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Effects of green tea polyphenol on Sjogren's syndrome

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Abstract : Sjogren's syndrome (SS) is a relatively common autoimmune disorder .The most significant feature of (SS) is lymphocytic infiltration of the lacrimal and salivary glands, associated with destruction of their secretory functions, resulting in xerostomia and xerophthalmia . The green tea polyphenol Epigallocatechin-3-gallate (EGCG) can effect this syndrome in different ways, and can interfere with the symptoms by reducing it with different mechanisms .This paper, will briefly discuss it's effects on (SS).

Introduction : To start, an autoimmune disease is a condition in which your immune system mistakenly attacks your body. Sjogren's syndrome, autoimmune disorder characterized by lymphocytic infiltration and acinar destruction of salivary and lacrimal glands leading to dry mouth and dry eyes, with a poorly understood etiology. The presented theory is that an environmental factor may trigger an immune reaction, and even genetic factors appear to contribute in the etiology. 90% of patients of (SS) are women with a mean age of 50 years, this suggested that there might be a gender like susceptibility. In about half of the cases the syndrome occurs in association with another autoimmune disease, on this basis the syndrome is divided into:

1. Primary Sjogren's : dry eyes (xerophthalmia or keratoconjunctivitis) and dry mouth (xerostomia) are the main features.

2. Secondary Sjogren syndrome: the traid of xerostomia, xerophthalmia, and an autoimmune connective tissue disease (usually rheumatoid arthritis). In the US, Sjogren's syndrome affects about 1%

of the population . (1) In China, a one regional study with 26,000 subjects, suggested that the prevalence of primary SS was only 0.03% . (2) For xerostomia a study showed that in a group of 1003 Japanese individuals with an average age of 66, 9.1% experienced dry mouth during eating , while in the US, one study found out that in group of 2481 individuals of mean age 65-84 years old, 27% reported with either dry eyes or dry mouth.(3) The herbal extract and Chinese traditional medicine have been used to treat SS and xerostomia with a degree of success. These naturally materials may provide an alternative therapy for SS disorders which may be the cause of this geographical distribution of the disease . One group of potentially useful catechins is green tea polyphenols (GTPs) is a group of polyphenolic compounds present in leaves of *Camellia sinensis*. The major ones are: epicatechin (EC), epigallocatechin(EGC),epicatechin-3-gallate(ECG),and lastly epigallocatechin-3-gallate (EGCG) is the most abundant and widely studied of these compounds.(4-5) More recently, a large number of in-vitro and in-vivo scientific studies have supported this ancient contention that the polyphenols from green tea can provide a number of health benefits. discussing it's effects on Sjogren's syndrome specifically (EGCG).

Aims : To investigate if EGCG protects against certain autoimmune-induced pathological changes in salivary glands of non-obese diabetic mouse model for SS.

Materials and methods :

•**In source number 1:** (EGCG) normalizes the elevated levels of proliferating cell nuclear antigen (PCNA), a key component of DNA repair, in the NOD (non-obese diabetic) mouse model for SS. The current study examined levels of the antioxidant enzymes peroxiredoxin 6 (PRDX6), catalase and superoxide dismutase (SOD), as well as PCNA, in NOD mice, a model for primary SS, and determined the effect of EGCG on their expression .

•**In source number 2 :** Two groups 15 NOD mice were allowed to either water or 0.2% of GTPs starting at the 9th week of age after the onset of autoimmune disease, each animal we're allowed to progress with the disease for 3 weeks. To determine that the GTPs (EGCG) may provide the protection against autoimmune-induced tissue damage in SS.

Results :

Source number 1 showed that, EGCG-fed mice exhibited normal levels of PCNA and peroxiredoxin 6, comparable to healthy water fed group of mice. EGCG consumption normalizes the expression of these biomarkers in this model, these observations could lead to early diagnosis and intervention of autoimmune disease.

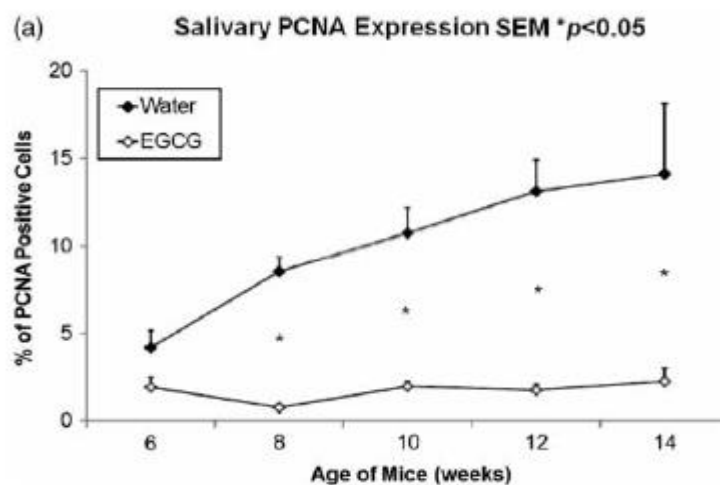


Figure1. Percentage of PCNA-positive cells in the submandibular salivary glands the of NOD.B10.Sn-H2 mice at the age 6-14 weeks. EGCG maintains a normal level of PCNA in the salivary gland in NOD.B10.Sn-H2 mice. A) EGCG-fed mice maintain a normal PNCA expression in salivary glands. (6)

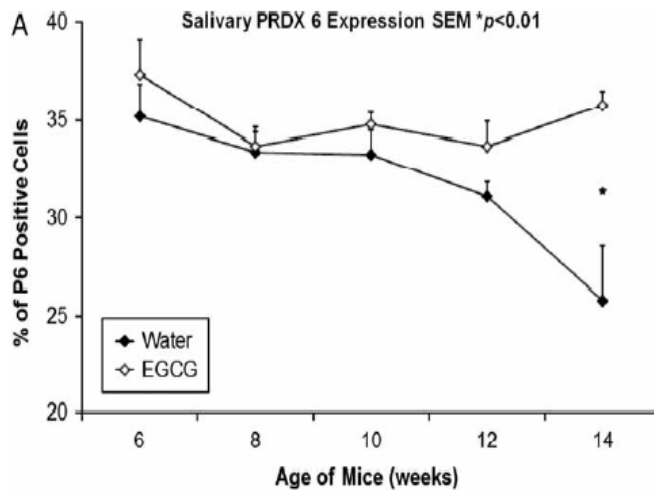


Figure 2. percentage of peroxiredoxin 6-positive cells in the salivary glands of NOD.B10.Sn-H2 mice at the age of 6-14 weeks . PRDX 6 expression is kept at normal at EGCG-fed mice in the salivary glands, EGCG-fed mice maintain PRDX 6 levels throughout the 14 weeks of treatment period while it decreases significantly in the water-fed mice. (3)

Source number 2 that in the NOD mouse, a model for human SS, oral administration of green tea extract reduced the serum total autoantibody levels and the autoimmune-induced lymphocytic infiltration of the submandibular gland. EGCG protect human salivary acinar cells from TNF- a-induced cytotoxicity by specific phosphorylation of p38 MAPK. Inhibitors of p38 MAPK blocked it's protective effect. So GTPs mediated in part through their activation of MAPK elements.

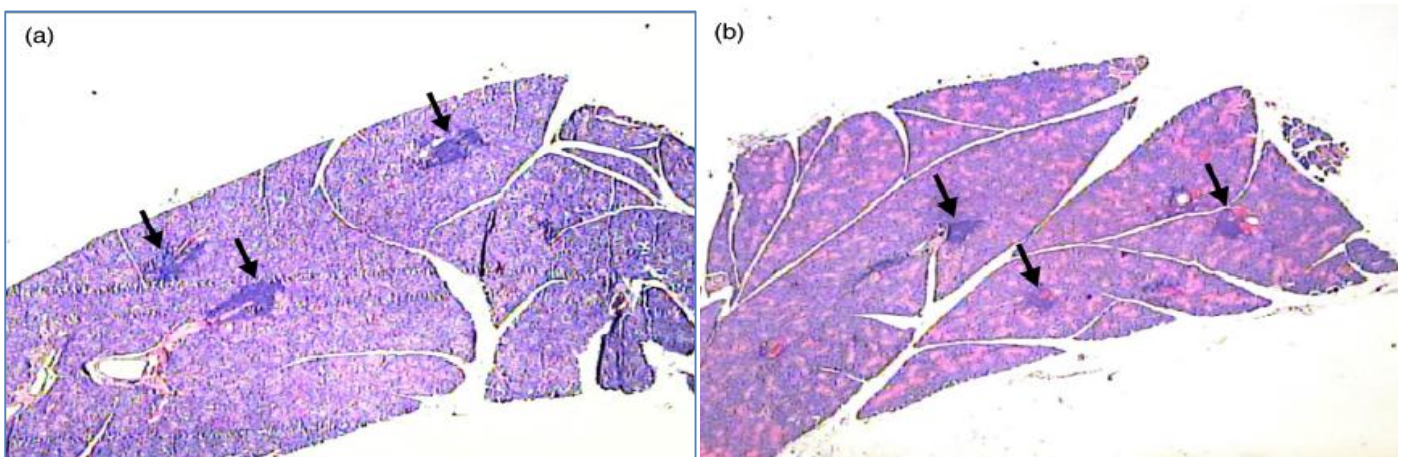


Figure 3. Representative H&E stained sub-mandibular gland sections. Glands were collected from (A) water only , (B) GTPs water treated NOD after autoimmune disease progressed 3 weeks in each animal. Arrows point to local lymphocytic infiltrations consisting of 50 or more lymphocyte. (7)

Discussion: Data from the different sources have been gathered, and they were as follows

Seiji Ohno and his Colleagues, says that markers for oxidative damage have been seen in Sjogren's syndrome patients after disease onset , the data results suggest that DNA damage caused by oxidative stress can be a bio-maker for salivary gland dysfunction. . PCNA is key protein for repair of damages DNA and synthesis of DNA. The increase in PCNA expression in the inflammatory gingival epithelium SS patients is consistent with oxidative DNA damage. Animals in EGCG consuming group exhibit normal levels of PCNA throughout the testing period in salivary glands, NOD mice fed with EGCG demonstrate delayed lymphocytic infiltration in the salivary glands and reduced SS-like symptoms. Seiji and his colleagues suggests that that DNA damage is caused by oxidative stress early in the disease progression can be prevented by using EGCG as it maintain PRDX6 (antioxidant defense protein) and catalase at normal levels. Also that oxidative stress can be detected by bio-maker such as PCNA at early stages (non-symptomatic). In other ways, Stephen D.Hsu and his colleagues in their study shows that GTPs can reduce the severity of autoimmune diseases by another mechanism which is the protective response in target cells activated by GTPs/EGCG possibly through modulation of the p38 MAPK (p38 mitogen-activated protein kinase) pathway. The current study specifically focused on GTPs oral consumption and their effect on lymphocytic infiltration in the salivary glands, the possible signal pathway is activated by EGCG phosphorylation in salivary acinar cells. oral administration of GTPs could protect salivary glands from SS-induced tissue destruction by decreasing one or more of cell based mechanisms of pathogenesis (apoptosis, autoantigen gene expression or cytokine production) via p38 activation in acinar cells. The multiple MAPK signal transduction pathway is involve in controlling diverse cellular events including (proliferation ,differentiation, apoptosis and gene expression) in salivary epithelial cells. The p38 MAPK pathway is important in transducing stress signals, and it's strongly , rapidly activated by stresses and inflammatory cytokines. The results shows that the GTPs modulate the MAPK pathways thus, EGCG can activate p38 signaling, and may there lead to activation of protective response within acinar cells or/and beneficial modulation of cytokine signaling.

Conclusion: In conclusion, both studies agree that the administration of the most abundant green tea polyphenol (EGCG), has inhibitory effects on lymphocytic infiltration, serum autoantibody production and oxidative stress in salivary glands, also based on the observations presented EGCG consumption normalizes the expression biomarkers in symptom-free stages allowing it's early diagnosis and intervention.

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