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## Green Tea: A Phytopharmaceutical 'Wonder' Extract for Ischaemic Stroke

Alka Gupta<sup>\*</sup>, Bhawna Khurana, Indira Raheja.

Maharaja Surajmal Institute of Pharmacy, affiliated to Guru Gobind Singh Indraprastha University, New Delhi.

### ABSTRACT

Stroke is contemplated as the worst symbol of morbidity and mortality, also being considered worse than death, as more than 25% of stroke patient suffered from disabilities of varying degree. Lifelong diseases like paralysis, spatial-perpetual and memory related problems, speech deficits etc are certain deformities occurring due to disrupted blood flow. Green tea, produced from plant *Camellia sinensis*, is a rich source of polyphenolic compound epigallocatechin-3-gallate (EGCG), the most abundant catechin and strongest antioxidant found in green tea along with theanine and caffeine(main constituent of coffee), are believed to possess the stroke preventing qualities. Epigallocatechin-3-gallate (EGCG) being an anti-oxidant act directly on heart, while theanine can cross the BBB and competes with glutamate for glutamate receptors. This action can be considered to be of significance as glutamate release is found to be associated with occurrence of stroke. As per the past surveys and recent case control studies conducted on IS patients in different countries, it was observed that the subjects who drank at least one cup of green tea a day (180-230ml) reduced their risk of IS by significant amount, while those who drank more than 3 cups daily, displayed a reduction in stroke frequency by as much as 60%. Thus it may be concluded that regular intake of green tea as a beverage has prophylactic potential against stroke incidence.

**Keywords:** Green tea, ischemic stroke (IS), epigallocatechin-3-gallate (EGCG), Theanine, glutamate, antioxidant.

*\*Corresponding author*

Email: alka.msip@gmail.com

## INTRODUCTION

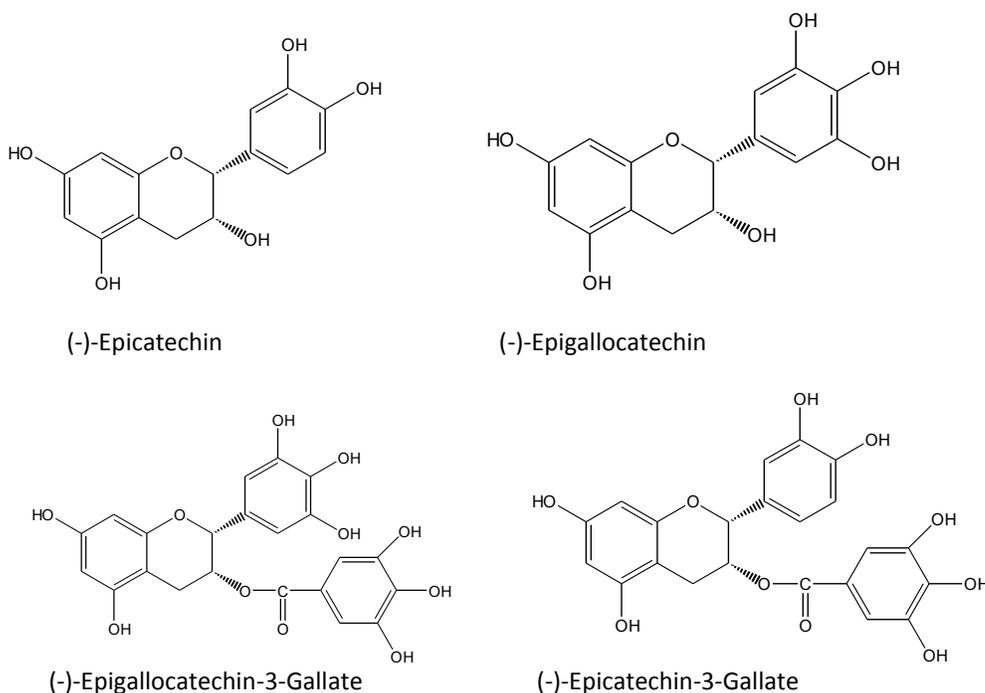
Worldwide, cerebrovascular disease causes an estimated 5.4 million deaths per year. Stroke can have a reflective sway on the individual and their families. Survivors frequently experience hemiparesis, aphasia, hemianopia, depressive symptoms, dysphagia, incontinence, and difficulty walking. Stroke essentially is a result of high blood pressure, smoking, waist-to-hip ratio, diet, physical activity, lipids, diabetes mellitus, alcohol intake, stress and depression, and heart disorders. Hamilton revealed that a stroke could be predicted, and that simple measures could reduce the burden of heart disease. [1]

Tissue plasminogen activator (TPA) like alteplase, heparin and aspirin, management of medical problems, [2] tea like green tea and black tea,[3] process like rehabilitation etc are the diverse customs for prevention of stroke.[2] With the limitation, green tea and black tea are the emerging areas of interest.

Green tea (*Camellia sinensis*) has been studied for its effect on the prevention of many diseases like cancer (cervical cancer, ovarian cancer, liver cancer, mesothelioma, esophageal cancer etc), heart disease risk, belly fat, brain abnormalities, etc. [4]

A recent study conducted by researchers at the University of California, Los Angeles (UCLA), found that drinking three cups of green or black tea each day reduced the risk of stroke. Since there are few ways to prevent a stroke, these findings are imperative since it is one more step in the direction of finding prevention for stroke. [5]

**Fig. 1: Major Polyphenols present in Green Tea**



## PHARMACODYNAMICS OF PHYTOCONSTITUENTS

Chemically, green tea is an affluent source of polyphenols including epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate and 3-epigallocatechin, caffeine, theanine, vitamins, inorganic elements etc. [6] The largest and most important chemical compound is polyphenols. This is because they contain flavonoids - an important class of antioxidants. Chinese and Japanese green tea plants tend to have lower level of polyphenols. [7] Now, 80% reduction in stroke size followed by reduction in the number of brain cells dying by up to 50% was achieved by both green tea extract and EGCG, the strongest antioxidant in green tea. Dr. Kuriyama agreed with the above fact. He also noted Biological mechanisms including:

1. Radical scavenging and antioxidant properties for different models of chronic disease made it possible that green tea polyphenols might directly affect atherosclerosis itself, irrespective of traditional cardiovascular risk profiles. In addition, he said that the inverse association between green tea consumption and stroke mortality appeared to be a threshold effect rather than a dose-response relationship, suggesting that even one cup of tea each day might provide some protective benefits. However, he stressed that additional clinical trials are necessary to confirm the findings.[8]
2. A second mechanism is through a crash of tea or catechin consumption on nitric oxide formation. [9] Catechin ingestion will block an increase in serum nitric oxide concentration after reperfusion and tea has a verified effect on endothelial function. Ingested tea can also enhance endothelial function, especially among those with compromised functionality.[10, 11]Because cerebral blood flow is particularly impaired in elderly with reduced endothelial function, and vascularization of the brain impacts stroke risk, this is a possible mechanism.[12]
3. The third prospect is through effects an amino acid, theanine in high concentrations in and coming almost utterly from the tea plant. Theanine is readily bioavailable from green tea, crosses the blood-brain barrier, and has established effects on brain function. [13] The chemical structure of theanine, which contains the glutamate molecule, suggests that it might reduce glutamate-related endothelial damage. Studies conducted on middle cerebral artery occlusion of mice have confirmed a neuroprotective effect of  $\gamma$ -glutamylethylamide (theanine). In this model, functional  $\gamma$ -aminobutyric acid<sub>A</sub> receptors, present only in the brain, emerge to be receptive to theanine.
4. An alternative hypothesis of focal ischemia shows that regular tea consumption, instead of preventing explicit stroke, may instead reduce the post ischemic damage to a level that results in sub clinical ischemia or hidden strokes.

**PAST ACKNOWLEDGEMENTS OF GREEN TEA**

Till 1989, there was no epidemiological survey on green tea effect on IS, was conducted despite the popularity of this beverage among example Japanese population [14]. Before epidemiological studies, frequency of daily green tea intake was investigated by questionnaires as a part of ‘Health & Environment’ study in rural area and in a prefectural city to investigate the possible effects on prevention of stroke. This questionnaire was given personally to each individual. This survey was based on tea consumption (according to no. of cups and cups may range from 1 to  $\geq 5$ ). Survey conducted by Y.Sato et al, also considered various interfering factors such as drinking, smoking, sex, salt intake, miso and pickle consumption.[15] Results obtained by him are summarized in table 1.

**Table1 Reduction of stroke history on consumption green tea [14, 15]**

Area of Survey	Rate of Collection	No. of Subjects	No. of Cups	Outcome
1. Rural		1673	$\geq 5$	0.44% reduction in stroke
i. Tajiri	95%			
ii. Wakya	93%			
2. Urban (6 primary school sector in Central Sendai)	81%	2273	$\geq 5$	0.42% reduction in stroke
I. Person consuming alcohol (drinking) & tobacco (smoking) were excluded from the survey. II. No analysis was conducted on men as most of them were either drinker or smoker. III. Stroke reduction was 0.38% in miso and pickle consuming subjects.				

**SCIENTIFIC EVIDENCES: CASE CONTROL STUDIES**

The study tracked green tea consumption among IS patients in China,[4,16,17] Japan,[18] Australia,[4,16] Netherlands[4] (9 countries were involved in epidemiological studies out of which above four are involved in case control study as founded by UCLA researchers[16,19]). A significant decrease in ISR was observed for drinking at least one cup of green tea weekly compared with infrequent or non drinkers. The risk reduction being largest by drinking more than 1 cup a day. According to Arab’s linearity curve, if one drinks three cups a day, the risk falls by 21 percent; follow that with another three cups and the risk drops another 21 percent.[8] Overall it was concluded that drinking 1-5 cups of green tea a day reduces the risk of IS by 40-65%. The study conducted by the various researchers not only based on the no. of cups but on the other factors like diet, lifestyle etc. Taste of the Australian people changes from time to time was also considered as an important factor. Table2 explains the case control studies of different countries. [20]

**Table 2- Case control studies on green tea in stroke**

Country	No. of subjects	Age groups	Various factors with drinking habits	No. of cups of green tea (cups/day)	Outcome
China [4, 16, 17]	14,000	Adults	Diet, lifestyle	$\geq 1$ (P=0.015)*	65% dec. in ISR**
Japan [18]	40,000	Middle aged people	-do-	$\geq 5$	40 to 60% dec. in ISR
	6,000	Middle aged women	-do-	$\geq 5$	50% dec. in ISR
Netherlands [4]	552	15 years man	Diet, lifestyle & climate	3-4	55-65% dec. in ISR
Australia [4, 16]	-	-	Diet, lifestyle, taste	2	60% dec. in ISR
<p>* P is the amount of grams of active constituent (which fight against stroke) present in the tea...</p> <p>** ISR-ischemic stroke risk</p>					

The studies conducted by various countries need to perform various clinical trials in order to come to the conclusion. But such clinical trials would be difficult at this point and require many subjects, said Joseph Broderick, MD, Neurology Chair at the University Of Cincinnati College Of Medicine. Dr. Broderick was not involved with the study. While the Japanese study shows a very interesting connection between green tea and stroke and cardiovascular risk and ropes the findings of earlier studies in smaller groups, he said it was limited by significant loss to follow-up in the original legion and the fact that the questionnaire was administered only at the beginning of the study. In addition, the amount of tea drinking was also associated with other key variables known to be related to survival and cardiovascular disease such as age, exercise, hypertension, and smoking.

These confounders may make it more difficult to tease out the true effects of tea drinking. The statistical analyses that were used tried to adjust for these other variables, but they also assume that the risk for all of these variables is constant throughout the time period and that the risk for each variable remains unchanged. They did not have this information so it is unclear whether these assumptions are valid or not. [8]

**COMPARITIVE EVALUATION OF GREEN TEA vs. COFFEE PERTAINING TO STROKE**

Conventionally, coffee is seen as a dangerous substance that may increase blood pressure, cholesterol, and strokes. [2] However, in a study conducted on 23,000 men and women who were followed for an average of 12 years by Yangmei Li, an epidemiologist at the University of Cambridge in England show an inverse relationship between the consumption of coffee and strokes[22] (excluding thromboembolic stroke[22]). Similarly, other study which followed 83,000 women for 24 years, researchers found that those who drank four or more cups of coffee a day were 20 percent less likely to have a stroke than those who drank less than one cup a month. Those who drank two to three cups a day had a 19 percent reduced risk and those who drank five to seven cups a week had a 12 percent reduction in risk, according to the Nurses' Health Study published last month in the journal Stroke. The researchers warned that any beneficial effects of coffee cannot counterbalance the ill effects of smoking. They added that the effects can be applied only to healthy people. [23] On the contrary, green tea was found to be better than the coffee. This can be explained on the basis of above green tea analysis (in the above text) and caffeine content present in the tea and the coffee. The mechanism by which coffee act in our body is through tannins. When coffee is consumed by our body, the tannins cause our body to absorb the caffeine very quickly causing a sudden jolt of energy. This jolt can make you jittery and cause restlessness. This wasn't cause jitter and doesn't allow insomnia to occur (as seen in case of coffee). On the other hand, green tea is found to possess antioxidants and flavanoids which are responsible for fighting free radicals in the body.[24] Coffee consumption is also associated with a lower risk of developing type 2 diabetes -a major risk factor for stroke, Lackland said. "Typically, they rely on self-reports, how much coffee you say you drink," Lackland said. "But what might be two cups for me might be an entirely different two cups for you."So, there are no official suggestions that people drink coffee to lower their risk of stroke, Lackland said. "There has been no study designed to produce the kind of evidence needed to make recommendations," he said. [22]

**Table 3 Green tea vs. coffee**

PROPERTIES	GREEN TEA	COFFEE
Mechanism of action (as assumed)	Flavanoids and epigallocatechin-3-gallate (EGCG)	Caffeine and tannins
% of stroke reduction	65-69% with 4-5 cups per day	43%* with 3-4 cups per day
Harmful effects	Insomnia is absent	Insomnia is prominent

**GENERAL DISCUSSIONS AND INFERENCES**

Study conducted by various researchers, clearly demonstrated inverse association between consumption of green tea and the risk of stroke. Consuming more than 2-3 cups of green tea every 2-3 days was associated with a risk reduction of more than 50% of total stroke,

cerebral infraction and cerebral hemorrhage events.[18] The effect doesn't appear to be specific to green tea or to Asian on non-Asian populations. Finding suggests that tea drinking may be one of the most actionable lifestyle changes to significantly reduce risk of stroke. [3]

These studies were epidemiological studies but out of this case control studies tend to have high potential recall & selection bias. Although, there saw a little or no difference in results between cohort and case control studies. For stroke, it remains unclear if the differences were due to regional differences or differences in study design. [25] Furthermore, stroke as an outcome would be separated into different subcategories without combining ischemic stroke and hemorrhagic stroke. This would be particularly interesting because animal evidence suggests that tea consumption may reduce the damage of ischemic stroke but increases risk of hemorrhagic. [26]

However, most of the studies combine all strokes and the few addressing strictly subarachnoid hemorrhage and hemorrhagic stroke. The mechanism of action by which tea may protect against stroke remains speculative. Although antioxidant functions and anti-inflammatory actions are often mentioned, 3 mechanisms have some in vivo evidence of effect or lack of it. [27] A second mechanism is through an impact of tea or catechin consumption on nitric oxide formation. [9] The third possibility is through effects of theanine, an amino acid in high concentrations in and coming almost exclusively from the tea plant. Theanine is readily bioavailable from both green and black tea, crosses the blood-brain barrier, and has demonstrated effects on brain function. [13]

The chemical structure of theanine, which contains the glutamate molecule, suggests that it might reduce glutamate-related endothelial damage.[28] An alternative hypothesis, supported by the experiments with induced focal ischemia, is that regular tea consumption, instead of preventing overt stroke, may instead reduce the post ischemic damage to a level that results in sub clinical ischemia or hidden strokes. This would result in the diagnosis of stroke only in individuals with more extensive post ischemic damage or a greater stroke volume. Green tea consumption mechanism positively associated with consumptions of soybean paste soup, fish, vegetables and fruits. Although adjustment of these factors did not alter the relationship between green tea consumption and stroke incidence. [17]

## CONCLUSIONS

Questionnaire survey and case control studies (epidemiological studies) demonstrated that there is reverse relation between the habits of green tea drinking and frequency of having the history of stroke. Though the results were same in both the cases, the major drawback of questionnaire survey is the reverse relation in the time of occurrence of the disease and tea habits (recorded at the time of survey). It is further possible that the habits of drinking green tea may vary during life and the habits at the time of survey could be the reflection of the disease history and medical intervention. Coping with such difficulties, the follow up of the study group, although of relatively short time period of 4 year, made it clear that the mortality due to stroke is twice or even more times higher among those who took less green tea as

compared with those with larger green tea consumer. After this came the epidemiological studies (only case control studies are discussed here) which although shows the same results but overcome the drawbacks which were the hurdles of questionnaire survey. During this phase of epidemiological studies, coffee also comes to limelight and shows their positive effect on prevention of stroke. Further, comparison was made between the two (coffee and green tea) and it's very much obvious that consumption coffee is high than the green tea. It was established that the coffee can also reduce the risk of stroke. But due to side-effects and incomplete study results, it stills a mystery. Lastly, it can be concluded that further studies are required to verify the casual relationship between green tea consumption and reduced risk of stroke incidence.

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