



## Excessive Green Tea Intake Alters Hemoglobin (Hb) Concentration and Histoarchitecture of Liver

Swarup Kumar Kundu<sup>1,a,\*</sup>, Shonkor Kumar Das<sup>2,b</sup>

<sup>1</sup>Department of Anatomy and Histology, Faculty of Veterinary, Animal and Biomedical Sciences, Khulna Agricultural University, Khulna-9202, Bangladesh

<sup>2</sup>Department of Anatomy and Histology, Faculty of Veterinary Science, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh

\*Corresponding author

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### ABSTRACT

A myriad of health claims are being made in favor of the consumption of green tea due to its easy availability and greater popularity. On the contrary, certain health risks of excessive green tea consumption have begun to emerge. The aim of the present research was to observe the baleful effects of excessive green tea intake on hematological parameter and histoarchitecture of liver. A total of thirty (n=30) Swiss albino mice were taken and randomly divided into Control C, Treated T<sub>1</sub>, and Treated T<sub>2</sub> groups. Each group consisted of ten (5 male+5 female) mice. The Control C group was fed with normal mice pellet and water (3ml/mice) orally but the treated T<sub>1</sub> group was supplied mice pellet with 2ml/mice of green tea+1ml/mice of water orally as well as treated T<sub>2</sub> group was given mice pellet and 3ml/mice of green tea orally two times in a day for 60 days. After the experimental tenure, mice of each group were sacrificed ethically and samples (Blood, liver and lungs) were collected for further hematological and histomorphological studies. Treated T<sub>2</sub> group of mice were motionless (inactive and stagnant). Anatomopathologically, the liver surface became dark red in color with considerable hepatomegaly and mild hemorrhage also found on lung surface. Histologically, mild central vein congestion and severe venous congestion with dilation were found in the portal vein of the liver of the treated T<sub>2</sub> group of mice. Hematologically, hemoglobin level significantly reduced in the treated T<sub>2</sub> group of mice than the others. Within this experimental period, female mice of each group gave birth (15-18 pups) that were devoid of any abnormality. Therefore, it can be concluded that excessive green tea intake in a day might have baleful effects on hematological parameter (Hb concentration) and histoarchitecture of liver in Swiss albino mice.

<sup>a</sup> [swarupkundu@kau.edu.bd](mailto:swarupkundu@kau.edu.bd)

<sup>1</sup> <https://orcid.org/0000-0003-2951-2010>

<sup>b</sup> [skdas76@yahoo.com](mailto:skdas76@yahoo.com)

<sup>2</sup> <https://orcid.org/0000-0001-8958-4847>



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## Introduction

Tea is one of the most popular beverages commonly used in China and Japan (Nawab and Farooq, 2015). Green tea is an evergreen shrub derived from *Camellia sinensis* (L.) Kuntze (Theaceae).

### Plant morphology of *Camellia sinensis* (L.) Kuntze

*Camellia sinensis* (L.) Kuntze is in the member of Theaceae family. The leaves of green tea are short stalked, light green, coriaceous, lanceolate, alternate, serrate margin, glabrous or pubescent beneath, varying in length from 6 - 30 cm and about 4.5 cm width. Flowers of the tree bear huge amount of stamens with yellow anther and produce brownish red capsules (Ross, 2005). Fruit is a smooth, flattened, rounded trigonous three celled capsule, seed solitary in each, size of a small nut (Biswas, 2006).

### Chemical constituents and possible effects

Active ingredients of green tea are including polyphenolic compounds such as epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and

epigallocatechin-3-gallate (EGCG). Flavones and their glycosides are the other polyphenols of green tea (Liu et al., 2008). Green tea offers many attractive beneficial effects. It possesses antioxidant, antiproliferative, antitumor, anticarcinogenic, cardioprotective, neuroprotective, anti-diabetic, and antimicrobial properties (Alschuler, 1998; Augustyniak, 2005; Cooper, 2005; Liao, 2001; Kundu et al., 2021). Green tea is also used as protective agent in exercise enhancement, inflammatory bowel disease, diabetes, hair loss, skin disorders, weight loss and iron overload (Sinija and Mishra, 2008). Green tea extracts exhibit stronger antioxidant effect than vitamin C and vitamin E. This antioxidant protects cells from damaging effect of reactive oxygen species such as singlet oxygen, super oxide and hydroxyl radical (Sengottuvelu et al., 2008). According to the experimental report, green tea consumption alleviates non-alcoholic fatty liver disease (NAFLD) by reducing the fat deposition in hepatocytes (Daniells, 2008). Green tea extract possess protective effects against arthritis, infection, and impaired immune function (Van, 1999) and also reduce

the cholesterol synthesise in liver (Bursill et al., 2007). But conflicting results have also been reported. Green tea is also a rich source of caffeine that maintains body systems (Cavalli and Tavani, 2016). Harmful effects of tea overconsumption (black or green) are primarily due to three main factors: (I) its caffeine content, (II) presence of aluminum, and (III) the effects of tea PPs (TPP) on iron bioavailability. The negative effects produced by caffeine present in many tea products are nervousness, restlessness, tremors, palpitations, sleep disorders, vomiting, diarrhea, headaches, epigastric pain, and tachycardia. However, research on the effects of caffeine in children is limited. Negative effects of theophylline (member of the xanthine family of stimulants) are similar to those of caffeine, but they only occur with high quantities intake. Thus, green tea should be avoided by the patients suffering from heart conditions or major cardiovascular problems (Higdon and Frei, 2006). Green tea intake may cause constipation and stomach upset, kidney problem and acute liver injury in case of high dose consumption in a day. Important ingredient of green tea is antioxidant. The average amount of antioxidant in green tea is 90 to 300 mg. But excess intake of this antioxidant (about over 800mg) causes liver damage (Navarro-Perán, 2005). High doses of green tea consumption (5–6 liters per day) may cause, dyspepsia, abdominal bloating/pain and diarrhea (Laurie et al., 2005) as well as excessive consumption of caffeine from green tea may also cause dizziness, tremors, insomnia, confusion, diuresis, psychomotor agitation and heart rate irregularities (Tomasulo, 2004). Regular intake of green tea may reduce the risk of cardiovascular disease (CVD) but has also been associated with liver toxicity in case of high doses (Chang, 2003; Frank et al., 2009; McCormick et al., 1999; Stratton et al., 2000). The hepatocellular alteration is probably occurs due to EGCG or its metabolites which can induce hepatic oxidative stress.

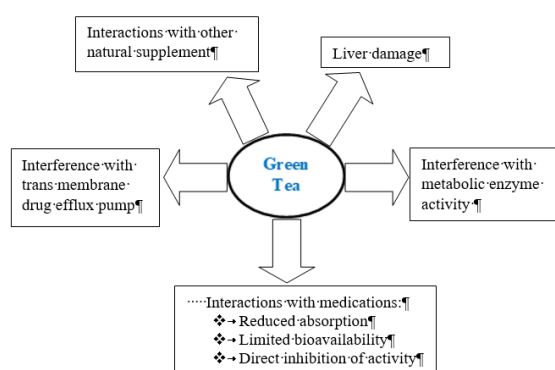


Chart 1. Possible effects of green tea extract (Schönthal, 2011)

### ***Mechanism of Iron Absorption Deterioration due to Excessive Green Tea Intake***

Owing to tannins present in black or green tea, its consumption with meal reduces the absorption of non-heme iron (Fe). For a meal comprising of hamburger the absorption reduces to 0.12 from 0.32 mg. It was found that on consuming tea the negative balance of iron increased for black and decaffeinated black tea consumption than for consuming no tea (Prystai et al., 1999). Several studies have demonstrated that black tea appears to inhibit the bioavailability of non-heme iron by 79–94% when both are

consumed concomitantly; the impact of this interaction depends on the Fe intake and Fe status of the individual. Similarly, green tea catechins may have an affinity for Fe, and green tea infusions can significantly decrease the Fe bioavailability from the diet. These studies affirmed that tea should not be consumed by patients suffering from anemia. For example, Fe-deficiency anemia among children in Saudi Arabia and the United Kingdom may be aggravated by the regular consumption of tea with meals. It is proposed that the interaction between green tea and Fe can be alleviated by the addition of lemon or consuming tea between meals (Cabrera, 2006). The authors of a systematic review of 35 studies on the effect of green tea drinking on Fe status in the UK concluded that tea drinking reduced the absorption of non-heme Fe from the diet and statistically significant relationships were observed between green tea drinking and poor Fe status (Nelson and Poulter, 2004). Hence, the aim of this present research was to find out the baleful effects of excessive green tea consumption on hematological parameter and histoarchitecture of liver in mice.

## **Materials and Methods**

### ***Statement of the Experiment***

The research was performed in the laboratory of the Department of Anatomy and Histology, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh and the samples were also processed in the same laboratory.

### ***Ethical Approval***

The present study and all experimental procedures were approved and performed according to the guidelines for the care and use of animals as established by Animal Welfare and Experimentation Ethics Committee, Bangladesh Agricultural University, Mymensingh, Bangladesh (Protocol Number: AWEEC/BAU/2019-62).

### ***Rearing and Care of the Experimental Animal***

Total thirty (30) experimental Swiss albino mice (at the age of 5 weeks and avg. weight 18-20g) were brought from ICDDR, B, Mohakhali, Dhaka, Bangladesh. Because over 95% of the Swiss albino mice genome is similar to that of human; making mice based research particularly applicable to human disease. Practically, mice are cost-effective and efficient tool to speed research and the development of drug therapies (Merck, 2005). The collected mice were adapted at Animal Care Room, for the period of 7 days before being used for the experiment and the room temperature was maintained between 20–26°C. The collected mice had neither any developmental disorders, detectable genital diseases nor other diseases that may hamper in the result of the experiment. On that time, mice were given free access to water with standard diet and allowed to acclimatize with the new environmental condition. Excreta were removed from the cages on every day. During the experimental period uniformity of the management practices was maintained.

### ***Experimental Design***

Total thirty (30) experimental Swiss albino mice (age of 5 weeks and avg. weight 18-20g) were taken and randomly divided into three (3) groups such as Control C, treated T<sub>1</sub> and treated T<sub>2</sub> groups, each group consisted of

ten (10) mice. The control C group (5 male+5 female) was orally fed with normal mice pellet and water (3ml/mice), treated T<sub>1</sub> group (5 male+5 female) was given orally mice pellet and 2ml/mice of green tea+1ml/mice of water as well as treated T<sub>2</sub> group (5 male+5 female) was supplied orally mice pellet and green tea (3ml/mice) two times in a day for 60 days (Figure 1). In this study, both male and female mice were reared in same group to observe the effect of excessive green tea intake in a day in case of pregnancy.

**Chemical Formulation of Supplied Green Tea**

Table 1. Essential ingredients with its possible contents

Chemical ingredients	Amount
Total Phenolic Content (TPC)	103.0±0.3 mg
Ferric Reducing Antioxidant Power (FRAP)	97.0±1.4 mg
DPPH Radical Scavenging Activity	19.0±3.0*
Total Antioxidant Capacity (TAC)	324.9±0.6 mg
Ferrous Ion Chelating (FIC) Ability	1.02±0.07mg

\* µg tea/mL hot water

**Preparation of green tea**

Fresh water was kept in a container for proper boiling (100°C). After it was done the water was let down 2min for cooling. Then 60ml of boiled water was taken in a glass and one bag (2g green tea) of green tea was added in the glass. After waiting about 5min for proper mixing of green tea in boiled water, the tea bag was removed from glass. Then liquid green tea was supplied after proper cooling to the each experimental mice in appropriate amount according to the experimental design.

**Sample collection**

After the experimental period (60 days), the mice of each group were sacrificed ethically by administering sedative for making animals unconscious and insensitive to pain and distress as quickly as possible. Then samples (liver and lungs) were collected in order to investigate the gross and histological study along with the blood sample was also collected about 0.5ml from each mice by cardiac puncture following dissection for hematological study. Finally liver sample stained with hematoxylin and eosin (H&E) and examined under a light microscope to observe the hepatocellular alteration.

**Statistical Analysis**

All the collected data were stored in Microsoft Excel-2013 and imported to Statistical Package for the Social Sciences (SPSS; version 20.0) software for data analysis. Statistical analysis was performed using one-way analysis of variance (ANOVA). Results were expressed as mean ± standard error (SE). The differences were expressed statistically significant when the p values were less than 0.05.

**Results**

The results of the present study showed that the treated T<sub>2</sub> group of mice became motionless (inactive and stagnant) than the control C and treated T<sub>1</sub> group of mice that was confirmed by naked eye observation of the appearance of each mice. On the other hand, within this experimental period female mice of each group gave birth (15-18 pups) which were devoid of any abnormality (Figure 2).



Figure 1. Feeding of mice pellet and water (Control C); mice pellet and green tea (Treated T<sub>1</sub> and T<sub>2</sub>)

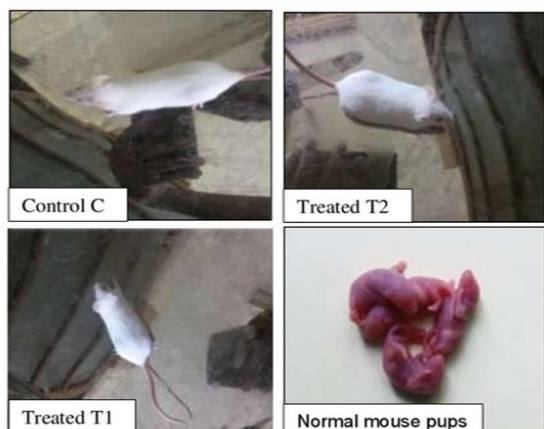


Figure 2. Active and alert mice (Control C and T<sub>1</sub>); motionless mice (Treated T<sub>2</sub>); normal mouse pups (Control C, treated T<sub>1</sub> and treated T<sub>2</sub>)

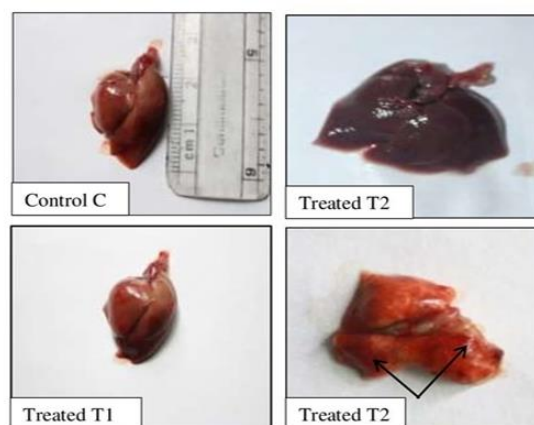


Figure 3. Photographs of liver represent normal morphological appearance

(Reddish, smooth and shiny surface) in control C and treated T<sub>1</sub>; dark red in color with considerable hepatomegaly as well as lung showing profuse hemorrhage (black arrow) in the treated T<sub>2</sub> group of mice.



### Gross morphological examination

In the gross study, liver surface became dark red in color with considerable hepatomegaly found in the treated T<sub>2</sub> group of mice. Mild hemorrhage was also observed in the surface of lungs of green tea treated group of mice (Figure 3).

### Histopathologic examination: Hematoxylin and eosin staining

Histopathologic examination revealed regular and normal cellular architecture with separated normal cords of hepatocytes, sinusoid, and central vein in liver tissues of control group mice. Whereas liver tissue of treated T<sub>2</sub> group showed severe venous congestion and dilation in portal vein, and mild central vein congestion (Figure 4).

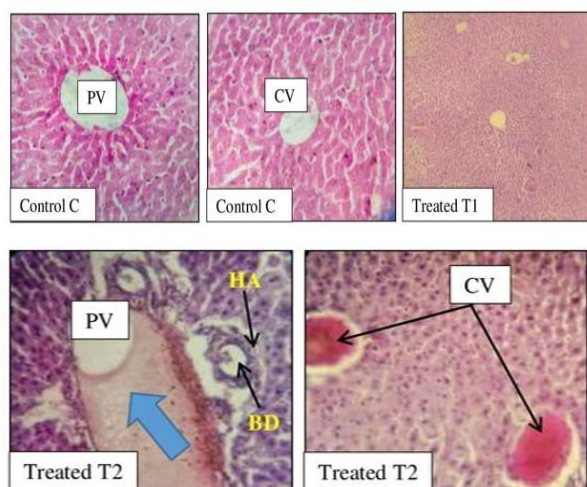


Figure 4. Photomicrographs of liver represent normal central vein (CV) and portal vein (PV) in control C and treated T<sub>1</sub> group of mice; liver showing severe congestion and dilation in portal vein (block arrow) and mild central vein congestion (arrow) in green tea consumed treated T<sub>2</sub> group of mice (BD= Bile duct, HA=Hepatic artery). Images were photographed with a 40X objective (H&E stain).

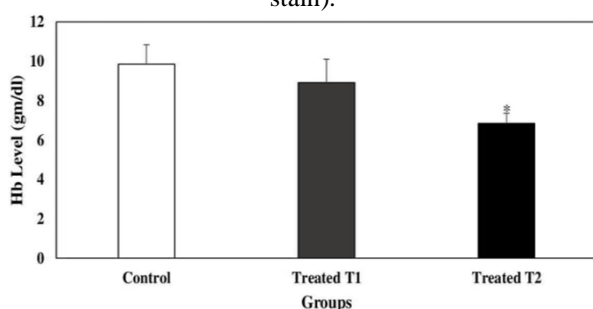


Figure 5. Value of hemoglobin (Hb) concentration significantly decrease in treated T<sub>2</sub> group compared to control C and treated T<sub>1</sub> group of mice. Data represented as mean  $\pm$  standard error (SE). \* $P < 0.05$  compared with the control C.

### Hematological observation

The mean value of hemoglobin (Hb) concentration significantly (\* $P < 0.05$ ) decreased in excessive green tea consumed treated T<sub>2</sub> (6.84 g/dl) group compared to control C (9.84 g/dl) and treated T<sub>1</sub> (8.92 g/dl) group of mice (Figure 5). It is worthy to mention that average Hb

concentration of male mice (5 mice) in treated T<sub>2</sub> group was 7.28g/dl and among the 5 female mice in treated T<sub>2</sub> group 2 female mice were pregnant. The average Hb concentration of pregnant mice (2 mice) and non-pregnant (3 mice) mice were respectively 6.80gm/dl and 6.44g/dl. In control group, the average Hb concentration of male mice (5 mice), pregnant mice (1) and non-pregnant mice (4 mice) were respectively 10.32g/dl, 9.48g/dl and 9.72g/dl. On the other hand, in the treated T<sub>1</sub> group, the average Hb concentration of male mice (5 mice), pregnant mice (2 mice) and non-pregnant mice (3 mice) were respectively 9.57g/dl, 8.42g/dl and 8.77g/dl.

### Discussion

Green tea is a natural antioxidant that has been used in the most enduring food cultures. The aim of this research was achieved in Swiss albino mice in where liver became dark red in color with considerable hepatomegaly, severe venous congestion and dilation in portal vein (PV) and mild central vein congestion were found due to green tea intake. Fung et al., (2013); Liu et al., (2008) and Mazzanti et al., (2009) reported that the principal active ingredients of green tea are polyphenolic compounds such as EC, ECG, EGC and EGCG and hepato cellular alteration is most probably occurs due to epigallocatechin gallate or its metabolites. EGCG intake at high doses has been shown to induce hepatotoxicity in animal models. Galati et al., (2006); Lambert et al., (2010), Wang et al., (2015) and Jimenez-Saenz and Del Carmen Martinez-Sanchez, (2006) stated that high doses of green tea in a day may also enhance liver injury (central and portal vein congestion). Concentrated extracts of green tea (*Camellia sinensis*) consumption possesses a real and growing risk to liver health. Pisters et al., (2001) observed their study, the liver sections of green tea extract-treated rats showed mild inflammation and necrosis of hepatocytes and vacuolation along with mild-to-moderate gastrointestinal, neurological, and cardiovascular effects at most dose levels. Individual cases of hepatic disorder, ranging from acute hepatitis to acute liver failure, from consuming large amounts of green tea are also reported by Lou et al., (1999). Liver toxicity (for example, hepatic necrosis) was also frequently observed in different studies but there was no evidence of liver carcinogenicity in animal experimental trial for high concentrations of green tea extracts which was proved by Yoshida et al., (2011). Green tea may contain solvent residues and other impurities that can cause liver damage in susceptible people. But of greatest significance, Jin et al., (2008) and Ui et al., (2009) reported their research that a specific compound in green tea that is most abundant (Epigallocatechingallate or EGCG), can saturate the liver and increasing the potential to liver disease in particular, liver cancer. Fan, (2016) suggesting that caffeine is a major constituent and if more than five cups of green tea are consumed daily it may cause insomnia, restlessness and upset stomach as well as iron deficiency anaemia also appears as its consequences. Main reason behind the iron deficiency anaemia for containing tannins that reduce iron availability before absorption through the formation of insoluble ant nutritional-mineral complexes. Kuriyama, (2008) and Hirai et al., (2007) observed their research that higher dosages of green tea can also cause irregular heart

rhythm, acutely harmful effects to the circulation system and can modulate the cardiac function. In our study, we found, hemoglobin level of the treated T<sub>2</sub> group of mice reduced significantly (\*p<0.05) than the control C group of mice. In the research of Navarro-Perán et al., (2005) it was stated that green tea is safe to drink in moderate amounts during pregnancy and epigallocatechin is an active ingredient and a powerful antioxidant which is important during pregnancy. In our study, we used both male and female mice to explore the detrimental effects of green tea consumption on pregnancy but in the present research mice of both (control and treated) groups gave births (18 pups) which were devoid of any abnormality. Lantika et al., (2020) and Sarma et al., (2008) found that maternal consumption of green tea extract during pregnancy and lactation did not promote alteration in body weight in mothers and pups as well as intake of green tea extract has no detrimental effects on new-born along with this can promote the reduction rate of retroperitoneal adipose tissue relative weight in 28d-old pups. A high dose of caffeine intake can sometime also affect the bioavailability of folic acid and reduce the serum folic acid levels. Depending on the brand, two to three cups of green tea per day (for a total of 240–320 mg polyphenols) or 100–750 mg per day of standardized green tea extract is recommended.

## Conclusion

Although green tea is found to be popular recently among the health conscious people but the exact baleful effects rendered by it on health is unclear until today for excessive intake in a day for long time. The present study indicates some detrimental effects on health especially hepatomegaly, decreasing hemoglobin concentration and massive congestion in both central and portal vein in case of excessive consumption of green tea in a day for longer period. In case of female, during their menstrual cycle excessive blood loss occurs, in that time if the female people are more attracted to green tea, hemoglobin concentration might be reduced, as a result, excessive intake of green tea occurs iron deficiency anaemia. For future it needs further investigation to understand the pathway of causing such baleful effects of excessive green tea intake on body both in gross and cellular level as well as to determine the actual quantity of daily green tea intake.

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## Authors Contribution

Shonkor Kumar Das designed and supervised the experiment. Swarup Kumar Kundu performed the research experiment, formulated, and collected all data, analyzed

data and wrote the initial draft of manuscript. Finally Shonkor Kumar Das revised and finalized the manuscript.

## Conflict of Interest

We declare that we have no conflicts of interest to disclose.

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