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Emerging Possibilities of Green Tea as a Potential Treatment Regimen for Hepatic Fibrosis

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Abstract

Green tea or green tea extract (GTE), pomegranate extract, and papaya extract and natural active ingredients like carotene, curcumin, epigallocatechingallate, genistein, resveratrol, gingerol, and capsaicin are those of natural products have been widely used to treat and prevent various diseases. Green tea is rich in small molecules that are phenolic/polyphenolic. Tea comes from the plant Camellia sinensis and the quality of tea depends on the cultivation of the plant, its region, and ultimately its roasting process to give white tea, yellow tea, oolong tea, and black tea and they are processed to attain a different level of oxidation. However, in the modern era although the use of these natural products is limited, yet there are an increasing demand and a great potential in using green tea in specific to treat diseases such as cancer, diabetes. This review article is meant to shed light on the emerging possibilities of green tea as a potential treatment regimen for hepatic fibrosis both as green tea extract and as green tea extract encapsulation.

Keywords: Green tea; Hepatic fibrosis; Regimen antioxidant

Abbreviations: ECM: Extracellular Matrix; HSC: Hepatic Stellate Cells; GTE: Green Tea Extract; CCl4: Carbon Tetrachloride; ECM: Extracellular Matrix

Introduction

After water, tea is the world's most widely consumed beverage. Tea is enjoyed by many people for its cooling and slightly bitter flavor and is known to have many particular health benefits [1-3]. There are several types of tea according to its fermentation processes such as black tea, oolong tea, white tea, yellow tea and green tea [4,5]. Green tea is, like many another type in general and green tea and white tea in particular, help to reduce the risk of cardiovascular disease, types of cancer, diabetes, promoting oral health, helping with weight control and lowering blood pressure of tea, made from leaves of the plant 'camellia sinensis'. However, taste, type, and packing are due to processing of tea involves the leaves being subjected to minimal oxidation. Health benefits of tea [6-8]. In a recent Journal of the American College of Nutrition review of the beneficial effects of green tea, the tea was described as having "anti-fibrotic properties, and neuro protective power". In this review article, a preview of several published works including our lab will be elaborated with regard to both green tea extract and nano-encapsulated green tea extract to shed light on the emerging possibilities of green tea as a potential treatment regimen for hepatic fibrosis [9 -20].

Chemical Composition of Tea

Types of Tea

Three major kinds of tea: Green tea, black tea, oolong tea, each processed differently, black tea, the fresh tea leave is withered by exposure to the air and is broken and left to ferment after picking, Oolong tea is treated similarly, but the withering process is much shorter, resulting in a partially fermented leaf and Green tea, the leaf is not fermented at all. Instead, it is steamed immediately to stop fermentation, then rolled and dried. Polphenols, the Powerful Health Promoters.

Poly phenols are found in certain fruits, vegetables, potatoes, and in garlic. The subgroups catechins (Figure 1) are particularly powerful disease fighter and potent antioxidants and Catechins appear in greatest quantity in fresh tea leaves. Other Health Promotion Ingrains Flavonols - subgroup of flavanoids, strong antioxidant destroy free radical, singlet oxygen and peroxides,

Vitamin C – helps reduce stress, fight infection, and strengthen the immune system.

Vitamin B complex – aids in the metabolism of carbohydrates, Vitamin E – helps retards aging, Fluoride – helps to harden tooth enamel, thus preventing cavities, Caffeine is a purine derivative, which is 1,3,7-tri- methyl xanthine, Tea fiber The leaf cell wall, containing cellulosic materials surrounded by hemicelluloses and a lignin seal, prevents the penetration of hydrolyzing enzymes. Carbohydrates - the free sugars found in tea shoot are glucose, fructose, sucrose, raffinose, and stachyose. Maltose in Assam variety and rhamnose in China variety appeared special. Pectin substances contain galactose, arabinose, galacturonic acid, rhamnose, and ribose. Amino acids Aspartic, glutamic, serine, glutamine, tyrosine, valine, phenylalanine, leucine, isoleucine, and theanine (5-N-ethylglutamine) were found to be the principal amino acids present in the tea leaf.

Theanine alone contributed around 60% of the total amino acid content. Asparagine was formed during withering. The amino acids play an important role in the development of tea aroma during the processing of black tea. Lipids and fatty acids the neutral, glycol and phospholipids contents and their fatty acid composition varied. Carotenoids - the four major carotenoids, ß-carotene, lutein, violaxanthin, and neoxanthinwere estimated spectroscopically in four different Tocklai released clones, namely, TV-1 (China hybrid), ii. TV-2 (Assam Betjan variety), TV-9 (Assam-Cambod variety) and TV-17 (China hybrid). The quantitative changes of these carotenoids in different stages of black tea manufacture were also studied in TV-2, and TV-17, clones against TV-1 as standard. A comparative study showed that TV-AnthocyanidinsDelphinidin and cyanidin were the major anthocyanidins present in the tea leaf. Anthocyanin contents were higher in tea shoots from pruned than those of un pruned bushes. Organic acids-citric, tartaric, malic, oxalic, fumaric and succinic acids were detected in Assam leaf. Green Tea Green tea Camellia sinensis belongs to the plant family of Thecae, native to East Asia, the Indian Subcontinent and Southeast Asia, but naturalized in many parts of the world. Green tea is consumed widely for its flavor and potential health benefits [1]. Experimental and epidemiologic studies have proved that regular consumption of green tea reduces the risk of cancer, diabetes, and obesity [1] (-)-epigallocatechin-3-gallate (EGCG) (Figure 1) is the key polyphenol in green tea [7]. Green tea extract retains several biological activities such as anti-oxidant [6], anticancer [5,9], anti-inflammatory [21], anti-arthritic [22], remedy of liver fibrosis [23] and neuroprotective effects [9], it also has a chemo protective and chemotherapeutic benefits for breast cancer [12] (EGCG in green tea extract, in particular, has been reported to exhibit protective effects against bupivacaine-induced neurotoxicity [7]. Green tea is a free radical scavenger; it is an anti-inflammatory, for the Nervous System.

Green Tea Catechins: Green tea is loaded with potent phenolic antioxidants. Polyphenols account for 30-40% of the green tea dry weight (5-9). Containing many bioactive compounds for human health associated with oxidative stress, thus, with antioxidant property, anticancer, and anti mutagenic and antibacterial activities [24]. Tea catechins have high affinity to metals, alkaloids and biological macromolecules, such as lipids, carbohydrates, proteins, and nucleic acids (7). The most important catechins in tea are shown (Figure 1). Green tea and its constituents are well established for their antioxidant properties, encompassing applications in various diseases associated with reactive oxygen species (ROS). Such as cancer, diabetes, neurological and cardiovascular diseases and for oral health [25,26].

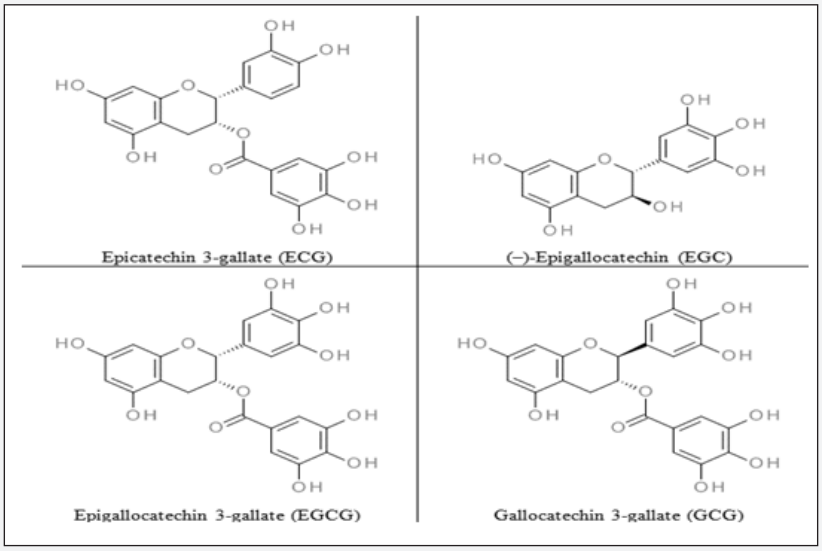

Figure 1: Green tea catechins.

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Nano green tea : Recently our laboratory has been actively involved in synthesizing and encapsulating nano green tea in chitosan nanoparticles of particle size 100 – 200nm (Figure 2) [1, 22-24]. We were the first group to introduce the concept of "Nano green tea extract," utilizing cutting edge nanotechnology to deliver the green tea to remedy hepatic fibrosis in a rat model [25,26] To maximize the effectiveness of green tea extract as crude, we used a naturally occurring chitosan to encapsulate and deliver nano green tea extractor the liver. This can increase the efficacy of natural products like GTE in hepatic fibrosis. Green tea also act as iron chelating agent [27].

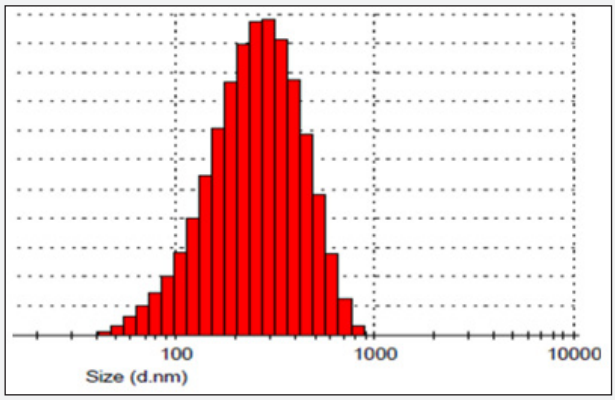

Figure 2: Size determination of green tea nano-particle before use in the experiments.

Green Tea and Hepatic Fibrosis: Liver fibrosis is characterized by increased deposition and altered composition of extracellular matrix (ECM), with an excess of proteinaceous fibers such as collagens I, III, and IV (15, 16). Ultimately, the liver architecture is distorted by a collection of dense collagen fibers. The fibers entangle themselves with the adjacent vascular structures and surround islands of regenerating hepatic parenchyma. Tens of research articles have written on green tea and hepatic fibrosis [27-29] gave a wealth of evidence that hepatic stellate cells (HSC,1 lipocytes, fat-storing, or Ito cells) are central to the process of fibrosis as the major source of fibrillar and non fibrillar matrix proteins (1). Quiescent HSC synthesizes low levels of matrix proteins, but, as a result of injury, HSCs proliferate and transform to a myofibroblast-like phenotype, a process termed activation [1]. When HSCs get triggered they express a-smooth muscle actin (a-SMA) and procollagen-I [1] and are known to be the major source of collagens and other ECM proteins that are deposited in fibrosis. Accumulation of matrix, therefore, occurs as a consequence of both an increase in the numbers of HSCs, in addition to their increased synthesis and secretion of matrix proteins when in the activated phenotype [2]. Resolution of liver fibrosis could be associated with a reversal of activated HSCs to a quiescent phenotype or by a change in the balance of cell death over proliferation resulting in a net loss of activated HSCs.

Growing evidence suggests that a major mechanism mediating the loss of cells that are redundant or unwanted after growth, development, or a pathological process is "programmed cell death" or apoptosis [5-8]. Many labs therefore, examined an experimental model of fibrosis through a progressive and recovery phase to determine whether activated HSCs undergo apoptosis during spontaneous resolution of fibrosis *in vivo* [2-4]. The loss of activated HSCs is not in itself sufficient to allow a remodeling of the existing excess collagens. For this to occur, matrix degradation must be up regulated. The key enzyme in the degradation of interstitial collagens I and III are interstitial collagenase (MMP-1). Degradation of collagen I and III in the rat model appears to be mediated by a further collagenase, Liver fibrosis results from the excessive secretion of matrix proteins by hepatic stellate cells (HSCs), which proliferate during a fibrotic liver injury.

During our previous studies of the effect of green tea extract (GTE) on the liver, kidney, and stomach, we presented various observations on how GTE had a role in changing the deleterious effects caused by a drug such as reserpine in just 30 days after administration [7,8,22,30]. This encouraged us to study the effect of GTE on the ameliorating hepatic fibrosis caused by carbon tetrachloride (CCl_4), which induces hepatic fibrosis through oxidative stress This causes HSC to be over-active [6] and trigger the ECM synthesis to increase, collagen fibers deposit in the extra-cellular spaces of the liver cells and causes them to lose blood infusion and to harden, leading to liver fibrosis [4,6,31]. In our lab, we have studied the effect of chitosan nano green tea on ameliorating hepatic fibrosis induced by two powerful hepatic carcinogens, carbon tetrachloride (CCl_4) and ethanol. Hepatic fibrosis brings about a histological change due to inflammation that causes hepatic stellate cells to be over-active.

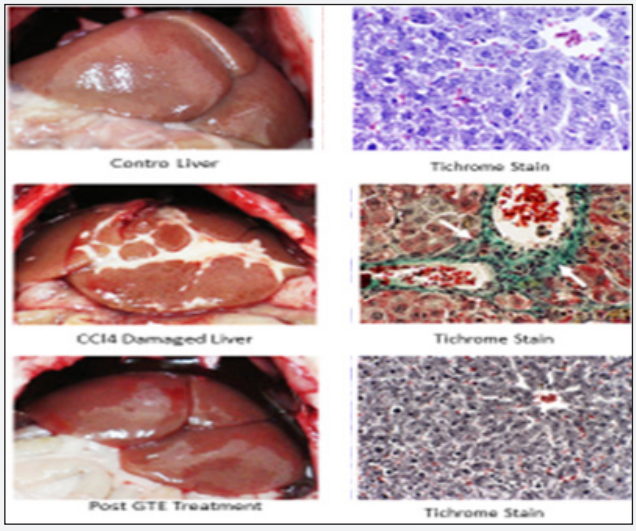

Figure 3: Composite image showing gross anatomy of fibrotic rat liver (left) and liver section stained with Masson's trichrome for fibers (right) - upper row and gross anatomy of rat liver three weeks after treatment with nano green tea extract (left) and liver section stained with Masson's trichrome devoid of fibers - bottom row.

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This activity triggers the ECM synthesis and collagen fibers deposit in the extra-cellular spaces of the liver cells. In this process, blood infusion is lost and the tissue hardens, leading to liver fibrosis [32-34].This phenomenon is clearly shown in a series of histological, histochemical, and nanoscopic assessment with hepatic fibrosis in art model by Safer et al. [10-20]. In principle, there are two regions to look at in hepatic fibrosis i.e. ECM proteinaceous contents such as over production of collagen fibers which is the most abundant protein in mammals, and hepatic cell organelles displacement and damage. Due to its unique properties, it is hoped that nano green tea extract be used as a means of repairing and curing biomaterial, scaffold, not only for liver fibrosis but also for cell and tissue regeneration studies. Collagen is a fibrous protein that assembles from basic tropocollagen subunits to form extracellular supra-molecular fiber networks within connective tissue. In hepatic fibrosis greater levels of extracellular matrix proteinaceous fibers appear, filling the matrix with an abnormal quantity along with mature collagen fibrils ranging from 10 to 500 nm in diameter [35]. The collagen fibrils display a characteristic 67nm repeat because of the staggering of individual collagen molecules with respect to each other (Figure 3).

Various protocols demonstrate how to investigate and analyze collagen fibers within the ECM like SEM (Figure 4 & 5) and AFM [36]. In a series of studies, we report the synthesis and characterization of chitosan NPs using the natural polymer chitosan obtained from mushroom and encapsulating GTE (GTECS NPs) [35-38]. The efficient uptake of these NPs labeled with dye was also studied. A method to analyze and quantify different bioactive compounds in GTE by LC-MS/MS is also reported [39]. The present review covers these analyses and characterizes the collagen structure that accumulates at the extracellular matrix (ECM) and also the cell organelles and how they are back to their normal norm in the cytoplasm of hepatocytes in a hepatic fibrosis subjected to three to four weeks of nano green tea extract [40] and also shed light on the emerging possibilities of green tea as a potential treatment regimen for hepatic fibrosis.

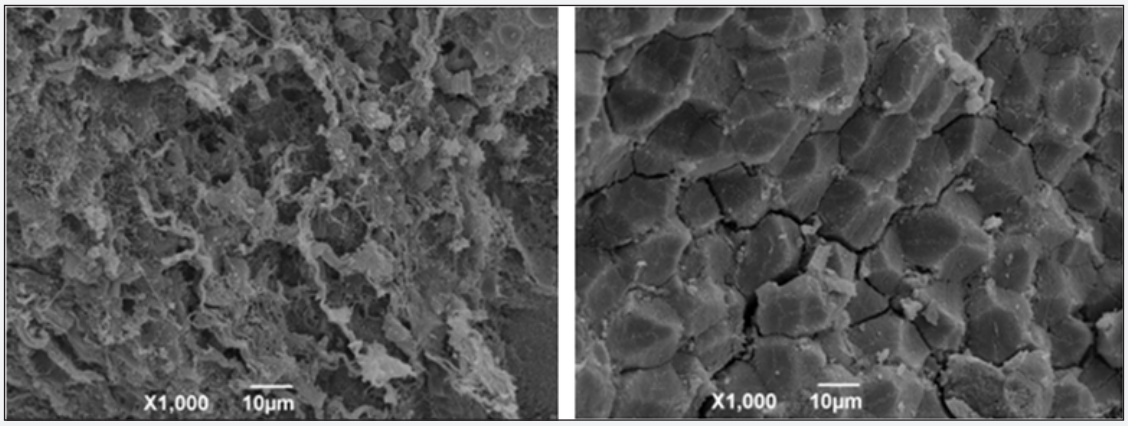

Figure 4: SEM image of a rat liver showing the effect of Ethan + CCl4 after a period of three weeks. ECM is loaded with protein fibers and damaged hepatocytes (left). SEM image treated with nano green tea extract showing intact hepatocytes and no fibers (right).

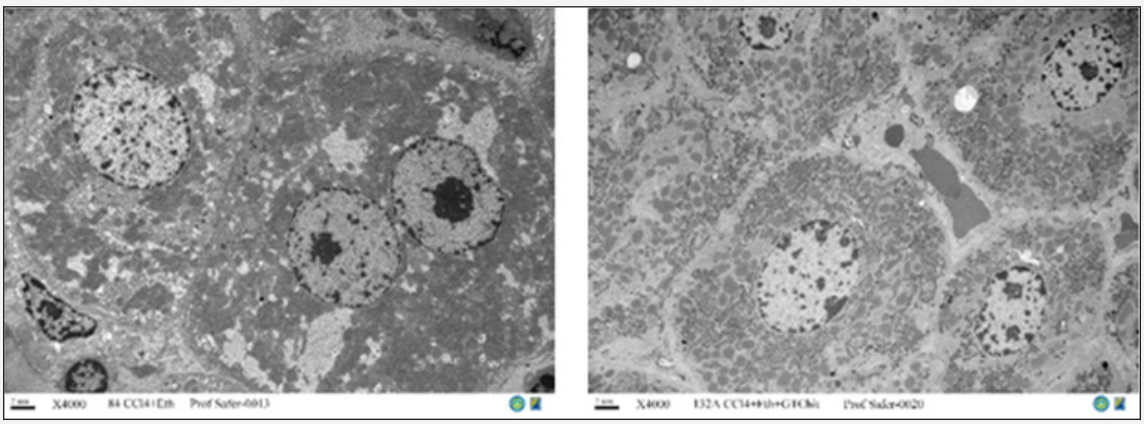

Figure 5: TEM image of a rat liver showing the effect of Ethan + CCl4 after a period of three weeks. Hepatocyte's interior is damaged (left). TEM image treated with nano green tea extract showing intact hepatocytes and almost all cell organelles are in the right location (right).

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