effect</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Primary osteoarthritic chondrocytes</td>
<td>EGCG</td>
<td>Inhibiting the activation of NF-κB and c-Jun N-JNK-MAPK in human chondrocytes.</td>
<td>(29)</td>
</tr>
<tr>
<td>Bovine chondrocytes</td>
<td>EGCG</td>
<td>The GAG content was increased and the percentage of collagen type II immunoreactive cells increased over the time.</td>
<td>(30)</td>
</tr>
<tr>
<td>Patients with rRA</td>
<td>Aqueous green tea extract</td>
<td>Joint protective and anti-inflammatory action against RA by lowering disease activity parameters and improving COMP, HA, IL-6, and TNF-α level to normal.</td>
<td>(19)</td>
</tr>
<tr>
<td>Posttraumatic OA mouse model</td>
<td>EGCG</td>
<td>Articular cartilage in mice exhibited reduced levels of MMP1, MMP3, MMP8, MMP13, ADAMTS-5, IL-1β and TNF-α mRNA and elevated gene expression of the MMP regulator Cbp/p300 interacting transactivator 2.</td>
<td>(31)</td>
</tr>
<tr>
<td>Rabbit articular chondrocytes</td>
<td>EGCG</td>
<td>Promote chondrocyte growth, proliferation, and enhance the secretion and synthesis of the cartilage extracellular matrix by upregulating expression levels of aggrecan, collagen II and Sox9 genes.</td>
<td>(32)</td>
</tr>
<tr>
<td>Patients with RA</td>
<td>Aqueous green tea extracts</td>
<td>Significant improvement in disease activity parameters, including CRP, and ESR, swollen and tender joints counts, and modified Stanford HAQ score.</td>
<td>(33)</td>
</tr>
<tr>
<td>Samples of human OA articular cartilage</td>
<td>EGCG</td>
<td>Reduction of ROS and NO radicals in chondrocytes.</td>
<td>(34)</td>
</tr>
</tbody>
</table>

EGCG= (-) epigallocatechin -3-gallate; OA=osteoarthritis; RA=rheumatoid arthritis; PGE-2-prostaglandin E2; iNOS = inducible nitric oxide synthases; COX-2=cyclooxygenase-2; IL-1 β = interleukin-1 beta; N-terminal kinase activity = JNK; NO=nitric oxide; NF-kappaB=nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK=mitogen activated protein kinase; MMP=matrix metalloproteinases; TIMPs=tissue inhibitors of metalloproteinases; ADAMTS=adam with thrombospondin motifs; AP-1=activator protein-1; TNF-α = tumor necrosis factor alpha; GAG= glycosaminoglycan; COMP= cartilage oligomeric matrix protein; HA= hyaluronic acid; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; HAQ= Health Assessment Questionnaire; ROS=reactive oxygen species.

### CONCLUSION

Green tea extract or EGCG can slowing the cartilage breakdown by inhibiting the proteoglycan and type II collagen breakdown, production of PGE-2, iNOS and COX-2, IL-1β-induced production of NO in human chondrocytes by interfering with the activation of NF-kappa B, gelatinolytic activity of MMP-2, IL-1β-induced catabolic effects in OA chondrocytes that are dependent on c-Jun JNK, ADAMTS-1, -4 and -5 aggrecan-degrading activity, expression and activities of MMP-1, MMP-3, and MMP-8, IL-1β-activated MAPK, NF-kappaB, and AP-1 that signaling pathway, advance glycation end products induced expression of TNF-α and MMP-13, the activation of c-Jun N-JNK-MAPK.

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improving the level of COMP, HA, IL-6, and TNF-α, and causes reduction of ROS and NO radicals in chondrocytes and enhanced pro- and activated MMP-2 binding to TIMP-2. It also can reduce the elevated gene expression of the MMP regulator Cbp/p300 interacting transactivator 2, CRP, and ESR, swollen and tender joints count, and modified Stanford HAQ score.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES


