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EPIGALOCATEQUINA-GALATO COMO POTENCIAL TERAPÊUTICO NO TRATAMENTO DE DOENÇAS INFLAMATÓRIAS RARAS INTRATÁVEIS

EPIGALLOCATECHIN-GALLATE AS POTENTIAL THERAPEUTIC IN THE TREATMENT OF INTRACTABLE RARE INFLAMMATORY DISEASES

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RESUMO

A epigalocatequina-galato é a principal catequina do chá verde e apresenta diversos efeitos benéficos à saúde humana por seu poder sobre os marcadores de estresse oxidativo, antiinflamatório e antiangiogênico. O chá verde é uma rica fonte de compostos antioxidantes capazes de remover espécies reativas de oxigênio. A Fibrodisplasia Ossificante Progressiva (FOP) é uma doença genética rara, crônico-degenerativa devastadora, de ossificação ectópica sem tratamento efetivo, cuja fisiopatologia envolve mecanismos pró-inflamatórios de difícil regulação. Sendo assim, catequinas do chá verde, principalmente a epigalocatequina-galato, poderão ser incluídas na lista de potenciais compostos na elaboração de agentes farmacológicos visando benefícios doenças inflamatórias raras como FOP.

Palavras-chave: Epigalocatequina-galato. Fibrodisplasia ossificante progressiva (FOP). Anti-inflamatório. Antiangiogênico. Chá-verde.

ABSTRACT

Epigallocatechin-gallate is the main catechin in green tea and has several beneficial effects on human health due to its power in anti-inflammatory and antiangiogenic markers of oxidative stress. Green tea is a rich source of antioxidant compounds that can scavenge oxygen radical species. Fibrodysplasia Ossificans Progressiva (FOP) is a devastating, rare, chronic degenerative genetic disease of ectopic ossification without effective treatment, whose pathophysiology involves pro-inflammatory mechanisms that are difficult to regulate. Therefore, green tea catechins, especially epigallocatechin-gallate, may be included in the list of potential compounds in the preparation of pharmacological agents aiming at benefits for intractable rare inflammatory diseases such as FOP.

Keywords: Epigallocatechin-gallate. Fibrodysplasia Ossificans progressiva (FOP). Anti-inflammatory. Antiangiogenic. Green tea.

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA AS A RARE INTRACTABLE MODEL DISEASE TARGET FOR EPIGALLOCATECHIN-GALLATE

Fibrodysplasia Ossificans Progressiva (FOP) is a rare and intractable genetic disease, clinically characterized at birth by a change in the hallux (*hallux valgus*) seen in the newborn. FOP is correlated with a classic mutation in the ACVR1 gene (type I activin receptor or ALK 2 receptor), and may show variations of mutations in the same protein, with clinical consequences that are often attenuated, while protein mutation at position 206 (H206R) prevails and is drastic (KAPLAN et al., 2017; HINO et al., 2017).

The child begins to present crises called flare-ups after three years old, on average, which, due to external or invasive traumas, or even immunogenic ones, determine inflammatory endochondral processes that are difficult to control and treat, which possibly result in irreversible heterotopic ossifications. These symptoms can occur throughout the individual's life, and may culminate in partial or total disability, restriction by joint immobilization with irreparable bone plates. Surgical attempts are not advisable due to the formation of ectopic bone in the regions affected by any surgical trauma or invasive procedure (KAPLAN et al., 2017; WENTWORTH, MASHARANI, and HSIAO, 2019 *apud* NASCIMENTO et al., 2021; BALANIUC et al., 2019).

Studies of possible treatments have been carried out by PALHARES et al., since 1997 (PALHARES, 1997; PALHARES and LEME, 2001; PALHARES et al., 2010; PALHARES et al., 2019), and by other research groups (WENTWORTH, MASHARANI, and HSIAO, 2019; MENG, WANG and HAO, 2022). However, despite the benefits achieved in the clinical stabilization of patients (PALHARES et al., 2019), there is still a long way to go to treat this disease due to its multifactorial aspect that involves a complex pathophysiology and with modifications of several genes involved, such as reported by Nascimento et al. (NASCIMENTO, 2018 (Thesis); NASCIMENTO et al., 2017; NASCIMENTO et al., 2021).

Treatment studies that aim to control FOP flare-ups without causing compromising adverse effects still need to be developed with great care. In the case of an orphan disease, clinical studies of treatments can be carried out by skipping pre-clinical steps, taking advantage of already known drugs and natural substances of an anti-inflammatory and antiangiogenic nature that do not compromise the quality of life of these patients (VENTURA et al., 2021), as is the case of the use of anti-ACVR1 antibodies, whose

monoclonal antibodies, depending on the dose, can stimulate heterotopic ossification and activated the signaling of the FOP ACVR1 mutant, according to Aykulet al., (2022).

Ideally, the use of placebos in these clinical trials should be short-term, as the quality of life of patients with FOP can be compromised extremely quickly. In addition, once obvious benefits of the tested medication are found, it should be made available to patients as soon as possible (HSIAO et al., 2018; SMILDE et al. 2022).

In this sense, the present review aims to consider epigallocatechin gallate (EGCG), a substance known but not yet verified for the treatment of rare diseases, as potentially beneficial in therapeutic associations for the treatment of Fibrodysplasia Ossificans Progressive.

EPIGALLOCATECHIN-GALLATE AS POTENTIAL THERAPEUTIC IN THE TREATMENT OF INTRACTABLE RARE INFLAMMATORY DISEASES

EGCG is the main catechin found in *Camellia sinensis* or green tea, which has been scientifically studied and reported to have benefits for human health, if consumed methodically and systematically, as a natural medicinal drug. In this brief review, we would like to emphasize the benefits of epigallocatechin, referring to its anti-inflammatory and antiangiogenic potential, mainly as a proposal for its use for patients with FOP. In addition, green tea has been reported to prevent neurodegenerative diseases such as Alzheimer's and Parkinson's disease, modulate blood cholesterol levels, have an antioxidant preventive effect on cancer and an anti-inflammatory effect on obesity (CARLSON et al., 2007; CHEN et al., 2018; WANG et al., 2014; HANG et al., 2005).

As functional foods, *Camellia sinensis* has been widely investigated due to its beneficial bioactive properties, as well its flavonoids, secondary metabolites of polyphenols responsible for several therapeutic properties (PIETAA, 2000)21. The bioactive interest of phyto-nutrients from *Camellia sinensis* flavonoids has also been observed in many studies, highlighting evidence of their potential in the prevention and treatment of several diseases. In addition to antioxidants and anti-inflammatory effects, Camellia sinensis flavonoids have physiological actions in humans, namely: antihypertensive, hypoglycemic, antimutagenic and antimicrobial effects (BASU, LUCAS, 2007; SENGER, SCHAWAKE, GOTTLIEB, 2010; CHAKRAWARTI, 2016, ARAÚJO, 2019; GONÇALVES, 2021).

Besides, the chemical composition of green tea includes several classes of phenolic compounds or flavonoids, in addition to caffeine. The main flavonoids present in green tea are catechin monomers. The main catechins that stand out for their concentration and structure are epicatechin (EC), epigallocatechin (EPGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) (CHE. et al., 2018; WANG et al., 2014).

EGCG, on the other hand, corresponds to the most abundant of the catechins in green tea, varying from 50 to 80% in concentration, which can correspond approximately between 200-300 mg per universal measure of tea, which corresponds to 240 ml. In addition, the catechin content in the vegetable depends on several external factors, such as the way the leaves are processed before drying, geographical location of planting and growing conditions (YANAGIMOTO, OCHI, LEE, 2003; SINGHET al., 2016).

Regarding the antioxidant potential, among the polyphenols of catechins, EGCG is a target of research, due to the notorious evidence of its anti-inflammatory activity associated with its antioxidant capacity. A vast scientific literature corroborates that the daily intake of antioxidants, mainly phenolic compounds, can delay the onset of numerous diseases that evolve with an important inflammatory process, such as carcinogenesis and diabetes mellitus (HAN et al., 2004; THAWONSUWANET al., 2010).

Furthermore, EGCG has high oxidative stability, due to its molecular structure and, therefore, plays a fundamental role in the prevention of free radicals (HALLIWELL; GUTTERIDGE, 2007; LUZ et al, 2011; Andrade-WARTHA, 2007). The modulating action of antioxidants from this compound has been mentioned within the context of oxidative stress, and may act on innate and adaptive immunity, stimulating the production of cytokines (SILVA et al., 2012; CASTRO et al, 2013).

Oxidative stress and inflammation are co-inherent in cell signaling and the perpetuation of the inflammatory response, both acting within a form of positive feedback, synergistically participate in a cascade of events that culminate in cell damage, including altering mitochondrial function (FARZAEIT al., 2019). Mitochondria produce energy, with consequent generation of free radicals, being a target of Reactive Oxygen Species (ROS) that play a crucial role in inflammation. Furthermore, they can cause oxidative damage to macromolecules and, consequently, interfere with vital cellular processes (VALENTI et al., 2018).

EGCG is able to exert its anti-inflammatory activity by modulating transcription and gene expression (CHU et al., 2017)38. An in vitro study showed a reduction in the expression of inflammatory factors such as toll-like receptor-4 (Toll 4), nuclear factor kappa-B (NF-κB) and inducible nitric oxide synthase (iNOS), by catechin activities, combined or individually, as well as downregulated the release of tumor necrosis factor (TNF-α), interleukin (IL-1 and IL-6), decreasing inflammation (LAKSHMI et al., 2020). Reddy et al. (2020)40 demonstrated that the suppression of the NF-kB pathway at the endothelial level indicated the important anti-inflammatory effect of EGCG and its therapeutic potential in cardiovascular diseases. It was also observed the inhibition of cell migration capacity, myeloperoxidase (MPO) activity and hypochlorous acid (HOCl) production and the suppression of ROS, nitric oxide and peroxynitrite production, as well as the induction of the activity of antioxidant enzymes and erythroid 2-related factor 2 (Nrf2 mRNA) levels, consequently, stimulating phagocytic capacity and calcium release in vitro (MARINOVIC, 2015).

Motor alterations, learning difficulties and moderate to severe cognitive deficits have already been reported in the literature in patients with Down syndrome (DS) and Alzheimer's disease (AD). Diseases where dysfunction of a protein called dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a (DYRK1A) is found. In animals and humans EGCG is able to decrease the activity of DYRK1A by its antioxidant action. The inhibitory effect of DYRK1A by the action of EGCG is associated with the control of early cellular aging by minimizing mitochondrial dysfunction and decreasing oxidative stress, which explains the improvement in cognitive function in patients with SD and AD (GONÇALVES, 2021; PERVIN, 2018).

In AD patients, EGCG would act on neuroinflammation caused by the formation of amyloid fibrils that accumulate, resulting in the aggregation of β-amyloid plaques (Aβ) in the brain, and by hyperphosphorylation of tau proteins, through its antioxidant, anti-inflammatory and neuroprotectors of EGCG (CASCELLA et al., 2017; XICOTA et al., 2017; ZHANG et al., 2020; BIRCH et al., 2014). In the same way that EGCG has its positive effects, especially in diseases as AD, Parkinson's, or even as a preventive of cardiovascular disease and atherosclerosis (YAMAGATA, 2020).

The installation of the oxidative stress process results from the existence of an imbalance between oxidant and antioxidant compounds. This promotes the excessive

generation of free radicals, or a delay in the speed of their removal. Such process leads to the oxidation of biomolecules with consequent loss of their biological functions, and/or homeostatic imbalance, whose manifestation is the potential oxidative damage against cells and tissues (Halliwell, Whiteman, 2004)48. In this context, EGCG is considered one of the most important antioxidant catechins for promoting anti-inflammatory properties and has been widely used as a strategy to modulate inflammation and oxidative stress (TRAN, 2013).

EGCG, in addition to increasing cell viability, decreasing ROS production and the expression of endoplasmic reticulum stress markers, improves mitochondrial function, attenuates inflammation by inhibiting pro-inflammatory mediators such as myeloperoxidases or the cyclooxygenase-2 enzyme (COX-2), through the elimination of ROS, promoting a decrease in the transcription of inflammatory factors at the systemic and brain level (FRANÇA, 2013; SINGH et al., 2016; CHU et al., 2017). EGCG can also induce the production of antioxidant enzymes (SHARMA, 2014; ZANWAR et al., 2014).

In addition to its anti-inflammatory effect, EGCG increased the activities of antioxidant enzymes such as superoxide dismutase and catalase in the brain in multiple sclerosis, an autoimmune disease with an inflammatory process of the central nervous system (LEVITES, 2002) 53. EGCG also altered the balance between T cell subsets, reducing Th1 and Th17 pro-inflammatory T cells and promoting regulatory T cells (TREG) with a consequent decrease in the production of interferon gamma (IFN-γ) and IL-17 (WANG, 2012).

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease, which means that the immune system attacks the patient's own healthy cells causing inflammation in the affected parts of the body, and an RA study evaluating the effectiveness of EGCG observed a lower incidence of arthritis and downregulation of the following inflammatory mediators IFN-γ, TNF-α, COX-2 (HAQQI, 1999).

Another action of EGCG is its antiangiogenic power, that is, anti-neovascularization (FERRARA 2001; LECOUTER, 2003). Angiogenesis depends on the proliferation of endothelial cells, which has the characteristic of lining blood vessels. There is normal or physiological angiogenesis, for example, when there is a need to repair tissue damaged by trauma. However, certain conditions arising from diseases, such as neoplasms,

rheumatoid arthritis, FOP, etc., are called pathological angiogenesis (FOLKMAN and KLAGSBRUN, 1987).

In angiogenesis, the vascular endothelial Growth Factor (VEGF) is the pro-angiogenic factor (SENGER et al., 1983). VEGF is emphasized, among the molecules that regulate tumor angiogenesis, (FERRARA, 2001). The authors KONDO et al., (2002), reported that green tea, which contains epigallocatechin, which, in addition to suppressing tumor cells, also inhibits angiogenesis cells (Rodriguez et al., 2006) 61, ; which was also reported by other authors (JUNG and ELLIS, 2001). EGCG inhibits endothelial proliferation cells, inhibits VEGF receptor binding, VEGFR-2 phosphorylation, VEGFR-2 expression and matrix metalloproteinase activity. in endothelial cells, all processes involved in angiogenesis (LEE et al., 2004; TANG, MEYDANI, 2001; LAMY et al., 2002).

Within this same context, Fibrodysplasia Ossificans Progressiva is a disease that develops with an inflammatory process and the formation of ectopic ossifications, and within this pathophysiological cascade, angiogenesis and neurogenesis are necessary to form ectopic ossifications. Therefore, it can be hypothesized that EGCG could have a protective effect in this orphan disease.

During flare-ups in FOP patients, there is an increase in tissue protein expression and in the blood circulation of several inflammatory cytokines (GILROY and DEMAEYER, 2015), from tissue destruction by the initial transformation into cartilaginous tissue and subsequent ectopic ossification (HILDEBRANd et al., 2017). In this context, it is believed that EGCG may have beneficial effects in the patient with FOP, who has a complex imbalance of many pro-inflammatory genes such as *TNFa* and pro-ossifying genes such as *Runx2* (Nascimento et al., 2021) 4, mainly in the pre-chondrogenesis phase that occurs right after flare-ups.

CONCLUSIONS

EGCG acts as an anti-inflammatory, antioxidant and antiangiogenic agent, acting to block pro-inflammatory cytokines. Therefore, EGCG probably has a potential effect in the therapeutic application for inflammatory diseases such as FOP.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

Abbreviations: ACVR1 gene - type I activin receptor or ALK 2 receptor; AD- Alzheimer's disease; Aβ -β-amyloid plaques; COX-2 - myeloperoxidases or the cyclooxygenase-2 enzyme; DS- Down syndrome; DYRK1A- dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a; EC- epicatechin; ECG- epicatechin gallate; EPGC- epigallocatechin; EGCG – epigallocatechin-gallate; FOP - Fibrodysplasia Ossificans Progressiva; H206R - protein mutation at position 206; HOCl- hypochlorous acid; IFN-γi - nterferon gamma; L-1- interleukin type 1; IL-17- interleukin type 17; IL-6- interleukin type 6; iNOS-Inducible nitric oxide synthase; MPO- myeloperoxidase; NF-κB - nuclear factor kappa-B; Nrf2 mRNA - erythroid 2-related factor 2; RA- Rheumatoid arthritis; ROS- Reactive Oxygen Species; Th1 – kind of the pro-inflammatory T cells; Th17- kind of the pro-inflammatory T cells; TNF-α- tumor necrosis factor; TOLL 4- toll-like receptor-4; TREG- promoting regulatory T-cells; VEGF - vascular endothelial Growth Factor; VEGFR-2 –vascular endothelial growth factor receptor type 2.

REFERENCES

AYKUL S, Huang L, WANG L, DAS NM, REISMAN S, RAY Y, et al. ACVR1 antibodies exacerbate heterotopic ossification in fibrodysplasia ossificans progressiva (FOP) by activating FOP-mutant ACVR1. Journal of Clinical Investigation. 2022 May 5; [cited 2022 Aug 15];132(12):153-82–89. doi: 10.1172/JC1153792.

BALANIUC SLB, NASCIMENTO DR, PALHARES DB, PALHARES MG, ALVES F, VIEIRA F de O, et al. Fibrodisplasia Ossificante Progressiva: genes pró-inflamatórios e pró-fibróticos como alvos de pesquisa e tratamento de sintomas clínicos desta rara e devastadora doença. NBC-Periódico Científico do Núcleo de Biociências [Internet]. 2019 Jul 9 [cited 2022 Aug 29];9(17). Available from: https://www.metodista.br/revistas/revistas-izabela/index.php/bio/article/view/1949.

BASU A, Lucas E. Special Article Mechanisms and Effects of Green Tea on Cardiovascular Health. Nutri Rev [Internet]. 2007 [cited 2022 Jun 12];361–75. Available from: https://academic.oup.com/nutritionreviews/article-pdf/65/8/361/24092193/nutritionreviews65-0361.pdf.

BIRCH AM, KATSOURI L, SASTRE M. Modulation of inflammation in transgenic models of Alzheimer's disease. Journal of Neuroinflammation. 2014;11(1):25.

CASCELLA M, BIMONTE S, MUZIO MR, SCHIAVONE V, CUOMO A. The efficacy of Epigallocatechin-3-gallate (green tea) in the treatment of Alzheimer's disease: an overview of pre-clinical studies and translational perspectives in clinical practice. Infectious Agents and Cancer. 2017 Jun 19;12(1).

CARLSON JR, BAUER BA, VINCENT A, LIMBURG PJ, WILSON T. Reading the Tea Leaves: Anticarcinogenic Properties of (-)-Epigallocatechin-3-Gallate. Mayo Clinic Proceedings [Internet]. 2007 Jun 1 [cited 2022 Aug 29];82(6):725–32. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0025619611611932.

CHAKRAWARTI L, AGRAWAL R, DANG S, GUPTA S, GABRANI R. Therapeutic effects of EGCG: a patent review. Expert Opinion on Therapeutic Patents [Internet]. 2016 Aug 1 [cited 2022 Aug 29];26(8):907–16. Available from: https://pubmed.ncbi.nlm.nih.gov/27338088/7.

CHEN S-Q, WANG Z-S, MA Y-X, ZHANG W, LU J-L, LIANG Y-R, et al. Neuroprotective Effects and Mechanisms of Tea Bioactive Components in Neurodegenerative Diseases. Molecules. 2018 Feb 25;23(3):512.

CASTRO VD DE, GUALTIERI K DE A, SAITO AY, TATAKIHARA RI, ODA JMM, CUSTODIO LA, et al. Análise dos efeitos da epigalocatequina-3-galato (EGCG) de Camelliasinensis (chá verde) em modelo de hepatotoxicidade químicaexperimental induzida pela Dietilnitrosamina (DEN). Semina cienc biol saude [Internet]. 2013 [cited 2022 Aug 29];215–28. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/lil-726428.

CHU C, DENG J, MAN Y, QU Y. Green Tea Extracts Epigallocatechin-3-gallate for Different Treatments. BioMed Research International [Internet]. 2017 [cited 2019 Jul 27];2017:1–9. Available from: https://www.hindawi.com/journals/bmri/2017/5615647/.

EVANS KN, FORSBERG JA, POTTER BK, HAWKSWORTH JS, BROWN TS, ANDERSEN R, et al. Inflammatory Cytokine and Chemokine Expression is Associated With Heterotopic Ossification in High-Energy Penetrating War Injuries. Journal of Orthopaedic Trauma. 2012 Nov;26(11):e204–13.

FARZAEI MH, BAHRAMSOLTANI R, ABBASABADI Z, BRAIDY N, NABAVI SM. Role of green tea catechins in prevention of age-related cognitive decline: Pharmacological targets and clinical perspective. Journal of Cellular Physiology. 2018 Sep 6;234(3):2447–59.

FERRARA N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. American Journal of Physiology-Cell Physiology. 2001 Jun 1;280(6):C1358–66.

FOLKMAN J, KLAGSBRUN M. Angiogenic factors. Science. 1987 Jan 23;235(4787):442–7.

FRANÇA BK, MELO ALVES MR, SILVEIRA SOUTO FM, TIZIANE L, FREIRE BOAVENTURA R, GUIMARÃES A, et al. Peroxidação lipídica e obesidade: Métodos para aferição do estresse oxidativo em obesos. GE Jornal Português de Gastrenterologia. 2013 Sep;20(5):199–206.

GILROY D, DE MAEYER R. New insights into the resolution of inflammation. Seminars in Immunology. 2015 May;27(3):161–8.

GONÇALVES PB, SODERO ACR, CORDEIRO Y. Green Tea Epigallocatechin-3-gallate (EGCG) Targeting Protein Misfolding in Drug Discovery for Neurodegenerative Diseases. Biomolecules [Internet]. 2021 May 20 [cited 2022 Aug 29];11(5):767. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8160836/

HAQQI TM, ANTHONY DD, GUPTA S, AHMAD N, LEE MS, KUMAR GK, et al. Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 1999 Apr 13 [cited 2022 Aug 29];96(8):4524–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10200295/.

HALLIWELL B, WHITEMAN M. Measuring reactive species and oxidative damagein vivoand in cell culture: how should you do it and what do the results mean? British Journal of Pharmacology [Internet]. 2004 May [cited 2019 Dec 18];142(2):231–55. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1574951/.

HAN D-W, PARK YH, KIM JK, LEE K-Y, HYON S-H, SUH H, et al. Effects of green tea polyphenol on preservation of human saphenous vein. Journal of Biotechnology [Internet]. 2004 May 27 [cited 2022 Aug 29];110(2):109–17. Available from: https://pubmed.ncbi.nlm.nih.gov/15121331/.

HILDEBRAND L, GABER T, KÜHNEN P, MORHART R, UNTERBÖRSCH H, SCHOMBURG L, et al. Trace element and cytokine concentrations in patients with Fibrodysplasia Ossificans Progressiva (FOP): A case control study. Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS) [Internet]. 2017 Jan 1 [cited 2022 Aug 29];39:186–92. Available from: https://pubmed.ncbi.nlm.nih.gov/27908413/.

HINO K, HORIGOME K, NISHIO M, KOMURA S, NAGATA S, ZHAO C, et al. Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva. The Journal of Clinical Investigation [Internet]. 2017 Sep 1 [cited 2022 Aug 29];127(9):3339–52. Available from: https://pubmed.ncbi.nlm.nih.gov/28758906/.

HALLIWELL B, GUTTERIDGE JMC. Free Radicals in Biology and Medicine [Internet]. Fifth Edition. Oxford University Press. Oxford, New York: Oxford University Press; 2015 [cited 2022 Aug 29]. Available from: https://global.oup.com/academic/product/free-radicals-in-biology-and-medicine-9780198717485?cc=pt&lang=en&.

HSIAO EC, DI ROCCO M, CALI A, ZASLOFF M, AL MUKADDAM M, PIGNOLO RJ, et al. Special considerations for clinical trials in fibrodysplasia ossificans progressiva (FOP). British Journal of Clinical Pharmacology [Internet]. 2019 Jun 1;85(6):1199–207. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533500/.

HUNG P-F, WU B-T, CHEN H-C, CHEN Y-H, CHEN C-L, WU M-H, et al. Antimitogenic effect of green tea (-)-epigallocatechin gallate on 3T3-L1 preadipocytes depends on the ERK and Cdk2 pathways. American Journal of Physiology Cell Physiology [Internet]. 2005 May 1;288(5):C1094-1108. Available from: https://pubmed.ncbi.nlm.nih.gov/15647388/.

JUNG YD, ELLIS LM. Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. International Journal of Experimental Pathology. 2002 Jan 5;82(6):309–16.

KAPLAN FS, PIGNOLO RJ, AL MUKADDAM MM, SHORE EM. Hard targets for a second skeleton: therapeutic horizons for fibrodysplasia ossificans progressiva (FOP). Expert Opinion on Orphan Drugs. 2017 Mar 17;5(4):291–4.

KONDO T, OHTA T, IGURA K, HARA Y, KAJI K. Tea catechins inhibit angiogenesis in vitro, measured by human endothelial cell growth, migration and tube formation, through inhibition of VEGF receptor binding. Cancer Letters. 2002 Jun;180(2):139–44.

LAKSHMI SP, REDDY AT, KODIDHELA LD, VARADACHARYULU NC. The tea catechin epigallocatechin gallate inhibits NF-κB-mediated transcriptional activation by covalent modification. Archives of Biochemistry and Biophysics [Internet]. 2020 Nov 30 [cited 2022 Aug 29];695:108620. Available from: https://pubmed.ncbi.nlm.nih.gov/33038311/.

LAMY S, GINGRAS D, BÉLIVEAU R. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation. Cancer Research [Internet]. 2002 Jan 15 [cited 2022 Aug 29];62(2):381–5. Available from: https://pubmed.ncbi.nlm.nih.gov/11809684/.

LEE YK, BONE ND, STREGE AK, SHANAFELT TD, JELINEK DF, KAY NE. VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. Blood. 2004 Aug 1;104(3):788–94.

LECOUTER J, MORITZ DR, LI B, PHILLIPS GL, LIANG XH, GERBER H-P, et al. Angiogenesis-Independent Endothelial Protection of Liver: Role of VEGFR-1. Science. 2003 Feb 7;299(5608):890–3.

LEVITES Y, WEINREB O, MAOR G, YOUDIM MBH, MANDEL S. Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. Journal of Neurochemistry. 2001 Dec 20;78(5):1073–82.

LUZ HKM, WANDERLEY LS, FAUSTINO LR, SILVA CMG DA, FIGUEIREDO JR DE, RODRIGUES APR. Role of Antioxidants Agents in Germ Cells and Embryos Cryopreservation [Internet]. Acta Scientiae Veterinariae. 2021 [cited 2022 Aug 29]. Available from: https://www.ufrgs.br/actavet/39-2/PUB%20956.pdf.

MARINOVIC MP, MORANDI AC, OTTON R. Green tea catechins alone or in combination alter functional parameters of human neutrophils via suppressing the activation of TLR-4/NFκB p65 signal pathway. Toxicology in Vitro. 2015 Oct;29(7):1766–78.

MENG X, WANG H, HAO J. Recent progress in drug development for fibrodysplasia ossificans progressiva. Molecular and Cellular Biochemistry. 2022 May 10; J Trace Elem Med Biol. 2017 Jan;39:186-192. Available from: doi: 10.1016/j.jtemb.2016.10.001.

NASCIMENTO DR, BALANIUC SLB, PALHARES DB, UNDERWOOD A, PALHARES MG, ALVES F, et al. Rare and intractable fibrodysplasia ossificans progressiva shows different PBMC phenotype possibly modulated by ascorbic acid and propranolol treatment. Intractable & Rare Diseases Research [Internet]. 2021 Aug 31 [cited 2022 Aug 29];10(3):179–89. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8397826/.

NASCIMENTO DR, GIULIANI LR, PALHARES MG, ALVES F, MARTINS SF, VIEIRA FO, et al. Ascorbic acid modulates the expression of genes involved in heterotopic ossification. NBC-Periódico Científico do Núcleo de Biociências [Internet]. 2017 Nov 29 [cited 2022 Aug 29];7(14). Available from: https://www.metodista.br/revistas-izabela/index.php/bio/article/view/1543.

NASCIMENTO, D. R. Estudo da genômica funcional da fibrodisplasia ossificante progressiva em células mononucleares de sangue periférico: modulação gênica pela vitamina C e pelo ß-bloqueador propranolol sobre a expressão de transcritos envolvidos na ossificação heterotópica. 2018. 93 f. Tese (Doutorado em Ciências da Saúde e Biológicas). Programa de Pós-Graduação em Saúde e Desenvolvimento na Região Centro-Oeste, Universidade Federal do Mato Grosso do Sul (UFMS), Campo Grande/MS, 2018.

NASCIMENTO, D. R. Estudo da genômica funcional da fibrodisplasia ossificante progressiva em células mononucleares de sangue periférico: modulação gênica pela vitamina C e pelo ß-bloqueador propranolol sobre a expressão de transcritos envolvidos na ossificação heterotópica. 2018. 93 f. Tese (Doutorado em Ciências da Saúde e Biológicas). Programa de Pós-Graduação em Saúde e Desenvolvimento na Região Centro-Oeste, Universidade Federal do Mato Grosso do Sul (UFMS), Campo Grande/MS, 2018.

PALHARES DB. Myositis Ossificans Progressive. Calcified Tissue International. 1997. Apr 1;60(4):394–4.

PALHARES DB, LEME LM. A perspective on the control of myositis ossificans progressiva. Jornal De Pediatria [Internet]. 2001 Sep 1 [cited 2022 Aug 29];77(5):431–4. Available from: https://pubmed.ncbi.nlm.nih.gov/14647850/

PALHARES DB, LEME LM, NAKA ÉN, MELNIKOV P. Fibrodysplasia Ossificans Progressiva: Oral Ascorbate and Intravenous Bisphosphonate during Flare-Ups. [Internet]. 2010. Available from:https://ouci.dntb.gov.ua/en/works/4Nan2ge7/.

PALHARES DB, NASCIMENTO DR, PALHARES MG, LOPES S, DE L, CRISTHINA P, et al. Propranolol and ascorbic acid in control of fibrodysplasia ossificans progressiva flare-ups due to accidental falls. Intractable & Rare Diseases Research [Internet]. 2019 Feb 1;8(1):24–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6409115/.

PERVIN M, UNNO K, OHISHI T, TANABE H, MIYOSHI N, NAKAMURA Y. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry [Internet]. 2018 May 29;23(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6099654/.

PIETTA, P.G. Flavonoids as Antioxidants [Internet]. Journal of natural products. 2000. Available from: https://pubmed.ncbi.nlm.nih.gov/10924197/.

REDDY AT, LAKSHMI SP, MARUTHI PRASAD E, VARADACHARYULU NCH, KODIDHELA LD. Epigallocatechin gallate suppresses inflammation in human coronary artery endothelial cells by inhibiting NF-κB. Life Sciences. 2020 Oct;258:118136.

RODRIGUEZ SK, GUO W, LIU L, BAND MA, PAULSON EK, MEYDANI M. Green tea catechin, epigallocatechin-3-gallate, inhibits vascular endothelial growth factor angiogenic signaling by disrupting the formation of a receptor complex. International Journal of Cancer. 2006 Apr 1;118(7):1635–44.

SHARMA, R. (2014). Chapter 59 - Polyphenols in Health and Disease: Practice and Mechanisms of Benefits. *In*: Watson RR, Preedy VR, Zibadi S. Polyphenols in Human Health and Disease. Elsevier; 2014.

SENGER D, GALLI S, DVORAK A, PERRUZZI C, HARVEY V, DVORAK H. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983 Feb 25;219(4587):983–5.

SENGER AEV, SCHWANKE CHA, GOTTLIEB MGV. Chá verde (Camellia sinensis) e suas propriedades funcionais nas doenças crônicas não transmissíveis. Sci med [Internet]. 2010 [cited 2022 Aug 29];292–300. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/lil-583408.

SILVA CSE DOS S, FRAZÃO F. Plantas utilizadas como chás com propriedades anti-inflamatórias e antioxidantes. [Internet]. 2012. Available from: https://recil.ensinolusofona.pt/bitstream/10437/3272/1/Carla_Silva_Monografia.pdf.

SINGH NA, MANDAL AKA, KHAN ZA. Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG). Nutrition Journal. 2015 Dec;15(1).

SMILDE BJ, STOCKKLAUSNER C, KEEN R, WHITTAKER A, BULLOCK AN, VON DELFT A, et al. Protocol paper: a multi-center, double-blinded, randomized, 6-month, placebo-controlled study followed by 12-month open label extension to evaluate the safety and efficacy of Saracatinib in Fibrodysplasia Ossificans Progressiva (STOPFOP). BMC Musculoskeletal Disorders. 2022 Jun 1;23(1).

THAWONSUWAN J, KIRON V, SATOH S, PANIGRAHI A, VERLHAC V. Epigallocatechin-3-gallate (EGCG) affects the antioxidant and immune defense of the rainbow trout, Oncorhynchus mykiss. Fish Physiology and Biochemistry [Internet]. 2010 Sep 1 [cited 2022 Aug 29];36(3):687–97. Available from: https://pubmed.ncbi.nlm.nih.gov/19680766/.

TANG F-Y, MEYDANI M. Green Tea Catechins and Vitamin E Inhibit Angiogenesis of Human Microvascular Endothelial Cells Through Suppression of IL-8 Production. Nutrition and Cancer. 2001 Sep;41(1-2):119–25.

TRAN J. Green Tea: A Potential Alternative Anti-Infectious Agent Catechins and Viral Infections. Advances in Anthropology. 2013;03(04):198–202.

VALENTI D, BRAIDY N, DE RASMO D, SIGNORILE A, ROSSI L, ATANASOV AG, et al. Mitochondria as pharmacological targets in Down syndrome. Free Radical Biology and Medicine. 2018 Jan;114:69–83.

VENTURA F, WILLIAMS E, IKEYA M, BULLOCK AN, TEN DIJKE P, GOUMANS M-J, et al. Challenges and Opportunities for Drug Repositioning in Fibrodysplasia Ossificans Progressiva. Biomedicines [Internet]. 2021 Feb 19 [cited 2022 Aug 29];9(2):213. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7922784/.

XICOTA L, RODRIGUEZ-MORATO J, DIERSSEN M, de la Torre R. Potential Role of (-)-Epigallocatechin-3-Gallate (EGCG) in the Secondary Prevention of Alzheimer Disease. Current Drug Targets. 2016 Dec 29;18(2):174–95.

ZHANG S, ZHU Q, CHEN J-Y, OUYANG D, LU J-H. The pharmacological activity of epigallocatechin-3-gallate (EGCG) on Alzheimer's disease animal model: A systematic review. Phytomedicine. 2020 Dec;79:153316.

ZANWAR, A. A., et al. (2014). Chapter 21 - Antioxidant Role of Catechin in Health and Disease. *In*: *In*: Watson RR, Preedy VR, Zibadi S. Polyphenols in Human Health and Disease. Elsevier; 2014.

ZEFERINO, ASS. Potencial antimicrobiano da epigalocatequina-3-galato do chá verde contra MRSA de isolados hospitalares e da comunidade [Internet]. repositorio.ipl.pt. 2020. Available from: https://repositorio.ipl.pt/handle/10400.21/12747

YAMAGATA K. Protective Effect of Epigallocatechin Gallate on Endothelial Disorders in Atherosclerosis. Journal of Cardiovascular Pharmacology. 2020 Apr;75(4):292–8.

YANAGIMOTO K, OCHI H, LEE K-G, SHIBAMOTO T. Antioxidative Activities of Volatile Extracts from Green Tea, Oolong Tea, and Black Tea. Journal of Agricultural and Food Chemistry. 2003 Dec;51(25):7396–401.

WANG J, REN Z, XU Y, XIAO S, MEYDANI SN, WU D. Epigallocatechin-3-Gallate Ameliorates Experimental Autoimmune Encephalomyelitis by Altering Balance among CD4+ T-Cell Subsets. The American Journal of Pathology. 2012 Jan;180(1):221–34.

WANG S, MOUSTAID-MOUSSA N, CHEN L, MO H, SHASTRI A, SU R, et al. Novel insights of dietary polyphenols and obesity. The Journal of Nutritional Biochemistry [Internet]. 2014 Jan;25(1):1–18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3926750/.

WARTHA ERS de A. Propriedades antioxidantes de clones do pedúnculo de Anacardium occidentale L.: feito sobre a lipoperoxidação e enzimas participantes do sistema antioxidante de defesa do organismo animal [Internet]. www.teses.usp.br. 2007 [cited 2022 Aug 29]. Available from: https://www.teses.usp.br/teses/disponiveis/9/9131/tde-08062017-112859/pt-br.php.

WENTWORTH KL, MASHARANI U, HSIAO EC. Therapeutic advances for blocking heterotopic ossification in fibrodysplasia ossificans progressiva. British Journal of Clinical Pharmacology. 2019 Jan 6;85(6):1180–7.