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# Green Tea: A biofactory for Antioxidant Compounds

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Green tea (*Camellia sinensis*) is one of the most popular and widely consumed beverages in the world second to water. Although most consumer does not aware that green tea contains variety of bioactive compounds that provide health benefits such as anti-inflammatory, anti-oxidative, anti-carcinogenic, anti-hypertensive, anti-proliferative, anti-thrombogenic, and lipid-lowering effects. However, so far most of the health benefits of green tea based on the antioxidant activities of the detected compounds. Epigallocatechin-3-gallate (EGCG) from catechins is the most active polyphenols of green tea. Since this plant is famous and some consumed it to improve their health, efficient extraction techniques of high yield and short time are needed. The process from obtaining raw materials and extraction process must not alter the efficacy and potency of the green tea bioactive compounds. Currently, ultrasound assisted techniques with combination of agitation system are used the extraction yield. In addition, bioavailability and mode of deliveries to body are important to ensure effective absorption and delivery to targeted part.

**Keywords: *Camellia sinensis*; antioxidant; polyphenols; catechins; bioavailability**

## INTRODUCTION

Antioxidants are molecules that are able to respond towards the damaging effects of the free radicals in cells. Antioxidants existed in numerous natural sources such as plant and microbial including yeast and fungi (Mustafa et al. 2016; El Sayed et al. 2016; Selvamani et al. 2018; Agouillal et al. 2018; Ambreen et al. 2019; Gomaa et al., 2019; Taher et al. 2019; El Sayed et al. 2020). Green tea which comes from leaves of *Camellia sinensis* plant are rich in antioxidant compounds. Green tea is originally come from Asia and has become one of the most famous, favorite and popular in the world. It has been studied extensively due to its capabilities to maintain health and prevent chronic diseases and cancer. In addition, regular consumption of green tea will reduce cholesterol levels thus can be preventing atherosclerosis (Chen et al. 2008). In 2013, Forester and Lambert reported that green tea can protect from chronic diseases and cancer. The antioxidant activity of polyphenols in green tea has cancer preventive effect. According to Bruno et al. (2014), the antioxidant properties in green tea will reduce the risk of obesity and its related disorder, cardiovascular diseases (CVD), and inflammation. The mechanism comes from catechins which exerts antioxidants and anti-inflammatory activities. However, the bioavailability of antioxidant properties in green

tea is relatively poor compared to the antioxidant in coffee (Belfarhi et al. 2020). High caffeine level in green tea may also help in body weight loss. A recent study of Lee et al. (2019b) clearly reported that people who consumed green tea products in regular basis has experienced decreasing of body weight, body mass index (BMI), body fat, level of visceral fat and size of waist together with hip. This is in agreement with the previous research by Golzarand et al. (2018) who reported also that green tea helps consumer to reduce excess weight, BMI and body circumference due to its anti-obesity effect. Moreover, some study also revealed that green tea also has benefits for diabetic patients and people with osteoporosis by improving the content of minerals in bone (Amorim et al. 2018).

Influenza is a highly infectious and a life-threatening disease of the respiratory tract due to its fast spreading by droplets and close contact. The antioxidant activities in green tea have the ability to inhibit influenza viral adsorption (Furushima et al. 2018). By consuming and gargling of green tea regularly, the body immunity will increase to protect against viral infection and development of influenza infections. This is agreed by Onishi et al. (2020) whom stated that consuming green tea can reduce incidence of influenza infections in human population. However, clinical researches are still limited and need more in-depth research to prove this matter. Since the past decades, green tea is also known to provide health benefits against diseases including antiviral activity against numerous viruses. Virus infection is also one of the serious threats to human health throughout the world, starting from acute to severe diseases (Xu et al. 2017).

Recent study in 2019 also clearly demonstrated that green tea possesses antimicrobial activities and have high potential to prevent infections very effectively including dental pathogens. The study showed that green tea can inhibit the growth of pathogens thus can prevent caries, tooth decay and maintain a healthy oral environment (Somasundaram et al. 2019). In 2020, Gartenmann et al. had stated that there are high possibilities that green tea has antiplaque and anti-gingivitis effects. Thus the one with anti-plaque activity can be used as active ingredients in oral health care products (Abdulbaqi et al. 2016). In the market, mouth rinse and other dental products which contain green tea extract are promoted for anti-plaque, anti-inflammatory, and anti-microbe to attract more buyers (Abdulkarim et al. 2019). The oral cavity of humans is prone to stress and inflammation which resulted from cigarette smoking and bad oral hygiene. Green tea protects against any bacterial induced dental diseases due to its antiviral and anti-microbe properties and ability to defend healthy cells from becoming cancerous (Narotzki et al. 2012). Regular consume of green tea or a minimum of one cup per day helps in reduces the risk of getting oral cancer in woman (Ide et al., 2007).

The benefits of green tea were also reported to possess anti-stress effect in both human and animals. After consuming green tea, the stress market in salivary glands decreases in conjunction with improvement of sleep parameters. It is suggested to ingest green tea regularly to lower stress level and enhance sleep quality (Unno et al. 2019a). Although it is proven that green tea promotes a healthy life, caffeine in green tea may interfere sleeping pattern. However, theanine content in green tea have the ability to block the effect of caffeine. The ingestion of green tea before sleep has improved early morning awakening in all stages of age (Unno and Nakamura, 2020). But, sleep efficiency was higher in middle-aged people.

In another study by Unno et al. (2019b), other than consuming green tea liquid directly, green tea cookies has given same effect in reducing stress among students. The stress marker, salivary α-amylase activity decreases after they consume green tea cookies. This proved that the stress-reducing effect of green tea is still effective although in made in confectionary products, since not all people can drink green tea as beverages.

In the world today, facial appearance is one of the most important factors in the society and in many situations. The hard truth is; we are judge by out facial appearance rather than personalities. For this matter, cosmeceuticals play a big part to improve such appearance, specifically for skin. A plant like green tea has been used widely as ingredients for antiaging. The major cause of aging is excessive production of reactive oxygen species and reduction of antioxidant activity in proportion of increasing age. Polyphenols like flavonoids in green tea can neutralize free radicals due to its ROS activities (Hong et al. 2014).

Green tea extracts are just not used for skincare as antiaging agent, but also can help to treat hypercholesterolemia and as protection against other disorders caused by aging process. More than that, green tea too is able to inhibit the activities of tyrosinase and collagenase thus improving skin health and conditions. Other than

antiaging, it is proved that green tea is used in cosmetics as anti-wrinkling or depigmenting agent (Hong et al. 2014).

## POLYPHENOLIC COMPOUNDS IN TEA EXTRACTS

Green tea extracts were evaluated for the presence of various phytoconstituents by performing a series of qualitative and quantitative chemical tests and showed the presence of flavonoid, which constitutes more than 70% of total phenolic compounds present in green tea (Lorenzo and Munekata, 2016). It was previously reported that green tea containing higher amount of gallic acid and flavonol (catechin) as compared to black tea. Green tea contains 4-16% fats, minerals, vitamins, protein, amino acids, sterols, flavors, triterpenoids, etc (Uzunalic et al. 2006; Leung and Foster, 1996). Polyphenols present in green tea also possesses anti-inflammation, antifungal, antimutagenic, anticlastogenic, anticarcinogenic, chemo-preventive and therapeutic properties (Erol, 2013).

Catechins are the most abundant type of flavonoids that present in tea leaves extract and well documented by other researchers (Velayutham et al. 2008). The most profound effects of green tea are attributed to the presence of polyphenolic compounds in green tea, predominantly the catechins. They can make up to 25-35% of total dry weight of green tea leaves (Abdel-Rahman et al. 2011; Zaveri, 2006; Balentine et al. 1997). These catechins are present in higher quantities in green tea than in black or oolong tea, because of the differences in fermentation level of tea leaves after harvesting process.

Current research in 2020 has identified a common chemical compounds present in black tea (*Camellia sinensis*) and rooibos tea (*Aspalathus linearis*) namely hydroxycaffeic acid, 1-threonate, caffeine, vanillic acid, n-acetylvaline, spinacetin-3-glucoside, quinolinic acid, coumestrol, phloroglucinol, 8-hydroxyquercetagetin, umbelliferone and ajoene (Xiao et al. 2020).

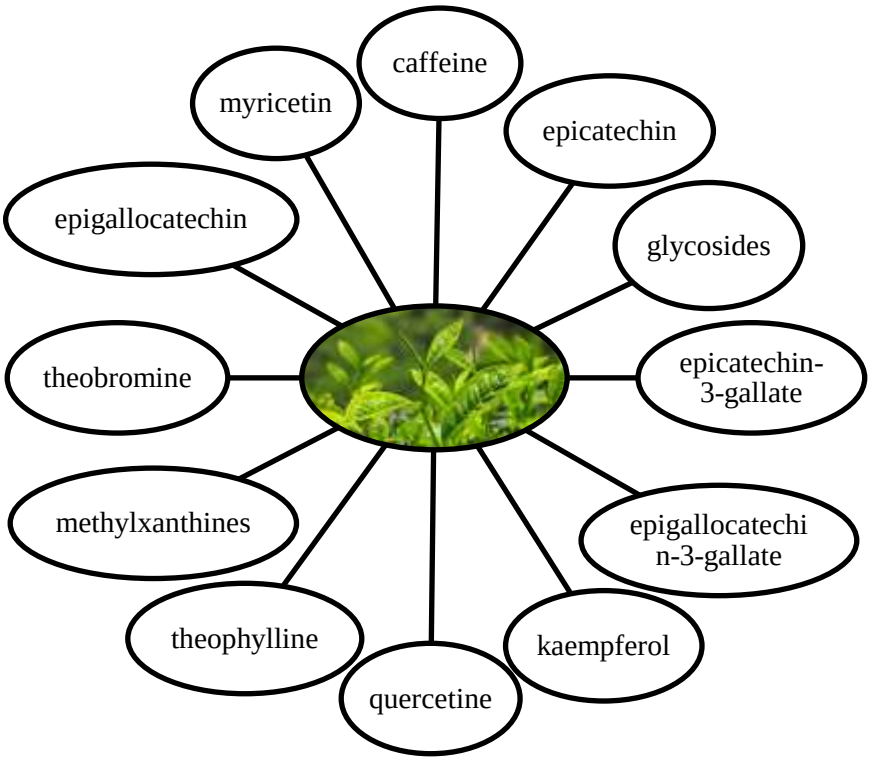



**Figure 1: Chemical composition of green tea**

**Structure-antioxidant activity relationship of tea polyphenols**

Antioxidant is one of the most studied topics for research in food science and nutrition because it is being used as food preservative before known for the abilities to inhibit oxidation process in both food and human metabolism. The interest for antioxidants are growing among researchers, focusing on antioxidant content in various types of food and to improve knowledge on the antioxidant physiological effects in human body (Comert and Gokmen. 2018). Phenols are the most important natural antioxidants which occur in plant materials that protects the oxidizable constituent from oxidation. Phenols act as an antioxidant by several ways such as their ability to chelate metal cation involved in the generation of free radical; by obstructing enzymes, which are involved in free radical production; by donating a hydrogen atom to reactive nitrogen/oxygen. The antioxidant delays the onset of oxidation until it is exhausted.

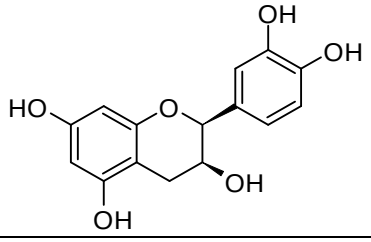
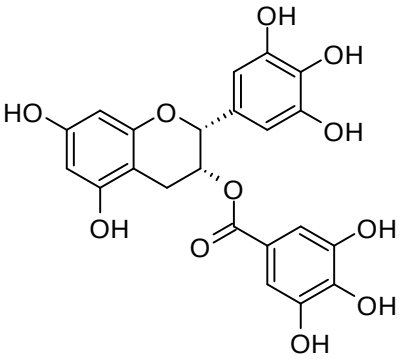
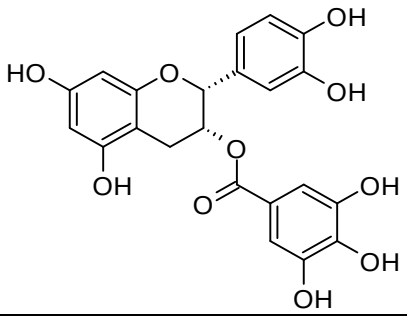
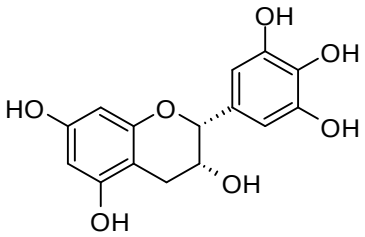
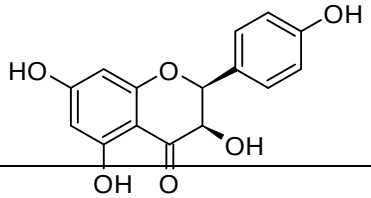
Green tea is among the most popular and widely used as and in dietary supplements due to its high antioxidant properties and diverse health claim. The market of green tea is growing as a trendy ingredient for nutraceuticals and functional foods (Senanayake. 2013). Recently in 2020, an extensive study has reported that higher consumption of total polyphenols in in coffee and green tea may be beneficial to alleviate photoaging of the skin and suppress skin hyperpigmentation through adding large amounts of total polyphenols in the diet (Fukushima et al. 2020). This statement was previously reported in 2018 where polyphenols in green tea have activities against skin disorder such as hyperpigmentation and others. They develop and clinically evaluated a facial tonner with green tea as active ingredients. The products are proved stable, causing no skin irritation, and the anti-sebum efficacy is significantly better than other products without green tea. The products are mainly used to treat oily face (Meetham et al. 2018).

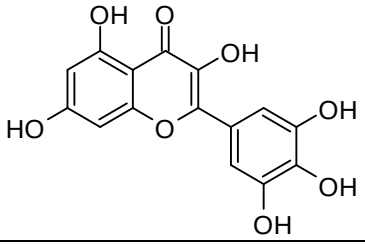
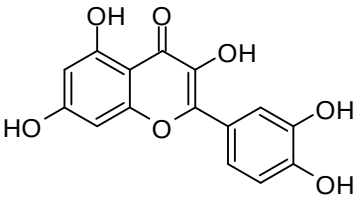
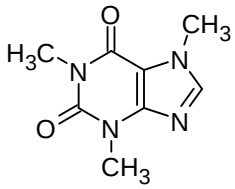
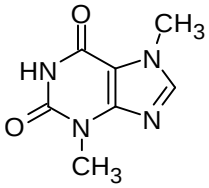
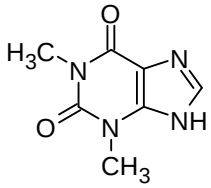
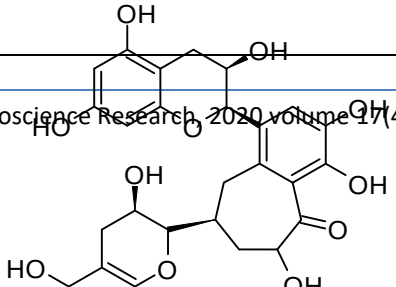
Green tea was defined by the most significant antioxidant properties, slightly lower potential was observed for red and white tea types, whereas black tea featured the lowest values. The same tendency was observed for kombucha prepared from a given tea type. In the case of DPPH, the fermentation process had an influence on the increase in antioxidant properties in reference to tea, and with subsequent days of fermentation, the potential decreased regardless of the tea type. A reverse situation was observed in the case of the reductive potential (FRAP). Fermentation had an influence on the decrease in reductive properties with reference to tea. The highest reductive potential was found for kombucha on the 7th day. Therefore, a strong positive correlation was observed between the time of fermentation and the reductive potential (FRAP) as well as polyphenol content (Jakubczyk et al. 2020).

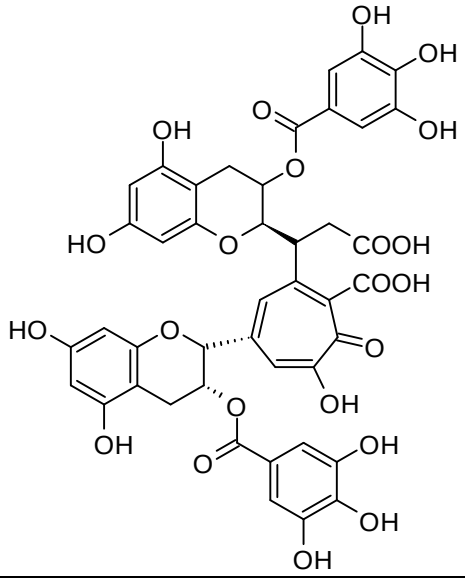
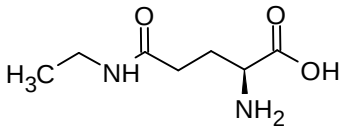
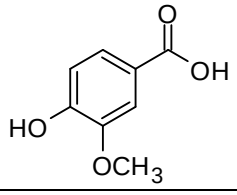
Although green tea extract contains many polyphenolics with antioxidant properties, the most dominant and active component is the catechins. Catechins are well established as antioxidants, but they can also be pro-oxidants and generate reactive oxygen species (ROS). ROS is the one, which is responsible for the alteration of cellular protein; lipid and nucleic acids functions, which can lead to several health problems (Dickinson and Chang, 2011). Oxidation process occurs in DNA will cause mutation and genetic instability thus becomes the major contributor in initiation, promotion and progression of carcinogenesis (Hussain et al. 2003). Green tea phytochemicals are a potent source of exogenous antioxidant candidates that could nullify excess endogenous ROS and RNS inside the body, and thereby diminish the impact of photoaging. Several previous *in vivo* and *in vitro* studies suggest that green tea supplementation increases the collagen and elastin fiber content, and suppresses collagen degrading enzyme MMP-3 production in the skin, conferring an anti-wrinkle effect. However, the precise mechanism behind the anti-photoaging effect of green tea has not been explored yet. Studies using the worm model have suggested that green tea mediated lifespan extension depends on the DAF-16 pathway. Apart from this, green tea has been reported to have stress resistance and neuroprotective properties (Prasanth et al. 2019).

The stability of green tea catechins are highly dependent on the pH and temperature. In acidic solutions (pH<4), green tea catechins exhibit exceptional stability; in alkaline solutions (pH>8), however, they are extremely unstable (Zhu et al. 1997). In a high temperature environment, green tea catechins are not very stable since heating may cause the conversion of green tea catechins to their respective isomers through epimerization process.

**Table 1 : Chemical compounds and their functional properties in green tea**

| Name of compounds | Chemical structure | Functional properties | Reference |
|---|---|---|---|
| Catechin CAS number: 7295-85-4 (anhydrous) |  | antioxidant | Grzesik et al., 2018 |
| | | anti-angiogenic | Li et al., 2013 |
| | | anticancer | Yang and Wang, 2016 |
| | | anti-inflammatory bowel disease | Fan et al., 2017 |
| | | anti-cardiovascular disease | Mangels and Mohler, 2017 |
| Epigallocatechin-3-gallate CAS number: 989-51-5 |  | antioxidant | Grzesik et al., 2018 |
| | | anticancer | Yang and Wang, 2016 |
| | | anti-skin tumor (anti-photoaging) | Meeran et al., 2006; Petruk et al., 2018 |
| | | antineurodegenerative diseases (Alzheimer's disease) | Li et al., 2018 |
| | | stress resistance lifespan extension neuroprotective and autophagy | Zarse et al., 2012 |
| | | memory function improvement | Ding et al., 2018 |
| | | anti-inflammatory | Li et al., 2011 |
| | | antimicrobial | Melok et al., 2018 |
| | | anti-fibrotic | Chen et al., 2020 |
| Epicatechin-3-gallate CAS number: 1257-08-5 |  | antioxidant | Grzesik et al., 2018 |
| | | anticancer | Yang and Wang, 2016 |
| Epigallocatechin CAS number: 970-74-1 |  | antioxidant | Grzesik et al., 2018 |
| | | anticancer | Yang and Wang, 2016 |
| Kaempferol CAS number: 520-18-3 |  | antioxidant | Sharifi-Rad et al., 2018 Imran et al., 2019 Verma et al., 2009 |
| | | anti-breast cancer | Lee et al., 2019b; Yi et al., 2016; Li et |

| | | | |
|---|---|---|---|
| | | | al., 2017 |
| | | anti-brain cancer | Colombo et al., 2018 |
| | | anti-liver cancer | Zhu et al., 2018 |
| | | anti-colon cancer | Riahi-Chebbi et al., 2019 |
| | | anti-prostate cancer | Halimah et al., 2015 |
| Myricetin CAS number: 529-44-2 |  | antioxidant | Guitard et al., 2016 |
| | | nephroprotective | Hassan et al., 2017 |
| Quercetin CAS number: 117-39-5 |  | antioxidant | Elsharkawy, 2017; Li et al., 2016 |
| | | anticancer | Park et al., 2017; Verma et al., 2009 |
| | | anti-hypertensive | Brull et al., 2015 |
| | | anti-inflammatory | Cui et al., 2019 |
| | | anti-hyperuricemic | Shi and Williamson, 2016 |
| | | improving the adiponectin-mediated insulin resistance and hormonal profile of women with polycystic ovary syndrome | Rezvan et al., 2017 |
| Caffeine CAS number: 58-08-2 |  | antioxidant | Vieira et al., 2020; Leon-Carmona and Galano, 2011; Hosny et al., 2019 |
| | | anti-fibrotic | Nilnumkhum et al., 2019 |
| | | anti-inflammatory | Hosny et al., 2019 |
| | | analgesic effect | Renner et al., 2007 |
| | | neuroprotective | Kolahdouzan and Hamadeh, 2017 |
| Theobromine CAS number: 83-67-0 |  | anti-diabetic | Papadimitriou et al., 2015 |
| | | anticancer | Sugimoto et al., 2014 |
| | | neuroprotective | Mitchell et al., 2011 |
| | | anti-obesity | Jang et al., 2015; Mitani et al., 2017 |
| Theophylline CAS number: 58-55-9 |  | antioxidant | Wu et al., 2019; Jorge and Galano, 2012 |
| | | anticancer | Ruddarraju et al., 2016 |
| | | antimicrobial | Ruddarraju et al., 2016 |
| | | anti-inflammatory | Talmon et al., 2019 |
| Theaflavin CAS number: 4670- |  | antioxidant | Gaggìa et al., 2019 |
| | | anticancer | Jakubczyk et al., |

| | | | |
|---|---|---|---|
| 05-7 | | | 2020; Pan et al., 2000 |
| | | anti-inflammatory | He, 2017 |
| | | antimicrobial | He, 2017 |
| Thearubigin CAS number: 12698-96-3 |  | antioxidant | Gaggìa et al., 2019; Jakubczyk et al., 2020 |
| | | anti-inflammatory | Guardia et al., 2001 |
| | | anticancer | Ren et al., 2003 |
| Theanine CAS number: 3081-61-6 |  | antioxidant | Tadesse et al., 2015 |
| | | stress resistance | Zarse et al., 2012; Kimura et al., 2007 |
| | | anti-anxiety | Kristy et al., 2004 |
| | | anti-obesity | Yamada et al., 2008 |
| | | anticancer | Liang et al., 2015; Zhang et al., 2014 |
| | | improve immunity system | Takagi et al., 2010 |
| | | minimize elevated blood pressure | Yoto et al., 2012 |
| | | anti-tumor | Liu et al., 2009; Zhang et al., 2013 |
| Vanillic acid CAS number: 121-34-6 |  | antioxidant | Bhuyan et al., 2020 |
| | | neuroprotective | Khoshnam et al., 2018 |
| | | anti-inflammatory | Singh et al., 2015 |

For example, as epimerization can occur at high temperature, epigallocatechin gallate in green tea extract may be converted into its epimer component which is gallocatechin gallate. Heat treatments decrease the antioxidant properties of green tea catechins due to oxidation, thermal degradation, epimerization and polymerization process (Ananingsih et al. 2013).

The most effective antioxidant catechins are epigallocatechin-3-gallate and epicatechin-3-gallate, other than that is epicatechin and epigallocatechin. From all the compounds, epigallocatechin-3-gallate is the most bioactive and fully understood. The polyphenols are able to delay lipid oxidation thus enhance shelf life of food products and are responsible for aroma, taste and color (Senanayake, 2013). According to Yan et al. (2020), tea polyphenols are the term used to describe polyphenols compound in tea, which proved to have activities of antioxidant, anti-inflammatory, cancer prevention and alteration of lipid metabolism. Due to its vast abilities, tea polyphenols are widely used as antioxidant to treat various diseases.

Epigallocatechin-3-gallate or EGCG is the most abundant and pharmaceutically active

polyphenols among others with more than 50% of total catechins content of green tea and a cup of green tea contain up to 200 mg of EGCG. Many studies have proved that EGCG are potential to be developed as fortification of food products to promote better health, this had resulted in vast products of ready-to-drink beverages and nutritional supplements made from green tea are available in the market (Lai et al. 2020). Poor stability and low bioavailability of EGCG are among the factors that hold up usage of the properties in functional food and other medicinal products. But, these problems can be solved by development of technologist for modification and therapeutics delivery (Lai et al.2020). Moreover, researcher should deeply and widely justify the usage of EGCG in functional food products for its quality, efficacy, safety, and efficiency (Vilela et al. 2020).

Various medicinal plants are used widely for prevention and treatment of many diseases across the globe, but, their therapeutic potential is still limited. In-depth research is necessary to prove for health properties of medicinal plants (Vilela et al. 2020). Although there is still no research has proved reduction percentage of EGCG against cariogenic microorganism among children. More clinical studies are needed to evaluate EGCG mouthwash and its safety and effectiveness (Vilela et al.2020).

Pereira et al. (2014) reported high phenolic contents for black, green and white *C. sinensis* and correlated them with the antioxidant properties of the studied teas. Damiani et al. (2019) also reported high phenolic properties for *A. linearis* and correlated the antioxidant activity of the tea to the phenolic content. Extensive researches have reported the antidiabetic and antioxidant properties (Fu et al.2017; Kumar and Rizvi 2015), which has been referred to its chemical constituents namely catechins and alkaloids in *C. sinensis* (Han et al. 2016; Williamson et al. 2011; Frei and Higdon 2003).

Many structure–activity relationship investigations have been performed on the antioxidant activity of flavonoids, including tea catechins (Farkas et al. 2004). According to these studies, the antioxidant activity of flavonoids depends substantially on the number and position of hydroxyl groups in the molecule (Farkas et al. 2004). In addition, several structural elements such as o-dihydroxyl catechol structure in the B-ring, the presence of unsaturation and 4-oxo group in the C-ring are also presumed to increase the antioxidant activity of flavonoids. The 2,3-double bond in the C-ring along with 4-oxo function in the C-ring facilitates electron delocalization from the B-ring. Moreover, hydroxyl groups at positions 3 and 5 providing hydrogen bonding to the 4-oxo group in the C-ring is another structural feature attributed to the antioxidant activity of flavonoids. The list of chemical components presents in green tea and their functional properties is summarizing in the table 1.

## CONSUMPTION AND TARGET DELIVERY

Previous studies have revealed the potential used of polyphenols in green tea as anticancer, antioxidant and antimicrobial agents. However, the green tea polyphenols into food formulation is limited due to their susceptibility to degradation at certain pH and temperature during preparation and extraction process, and low availability (Bora et al. 2018).

Microencapsulation technique is an effective option to preserve the efficiency of green tea polyphenols during processing. Moreover, microencapsulation also enables a targeted delivery after consumption. For the microencapsulation purposes, various methods are applied including freeze drying, spray drying, high-pressure homogenization, electrospraying, encapsulation via film formation, and complexion-encapsulation (Bora et al. 2018). The research showed that microencapsulation provide protection for green tea polyphenols against spray and freeze-drying, food processing, and loss of bioavailability. More than that, microencapsulation can increase the antioxidant activity of food products, thus lengthen the shelf life of products by preventing oxidation and mask any unwanted astringency and bitterness (Bora et al. 2018).

In the meantime, research by Shetta et al. has proved that green tea essential oil which encapsulated in chitosan nanoparticles have higher antimicrobial activities against *S. aureus* and *E. coli*, improving thermal stability and the total phenolic contents are more stable (Shetta et al., 2019).

The excessive reactive oxygen/ nitrogen species (ROS/ RNS) are the main causes of oxidative stress. The oxidative stress can damage DNA, RNA, protein and lipids when ROS attack bases in nucleic acid, amino acid side chain in proteins and double bonds in unsaturated fatty acids. The oxidative stress is might be the factor of increasing the risk of cardiovascular disease, cancer, autism and other diseases.

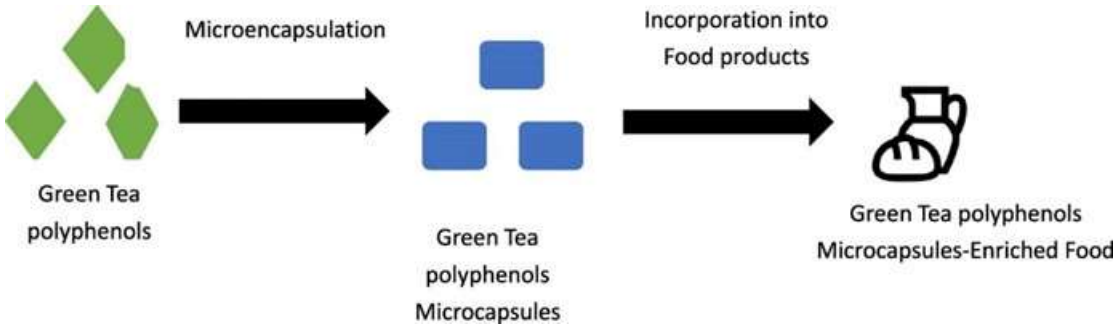



**Figure 2: Microencapsulation for delivery to body of green tea polyphenols (adapted from Bora et al., 2018)**

Consuming intracellular antioxidant enzymes and intake of dietary antioxidant such as green tea might be one of the solutions to maintain an adequate antioxidant in bodies. Moreover, green tea is rich in catechins, which comprised of more than eight polyphenolic compound. The compounds are possesses antioxidant properties and exhibit favourable effects on gene expression, signal transduction and other important cell functions. The potential mechanisms have been studied to explain the healthy benefits of tea catechins. These are including improving antioxidative activity, suppressing adipocyte differentiation, regulating the tumor-suppressor microRNAs, and inhibiting hepatocyte growth factor receptor activity (Cai et al. 2018).

## DOSAGE AND TOXICITY

The green tea has gained a lot of interest as increasing number of evidence on health benefits and as natural product remedies in prevention the diseases. The large numbers of scientific studies have assessed the possible health benefits of green tea. Several reports have shown the linkage between consumption of green tea in lowering the risk of coronary atherosclerosis (Sasazuki et al. 2000), neurodegenerative diseases (Schimidt et al. 2017), tumor activity (Safari et al. 2019), and obesity with high levels of low density lipoprotein-cholesterol (Huang et al. 2018). It might be due to green tea consists of antioxidant compound. At the same time, the public also concern on toxicity effect of green tea even the general believe that the green tea which natural origin is safe and free from serious side effect based on long history of use by humans. Consumption of green tea might be associated with adverse liver effects as the causative agent, which responsible for liver injury still not determined. The toxicity studies become more complex which the methods in consuming the green tea are varying depends on product manufactures or other condition. In addition, the green tea is more often used under self-medication without a medical supervision.

A study conducted by Schmidt et al. (2005) reported on the cytotoxicity of green tea in hepatocytes. The study was conducted by isolating the hepatocytes from adult male Wistar rat with weight ranged from 150 to 200 g and further with cytotoxicity testing. The study also reported that hydro-alcoholic green tea extracts tested showed the low cytotoxicity with no significant loss of resazurin reduction. The green tea constituent (-)-epicatechin, (-)-epigallocatechin-3-gallate, caffeine and theanine were tested at concentration reflecting them in a typical green tea extract. The green tea constituent (-)-epigallocatechin-3-gallate (EGCG) seems to be the major contributor to the cytotoxic effect of green tea extract in cultured rat hepatocytes. The data showed that hydro-alcoholic green tea extract could damage rat hepatocytes in vitro. However, the level required to elicit such effects were extremely high.

The study by Chan et al. (2010) investigated the toxicity effect of green tea extract in male and female F344/NTac rat and B6C3FI mice at doses up to 1,000 mg/kg. This experiment was conducted for 14 weeks. The results showed in clinical observation, which there was no abnormal behaviour for at least 3 weeks of the study. The toxicological effect of green tea extract in rat and mice included decreased in body weight gain and histopathological lesions in the liver, nose, spleen, lymph nodes and thymus. In the study, the male rats were more affected compare to female rats. The mechanism behind the weight reduction is still unknown. However, the study suggested it

might be due to change in food consumption, inhibition of intestinal lipid adsorption, increase in the expenditure of energy and stimulation of lipid oxidation. The study also suggested components that responsible for hepatotoxicity are the catechins, gallic acid and epigallocatechin-3-gallate. The most sensitive organ for detecting the green tea extract toxicity was the nose for both mice and rats. Nasal toxicity can also lead to nasal lesion. The study concluded that, there was no adverse effect for concentration of 500 mg/kg in liver for both species rats and mice.

Takami et al. conducted a study in 2008 to evaluate the toxicity effect of green tea catechins. The study was carried out for 90 days dietary administration on F344 rats. During the experimental period, the clinical signs and mortality were observed at least once a day. The individual body weights and food consumption per cage were measured once a week. At the end of the experiment, all rats were fasted overnight and euthanized by exsanguination with blood sample collection from abdominal aorta for haematology and serum biochemistry under deep ether anaesthesia. The study demonstrated that the rats reduced in body weight with treatments 5% concentration. The results showed no adverse effect level was estimated to be 1.25% (763.9 mg/kg body weight/day for males and 820.1 mg/kg body weight/day for females).

Kapetanovic et al. (2009) investigated on toxicity effect of standardized green extract which consist about 56 to 72% of (-)-epigallocatechin gallate as the main component. The study was conducted using Beagle dogs with approximately weight from 5.7 to 7.2 kg. The nine month chronic study was done in fasted dogs and non-fasted dog. The animals were dosed with 0, 200, 500, and 1000/800 mg/kg/day. The animals were observed twice daily. The observation was conducted to monitor their health general status and for sign of mortality or morbidity. The body weight measurements were evaluated weekly and food consumption was quantified daily. The results showed dosing in fed state lower and less variable than under fasted condition.

Zaki et al. (2017) studied on subchronic toxicity of green tea extract on the liver of the adult male albino rats. The study recommended the average consumption of green tea in the form of aqueous solution appears to be harmless as it takes at least 3 cups of green tea/day which providing a minimum of 250 mg/day catechins. The adult male albino Westar rats with weight ranged from 150 to 200 g were used in the study. The rats were divided into four group; I for normal as control, II for low dose green tea which the dose of 250 mg/kg/day, III for medium dose green tea which the dose of 500 mg/kg/day and 1v for high dose green tea which the dose of 1000 mg/kg/day. The doses of 500 mg/kg/day and 1000 g/kg/day showed the deleterious effect compared to 250 mg/kg/day.

Lee et al. (2019a) studied on acute and subchronic oral toxicity of fermented green tea. The CD1 (ICR) mice and CrljCD (SD) rats were used. During the experimental period, the animals were freely access to the feed and water. The oral administration was studied once a day for 13 weeks. The responsible component for hepatotoxicity might be cathechins. However, the acute and subchronic oral toxicity studies showed non-toxic safety of fermented freen tea up to 2 g/kg/ day.

In a study by Saratale et al. the absorption kinetics evaluation of nanoemulsified vitamin E and microsize green tea was done to analyze the absorption rate of the samples by examining time-dependent changes in the serum levels of catechins. The rats are given 2000 mg of nanoemulsion vitamin E and microsized green tea and proved to have no signs of acute toxicity or death in 14 observation days. More than that, the rats' macroscopic analysis also did not show any changes in organs. This has proved that nanosized vitamin E increases the absorption rate of microsized green tea and nanoscale materials are safe for human consumption (Saratale et al. 2018).

Chow et al. (2005) concluded in their study that greater oral bioavailability of catechins can be achieved by consume it on empty stomach after fasting overnight with dosage of 800 mg EGCG. The dosage also can optimize biological effects of catechins. This matter is supported by Naumovski et al. (2015) whom stated and proved that taking EGCG on empty stomach or after fasting is better to maximize the systemic absorption. However, EGCG need to be consume with addition of water for appropriate oral delivery.

## BIOAVAILABILITY

Nano-encapsulation is a unique method to enhance the bioavailability of nutraceuticals. Design and development in various lipid-based nano-encapsulation are needed to improve the bioavailability of phenolics content. Phenolics content of green tea possess many biological functions and therapeutic properties, which are not accessible due to their low stability, solubility,

absorption, and untargeted delivery. However, nano-encapsulation are able to overcome these limitations and improving the bioavailability of the phenolics content.

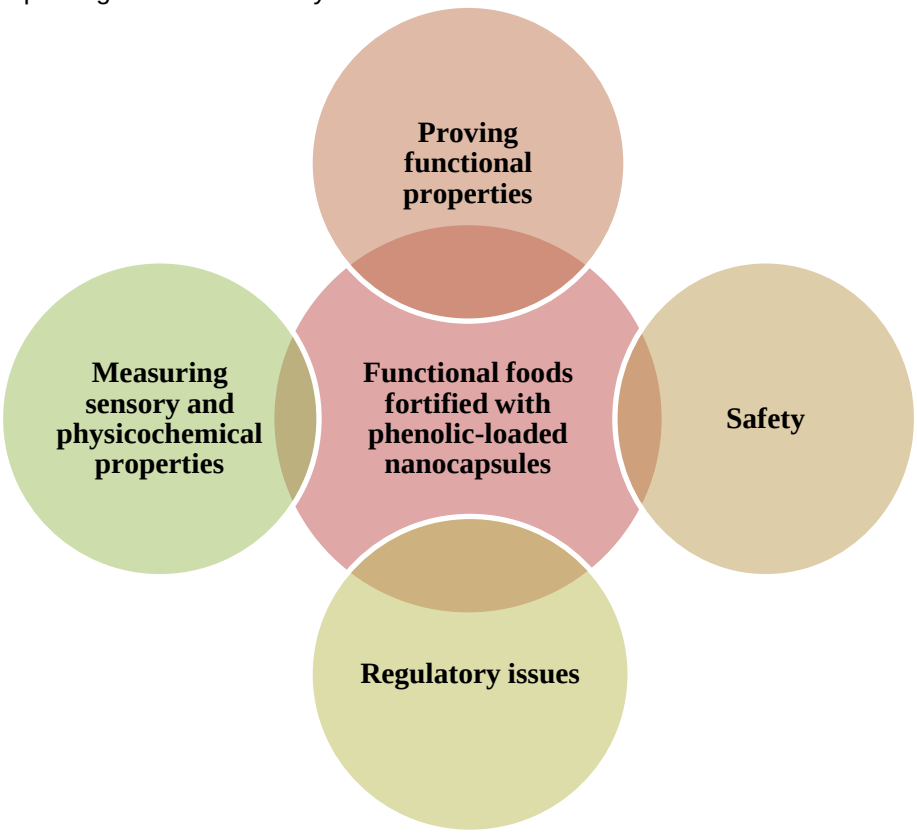



**Figure 3**: **Improving bioavailability of phenolic compounds (adapted from Esfanjani et al., 2018:)**

Esfanjani et al. (2018) stated that it is possible to use nano lipid carriers of phenolic to fortify milk or beverages and spray-dried powders to enhance powdered foods. However, the study of metabolism, absorption, and safety of the phenolic content loaded in lipid-based nanocarriers need to be considered to use them in the formulation of functional foods.

Yao et al. (2015) also stated that food-grade engineered nanoparticles might help to improve the oral bioavailability of nutraceuticals, which can increase the potential health benefits in humans. While Puligundla et al. (2017) stated that chemopreventive and therapeutics effects of green tea extracts are related to the presence of catechins. However, there are limited efficacy in clinical settings due to low bioavailability and poor oral absorption. Since then, many various and different techniques are proposed to improve the bioavailability of green tea polyphenols. Nanoparticles-based delivery systems are promising and can increase the therapeutic efficacy.

Nanostructure-based drug delivery systems, molecular modification and co-administration with other bioactive ingredients can improved and enhance the bioavailability of catechins. Other than that, increased bioavailability can be achieved by encapsulation of catechins on protein-based, lipid-based, and carbohydrate-based nanoparticles which improve stability and more sustainable release of the catechins (Cai et al. 2018). Other than that, Hof et al. (1998) prove in their study that addition of milk does not affect or impair the bioavailability of catechins in green tea. Blood catechins levels increase rapidly even after consuming the green tea with milk.

## CONCLUSION

**Extensive studies and health claims have made for green tea in nutraceuticals and functional foods market. Polyphenolic contents in green tea are the main precursor that is responsible for its therapeutic effect,**

**with the presence of flavanol monomers known as catechins from flavonoid group and thus give an effect as antioxidant, anti-diabetic, anti-inflammatory and anticancer agents. Therefore, a thorough research need to be explore to scrutinize the phytomedicinal properties of green tea in depth and further insight into antioxidant properties by *in vivo* assessment in future.**

## CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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## AUTHOR CONTRIBUTIONS

MY, NAZ, IMY, SN involved in data collection and writing the manuscript. RAM, SZH, SHMS designed the work, SE, TH, HAE, DJD reviewed the manuscript. All authors read and approved the final version.



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