Original Article

Hepatoprotective Effect Of Epigallocatechin-Gallate (Egcg) And Sorafenib Against Den Induced Hepato Cellular Carcinoma In Experimental Animals

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Abstract

Background
Hepatocellular carcinoma (HCC) arises from chronically inflamed and damaged liver tissue therefore, chemoprevention must be undertaken to reduce the incidence of HCC. Epigallocatechin gallate (EGCG) is a phytochemical, extracted from green tea. Past studies in animal models have revealed that it can suppress liver inflammation and fibrosis. Its role in HCC chemoprevention is not yet well established. Sorafenib is a chemotherapeutic agent, which significantly prolongs the survival of HCC patients with advanced-stage disease. The cost of sorafenib is very high, so combining this with EGCG can be cost-effective and as effective as sorafenib. Also to reduce the Side effects of Chemotherapeutic Drug. This study is aimed to assess the protective outcome of the phytochemical EGCG and chemotherapeutic drug Sorafenib in Hepatocellular carcinoma.

Materials and methods
Forty adult male Wistar albino rats of 3 months old were procured in this study. The rats were divided into 5 groups, 8 in each group. Group 1 has control rats and group 2 with negative control-treated only with Diethyl Nitrosamine (DEN). Group 3 is treated only with sorafenib and group 4 with EGCG alone and Group 5 received the combination of sorafenib and EGCG. After the probing period, the subjects were sacrificed and histopathological analysis was done. Alpha-fetoprotein level was measured by ELISA and liver enzymes were measured.

Result
Histopathological reports showed a satisfying decline in the degeneration and hyperchromatism among group 5 subjects. Alpha-fetoprotein level in group 5 was significantly lower than in group 2 and group 4 animals and it was statistically significant. Liver enzymes in group 5 were lower than in group 4 animals which indicate that group 5 subjects were doing better. We have found out that group 5 subjects had better antioxidant capacity when compared to group 2 and 3 animals.

Conclusion
We have reported that a combination ofsorafenib with EGCG has a comparable effect with standard-dose sorafenib. So we conclude that the combination of sorafenib and EGCG gives better chemoprotection and is effective against hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, Epigallocatechin gallate (EGCG), sorafenib, Alpha-fetoprotein

INTRODUCTION

Hepatocellular carcinoma (HCC) has gained attention in the recent decade both epidemiologically and clinically. It is the third most common cause of mortality among patients suffering from cancer and the fifth most frequent type of cancer origin across the globe (1). HCC usually occurs in normal cells of our body, which undergoes changes through various growth factors, proinflammatory cytokines, accumulation of many genetic factors, and nuclear factors (2).HCC doesn't have a standardized treatment and the role of chemotherapy is always controversial. So there is an utmost need for the development of new drugs. In order to boost the action and decrease the toxigenicity of the available conventional chemotherapeutic agents, researchers have targeted natural products and herbal agents as adjuvant therapy (3).

Epigallocatechin-gallate (EGCG) is a polyphenolic catechins, a natural agent found abundantly in green tea. It provides various benefits for healthy living including protection against cardiovascular, neoplastic, and neurological diseases (4,5). Past studies have revealed that the chemo-preventive effect of EGCG is mediated by the induction of apoptosis and cell cycle arrest and inhibition of angiogenesis, metastasis, and migration. Earlier literature supports the theory that EGCG is indeed an antineoplastic agent, based on experimental evidence from animal models (6, 7). The inhibition of tumorigenesis by multifaceted EGCG is attributed to a variety of unique combinations of antioxidants, and proapoptotic and antiproliferative effects (8, 9, 10). EGCG also shows antitumor activity against hepatocellular carcinoma by deactivating the growth factors like insulin-like growth factors and vascular endothelial growth factors (11, 12).

Sorafenib, an oral drug with biaryl urea kinase RAF inhibitor, works against (VEGF) vascular endothelial growth factor and also platelet-derived growth factor receptors, thereby targeting both angiogenesis and tumor cell proliferation (13). During the years 2005 and 2006, Sorafenib was approved to be used in renal cell carcinoma (metastatic) in the United States of America and European countries (14). Previous research revealed the anti-proliferative effect of this drug against various tumors by arresting the growth of tumors and cell death. It is also suggested that the induction of growth arrest is brought about by 45β (GADD45β) which is a DNA damage-inducible gene contributing to the programmed cell death or apoptosis in HCC cells by sorafenib (15).

So we intended to do the study on the protective sequel of the naturally occurring agent EGCG and the anti-cancer drug Sorafenib in Hepatocellular carcinoma, by evaluating the effect on oxidative and antioxidative activities and other parameters.

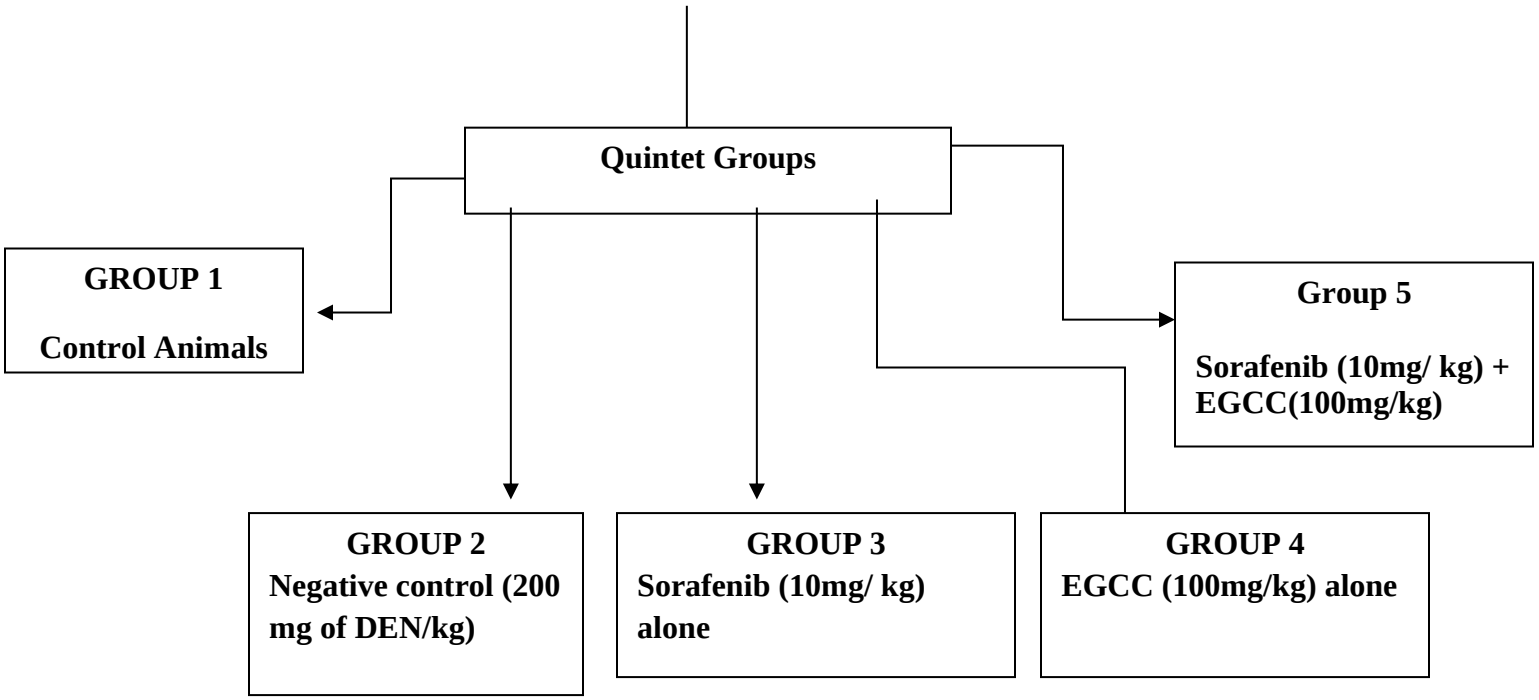
MATERIALS AND METHOD

Experimental Animals:

Forty adult male Wistar albino rats were procured from the enclosure (Animal House) from Sri Ramakrishna Institute of Para Medical Sciences, College Of Pharmacy, Department Of Pharmacology and were used in this inquiry. These animals were roughly 3 months old and weighed between 150-200gms. They are housed in a well-organized (12hlight/12hrs darkness), clean, wire cage with a temperature of 20-25^{o}C and were given free water ad libitum with a normal animal pellet diet during the period of experimentation.

Experimental design:

These experimental animals were arbitrarily divided into quintet (5) equal groups each of octad (8) rats as follows



Collection of blood and organs

After the probing period 90 days the subjects were fasted overnight and sacrificed by cervical decapitation, and blood collection was done followed by the segregation of plasma and serum to determine blood parameters. The liver and heart tissues were removed from every subject of the quinate groups, laved with wintry saline, blotted individually on filter paper and organ weights were measured. One portion of the liver and heart were fixed in 10% formalin for histopathological observations. The remaining liver and heart tissues were stored at -80°C and used for further studies. The liver and heart tissues have coalesced with motor-propelled Teflon overlayed homogenizer in wintry 0.1M Tris-HCl buffer pH 7.4 to acquire 10% homogenate. Attenuates were resolved based on the protein concentrations.

Weight of the body and organs

The body weight and the weight of organs like the liver and heart of all the animals were weighed and differences in weight between the groups were noted.

Histopathological analysis

A proportion of the hepatic and cardiac matter was unfastened instantly after sacrifice and moored in 10% formalin for histopathology. The tissues were cleansed in sprinting tap water, dehumidified in the subsiding grades of isopropanol, and eventually cleaned in xylene. The tissues were then implanted in liquefied paraffin wax. Segments were sliced at 5 µm extent, stained with hematoxylin and Eosin (H&E) and observed under an optical microscope for histopathological changes in the liver and heart of control and experimental animals.

Liver marker enzyme & AFP

The quantitative measurement of alpha-fetoprotein in ng/dl (AFP) is done by solid-phase enzyme-linked immunosorbent assay (ELISA). The liver marker enzyme such as Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST) in µmoles of pyruvate liberated / min / mg protein, Alkaline Phosphataes (ALP) in µmoles of phenol liberated / min / mg protein, Acid Phosphatase (ACP), Lactate Dehydrogenase (LDH) in µmoles of pyruvate liberated / min / mg protein, 5'- Nucleotides (5' –ND) in µmoles of phosphorus liberated / min / mg proteinwere assayed by the method of King (1965a)and (1965b) respectively.

Enzymatic & Non enzymatic Antioxidant

The enzymatic antioxidant of liver namely, catalase (CAT) in µmoles of H_2O_2 utilised/min/mg protein, Superoxide dismutase (SOD)units/mg protein, Glutathione peroxides (GPx)µmoles of GSH oxidised/min/mg protein was scrutinized by the approach of Sinha (1972), Marklund and Marklund (1974), and Rotrucket al. (1973) respectively. The non - enzymatic antioxidant of liver like, Vitamin C mg / g tissue, Vitamin Emg / g tissue, and GlutathionReductase (GR) µg of GSH / mg proteinwas appraised by the strategy of Omayeet al. (1979), Desai (1984),and Moron et al. (1979) respectively.

Statistical analysis

The quantitative variables with normal distribution and equal variance were compared with One-Way ANOVA test and post hoc Tukey test (Intergroup comparison) between the groups and expressed their mean, standard deviation and significanceFor all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analyses was performed by using a statistical software package SPSS, version 20.0

RESULTS

Table 1: Comparison of Body weight and Liver weight in grams between control and experimental animals by using One way – ANOVA

Weight in Grams	**Group 1 Mean ± SD**	**Group 2 Mean ± SD**	**Group 3 Mean ± SD**	**Group 4 Mean ± SD**	**Group 5 Mean ± SD**
Body Weight	344±36.2	276±26	295±30.1	351±34.4	336±32.6
Liver Weight	9.3±0.92	11.4±1.17	10.8±1.12	9.9±1.05	10.1±0.97
Group Comparison (post Hoc Tukey test)					
Body Weight	**1&2***, 2&4***, 2&5***				
Liver Weight	**1&2***, 2&3***, 2&4***, 2&5***				

(Values are expressed as mean ± SD for eight rats in each group; one way ANOVA' test, *p<0.05- ***p<0.01- statistically significant, ns- not significant. Inter -group comparison was done by Post Hoc –Tukey test. The mean difference is significant at the *p<0.05- ***p<0.01, NS – Not significant)

The body and liver weight of the animals were noted after the experiment and they were tabulated. Body weight and liver weight of group 5 were statistically significant when compared to group 1, 2 and 4 animals.

Table 2: Comparison of Liver marker enzymes & protein between control and experimental animals by using One way – ANOVA

Liver parameter	**Group 1 Mean ± SD**	**Group 2 Mean ± SD**	**Group 3 Mean ± SD**	**Group 4 Mean ± SD**	**Group 5 Mean ± SD**
ALT	52.36±5.66	67.34±5.68	53.12±4.86	58.22±5.28	**56.29±4.37**
AST	6.46±0.59	6.98±0.72	5.12±0.54	7.46±0.74	6.39±0.62
ALP	274.12±26.2	312.47±29.2	283.58±250.12	291.12±26.4	**296.45±25.1**
ACP	34.44±3.24	49.64±4.76	38.53±3.56	42.15±3.85	32.52±3.31

LDH	1.56±0.13	2.34±0.22	1.76±0.16	1.89±0.17	1.46±0.12
5'ND	4.34±0.48	7.11±0.68	5.43±0.49	6.62±0.59	4.74±0.44
AFP	0.5±0.04	1.2±0.12	0.86±0.078	0.69±0.073	**0.73±0.07**
Group Comparison (post Hoc Tukey test)					
ALT	**1&2***, 2&4***, 2&5***, 3&4***, 3&5***				
AST	**1&2***, 1&3***, 1&5*, 2&3*, 2&4***, 2&5***, 3&4***, 3&5***				
ALP	**1&2***, 1&3***, 1&5**, 2&3*, 2&4***, 2&5***, 3&4***, 3&5***				
ACP	**1&2***, 1&5***, 2&3***, 2&4***, 2&5*, 3&5***				
LDH	**1&2***, 1&3***, 1&4 ***, 1&5***, 2&3***, 2&4***, 2&5***, 3&4***, 3&5***				
5'ND	**1&2***, 1&3***, 1&4 ***, 1&5**, 2&3**, 2&5***, 3&4***				
AFP	**1&2***, 2&3***, 2&4***, 2&5***, 3&4***				

Values are expressed as mean ± SD for eight rats in each group; one way ANOVA' test, *p<0.05- ***p<0.01- statistically significant, ns- not significant. ALT - Alanine Transaminase, AST- Aspartate Aminotransferase, ALP- Alkaline Phosphataes, ACP- Acid Phosphatase, LDH- Lactate Dehydrogenase, 5'ND- 5'- Nucleotides, AFP- Alpha-fetoprotein levels (ng/dl). Inter -group comparison was done by Post Hoc –Tukey test. The mean difference is significant at the *p<0.05- ***p<0.001.

Table 2 illustrates the comparison of liver marker enzymes and proteins between groups. Important liver enzymes such as ALT, ALP and AFP have improved in group 5 when compared to other groups. This shows the significant effects of our drug combination when compared to other treatment group.

Table 3: Comparison of Enzymatic & Non enzymatic Antioxidant between control and experimental animals by using One way – ANOVA

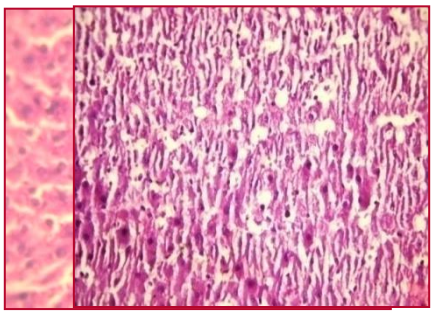
Enzymatic & Non enzymatic Antioxidant	**Group 1 Mean ± SD**	**Group 2 Mean ± SD**	**Group 3 Mean ± SD**	**Group 4 Mean ± SD**	**Group 5 Mean ± SD**
SOD	8.95±1.03	4.68±0.66	8.09±0.87	5.66±0.79	8.86±1.09
CAT	55.42±7.52	28.27±5.29	53.64±6.58	40.36±5.71	55.64±9.38
GPx	18.66±1.65	9.84±0.92	15.98±2.23	12.65±1.83	17.92±1.34
GR	54.51±5.65	38.12±3.37	48.78±4.17	44.24±3.02	51.28±4.54

GSH	0.73±0.08	0.41±0.03	0.69±0.06	0.57±0.04	0.74±0.09
Vitamin - C	0.85±0.09	0.66±0.07	0.86±0.08	0.72±0.06	0.91±0.09
Vitamin - E	0.87±0.09	0.62±0.05	0.86±0.07	0.73±0.06	0.92±0.19
Group Comparison (post Hoc Tukey test)					
SOD	**1&2***, 3&4***, 3&5***				
CAT	**1&2***, 1&3***, 2&3***, 2&4***, 2&5***, 3&4***, 3&5****				
GPx	**1&2***, 2&3***, 2&5***, 3&4***, 3&5****				
GR	**1&2***, 1&5***, 2&3***, 2&4***, 2&5***, 3&4***, 3&5****				
GSH	**1&2***, 1&3***, 1&5*, 2&4***, 2&5***, 3&4***, 3&5****				
Vitamin - C	**1&2***, 1&3***, 1&4 **, 1&5***, 2&4***, 2&5***, 3&4***, 3&5****				
Vitamin - E	**1&2***, 1&3***, 1&4 ***, 1&5***, 2&3***, 2&4***, 2&5***, 3&4***, 3&5****				

Values are expressed as mean ± SD for eight rats in each group; one way ANOVA' test, *p<0.05- ***p<0.01- statistically significant, ns- not significant. SOD- Super Oxide Dismutase, CAT- Catalase, GPx – Glutathione peroxides, GR- Glutathione Reductase, GSH – Glutathione, Inter -group comparison was done by Post Hoc –Tukey test. The mean difference is significant at the *p<0.05- ***p<0.01.

Table 3 depicts Comparison of Enzymatic & Non enzymatic Antioxidant between control and experimental animals. GSH, Vitamin C and Vitamin E have significantly increased in our target group when compared to all the other groups. The other anti- oxidant enzymes such as SOD, CAT, GPx and GR have significantly increased than other treatment groups and its levels are more or less similar to the control group. This shows that the combination of sorafenib and EGCG is extremely beneficial when compared to other groups.

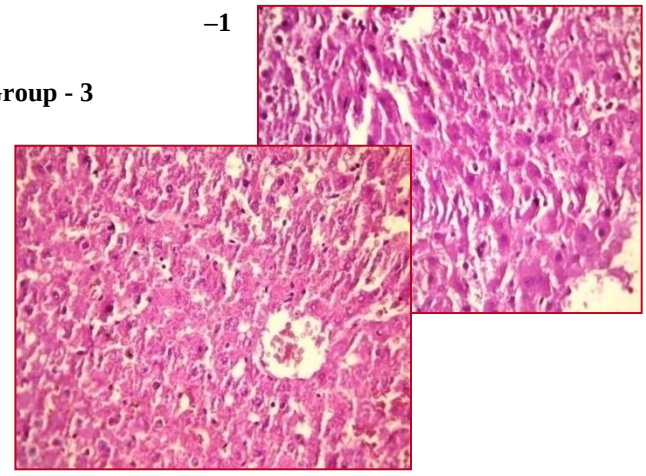
Histopathology:

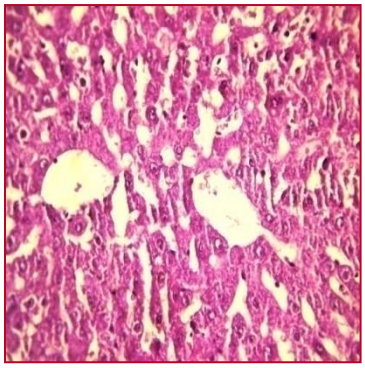


Group –1

Group - 2

Group - 3





Group – 4

Group -5

Group 1: Photomicrograph of hepatic viscera of oversees group shows hepatocytes in a customary framework.

Group 2: Photomicrograph of hepatology of DEN beget hepatocellular carcinoma group exposes the degradation of hepatic cells, ascend in nuclear size, hyperchromatism, hyperplasia and nodular collection of epithelial cells.

Group 3: Photomicrograph of bilious viscera of HCCsubjects tended with EGCG (100 mg/kg) group reveals abatement in the degeneracy of hepatocytes and hyperchromatism.

Group 4: Photomicrograph of hepatic organof HCC subjects of this study nursed with Sorafenib (10 mg/kg) group results in prime decrement in chromatin condensation and almost customary framework.

Group 5: Photomicrograph of hepatize of HCC animals served with Sorafenib (10 mg/kg) + EGCG (100 mg/kg) group shows satisfyingdecline in the degeneration and hyperchromatism

DISCUSSION:

Our results reveal that the chemotherapeutic drug (sorafenib), when administered together with an antioxidant (EGCG) in a specific dosage could definitely enhance the functioning of the drug under treatment rather than administering the chemotherapeutic drug alone. The laboratory animals have responded correspondingly to the synchronized activity of the chemotherapeutic drug combined with the antioxidant. The combined treatment yielded fruitful results in controlling the degeneration and hyperchromatism of hepatic cells in our study. The histopathological results of group 5 showed a satisfying decline in degeneration and hyperchromatism when compared to other groups.

Sorafenib works by inhibiting the activity of several tyrosine kinases involved in tumour angiogenesis and progression, including vascular endothelial growth factor receptor (VEGFR-2/3), and platelet-derived growth factor receptor (PDGF-R) while EGCG acts on growth factors, including PDGF.

As EGCG antioxidants are known to inhibit oxidation, it was believed that these agents would prevent the chemotherapy drugs from functioning properly. These drugs cause high catabolic stress and are said to use tensity procedures to do away with the cancer cells, but the oxidative stress may lessen the potent of the annihilator as a whole. Catabolic stress could slow the approach of replication but it is in the course of cell dupe, that the annihilator kills the carcinogenic cells (16), and obtuse replication indicates reduced effectiveness of chemotherapy. Another study addresses this problem implying that antioxidants could be administered in specific doses to reduce oxidative stress and also make the chemotherapy more effective (17). It has great potential in cancer prevention because of its safety, low cost, bioavailability, and various mechanisms of action. Our Revealed that EGCG reduces oxidative stress by reducing the serum levels of these liver functionenzymes.

We have also reported similar results with respect to alpha-fetoprotein and liver enzymes. Serum alpha-fetoprotein (AFP) has been considered to be a hallmark of the development of HCC. In our study group, 5 subjects had decreased AFP compared to groups 2 and 3 and it is statistically significant and the levels are as similar as group 4. Our treatment group showed improved results with respect to liver enzymes and antioxidants. A study demonstrated that ECGC improveshypercholesterolemia by interfering with the absorptionof dietary cholesterol (18)**.**In another study the degree of sorafenibresistance was correlated with the expression of the cholesterol sensor SCAP and consequent deposition of choles-terol.So combiningsorafenib with EGCG Will be a better treatment option as EGCG Decreases the Cholesterol level and Sorafenib can overcome the drug resistance (19). Our results also had similar findings.

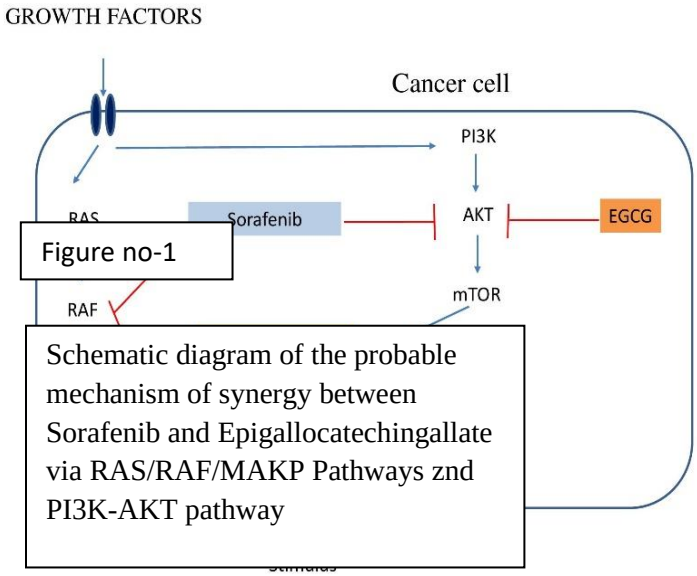


Figure no-1

Schematic diagram of the probable mechanism of synergy between Sorafenib and Epigallocatechingallate via RAS/RAF/MAKP Pathways znd PI3K-AKT pathway

The interaction between the antioxidants and the chemotherapy drugs is furthermore sophisticated in comparison with just advancing and preventing the catabolic stress, nevertheless, there are other tackles by which the annihilator and phytochemicals react in our body. Each antioxidant is unique in its interaction with the chemotherapeutic agent and at times its effect can greatly vary with its dosage. The present scenario is debatable, not in the usage of the antioxidants but in the dosage in which they have to be used, alongside chemotherapy. Many literature studies are also seen in accordance with the usage of the antioxidant along with chemotherapy, which reveals that these antioxidants are found to restore the body's natural antioxidant levels which are often being depleted during the process of chemotherapy.

Being a multikinase inhibitor, it has the capacity to impair STAT3 (Signal transducer and activator of transcription), the Raf/ (MEK) mitogen-activated protein kinase, (ERK) extracellular signal-regulated kinase pathway, or inhibit the BCR/ABL kinase activity (20,21,22, 23). The inhibition of Akt by EGCG and suggest that the inhibition of Akt is beneficial in pancreatic cancer, including as a target for combination treatment (24).Administration of EGCG with Sorafenib Synergistically act Through AKT signal pathway in Hepatocellular Carcinoma. Figure no 1

CONCLUSION:

Based on the current study we conclude that Epigallocatechin-gallate (EGCG) when administered along with Sorafenib shows better Chemopreventive and Hepato Protective effects. We have reported that a combination of sorafenib with EGCG has a comparable effect with standard-dose sorafenib, which is explained based on the anti-oxidant levels and Liver marker enzymes, Histopathological Reports in animal models.

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