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Antidyslipidemic Effect of Naringenin against 5-Fluorouracil Induced Dyslipidemia in *Wistar* Rats

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Abstract

The present study was conducted in forty adult male rats for 5-Fluorouracil (5-FU) chemotherapeutic drugdyslipidemia toxicity and to evaluate ameliorative effects of Naringenin (NG). The rats were randomly divided into four equal groups: Group 1 (Normal saline), Group 3 (NG) given orally, Group 2 5-FU (20 mg/kg body weight-five days-intraperitoneally), Group 4 received a combination of 5-FU and ameliorative agent for 28 days. Results showed that 5-FU increased heart weights, altered serum lipid profiles and caused noticeable ventricular hypertrophy. However, Group 4 displayed improved serum lipid levels, reduced heart weights due to mitigative action of ameliorative agent.

Key words: Triglycerides, lipoprotein, erythrocytes, 5-Fluorocytosine

5-FU is an antimetabolite that was first developed as pyrimidine analogues as a rational synthetic anticancer drug in 1957s. Numerous malignancies, including third stage of colorectal, breast, skin and aerodigestive tract cancers, are often treated with it (Longley *et al.,* 2023). On entering into the cell, it convert into various metabolites like 5-fluorocytosine, incorporate into DNA as well as into RNA, cause apoptotic and cytotoxic cell death (Kanduri*et al.,* 2019). In addition of killing tumour cells, it also affects normal cell death. The toxic effects of 5-FU are myelosuppression, mucositis, diarrhoea, nausea and vomiting and various organ toxicities mostly cardiotoxicity has been observed. The pathophysiological mechanism seems to be anischaemicevent result from an impairment of the rheological properties of blood resulting in an inadequate oxygen supply to the myocardium. The adoption of a sedentary lifestyle marked by a high diet of carbohydrates and fats mixed with low energy utilisation, which has a proven and significant link to an increased risk of liver and cardiac illnesses, is partly to blame for the rise in hyperlipidemia and obesity.5-fluorouracil has also been linked to the development of hyperlipidemia and myocardial damage (Lim *et al.,* 2012).

Naringenin (4′,5,7-trihydroxyflavanone), an aglycone of naringin, is a major flavanone abundant in the fruit-*ExocarpiumCitriGrandis* with various biochemical benefits to reduce oxidative stress by free radicals scavenging property (Zaidun*et al.,* 2018).There are no experimental data on the antihyperlipidemic effects of NG in 5-FU toxicity. In the present study, we evaluate the effect of orally administered naringenin on lipid profile in 5-FU induced toxicity in *Wistar* rats.

Materials and Methods

All chemicals are procured from Qualigens Private limited, India (Mumbai) and SRL Private limited, India. Naringenin (CAS No: 10236-47) was obtained from Sigma (SAC-St Louis, MO, USA).The study was conducted on 48 male *Wistar* rats (n=12), divided into 4 groups,

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weights 200-300 grams with age of 3 months, procured from Jeeva life sciences, ISO 9001:2015 certified company), Hyderabad, India.Group-1: Normal saline orally, Group-2: Rats were injected 5-FU @ 20 mg/kg b.wtfor five days through I/P, Group-3: NG @ 100 mg/ kg b.wt orally for 28 days, Group-4: NG+ 5-FU given same as above protocol.At the end of experimental period on 14th and 28th day, blood was collected and allowed to clot, followed by centrifuge and supernantant was collected and stored at -20 ^{0}C for further analysis. There after we collected heart weights and observed for gross pathology on 14th and 28th day of experiment.Serum lipid profile (TG, TC LDL- cholesterol and HDL-cholesterol) were assayed spectrophotometrically with the enzymatic colorimetric method described by authors (Burstein *et al.,* 1989).

Results and Discussion

In the present study, there is a significant (P<0.05) increase in the absolute weights of heart in groups 2 and 4 rats were recorded on 14th and 28th day of experiment indicates hypertrophy of heart which might be due to oxidative stress (Shushma *et al.*, 2021).Significantly, lowered mean values of absolute heart weights were recorded in the group 4 rats when compared to group 2 rats on day 14thand 28thday which might be due to antioxidant effect of NG (Turgut *et al.,* 2016) (Table.I).

In the present experimental study, the heart of group 2 rats revealed gross lesions *viz*., mild congestion, hypertrophy of ventricles of heart on 14th and 28th of experiment. Heart is the main organ for 5-FU induced toxicity might have triggered the changes by oxidative stress, infiltration of inflammatory cells, interstitial edema and fibrosis which leads to increase in thickness of ventricular wall (Shushma *et al.*, 2021). In group 4 rats, heart showed ameliorative effect of NG on heart which include restoration of size of left ventricles of heart due to presence of antioxidant property (Fig.1) (Moghaddam *et al.,* 2020).

It was discovered that stress in the form of fasting increased lipid peroxidation and changed the lipid profile in rabbits through previous literature. Lipid, lipoprotein metabolism and its physiology is a dynamic, interconnected process. Vascular disorders develop as a result of anomalies in lipoproteins that affect the

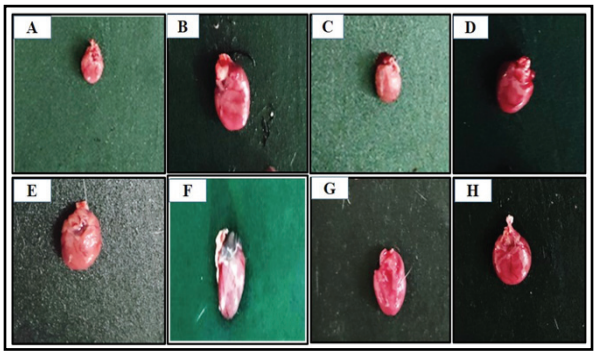

Fig 1: Gross images of heart caused by 5-FU. A, C-Normal apperance of heart on 14thday and E,F on 28th day in group-1 and 3 rats. B,C Congestion with hypertrophy of heart on 14th and 28th day respectively. D,H Mild congestion on 14th and 28th day of experiment.

levels of serum and cellular lipids.5-FU causeshypercholesteremia and triglyceridaemia, a risk factor for development of CVD, mainly related to myocardial ischemia, atherosclerosis and heart attack due to its structure and stability (Lata *et al.,* 2002). In the present study a significant (P<0.05) rise in TC, TG and LDL along with significant (P<0.05) decrease in HDL were observed in rats treated with 5-FU group compared to normal groups due to enhanced lipid synthesis by increasing cardiac adenosine monophosphate (Paritha and Devi, 1997) (Table. I). It might be due to unregulated accumulation of cholesterol by delaying lipolysis of cholesterol in various organs along with decrease in activity of lipoprotein lipase (LPL) activity resulting in decrease uptake of cholesterol along with degradation to bile acids and TG from circulation in 5-FU toxicity (EI-Azim, 2015). There was also a inhibitory activity of cytochrome P450 activity, which in turn depress cholesterol 7-hydroxylase activity, the key enzyme in theconversion of cholesterol to bile acids (Yahya *et al.,* 1919). Another mechanism of dyslipidemia by 5-FU is may be due to due to the inhibition of peroxisome proliferator-activated receptor (PPAR), which has a central role in controlling lipid homeostasis, thus block the adipogenic action and results in metabolic abnormality and high lipid content. But NG activates these receptor and maintain lipid heomostasis in previous experimental cardioprotective study (Lone *et al.,* 2022).In 5-FU, HDL prevents LDL from being absorbed into the arterial wall, allowing cholesterol to transport from the peripheral tissues to the liver, where it is catabolized and eliminated

Table. I: Effect of NG on heart weights (g), lipid profile test-TC, TG, LDL-c, HDL-c (mg/dL) Values are Mean ± SE (n=6); One-way ANOVA. Means with different superscripts in a column differ significantly at P<0.05 (*).

Groups	Group 1		Group 2		Group 3		Group 4	
days	14th	28th	14th	28th	14th	28th	14th	28th
Heart weights	1.26±0.05c	1.89±0.03c	1.89±0.05a	2.98±0.06a	1.31±0.04c	1.68±0.09c	1.63±0.03b	2.37±0.03b
Total cholesterol	90.18±1c	94.6±1.2c	226.50±1 a	241.6±6.8a	92.6±.07c	94.2±0.3c	135.11±0.8b	143.2±0.6b
Trigylcerides	133.2±0.6c	136.2±0.5c	195.46±1.3a	213.8±0.8a	133.5±0.6c	137.8±0.6c	151.6±0.7b	176.8±0.1b
Low-density lipoprotein	22.7±0.2c	25.1±.40c	71.21±.65a	81.7±0.6a	22.3±0.7c	24..32±0.6c	56.6±0.7b	64.5±0.4b
High-density lipoprotein	37.7±0.5c	38.21±0.3c	22.4±0.5a	26.4±1a	30.6±0.5c	37.8±1.2c	30.2±0.9b	34.6±0.6b

from the body (Elghareeb *et al.,*2020). Results of present study indicating that, when NG was given after 5-FU treatment, it significantly (P<0.05) ameliorated lipid lowering effect by its hypolipidemic role and elevating in NG treated group which are similar findings observed in Cisplatin, DOX induced cardiotoxicity and high cholesterol fed rabbits which might be due to antioxidant properties, antiatherogenic effect by decreased activity of HMG-CoA reductase which might be same reason for ameliorating effect of 5-FU induced cardiotoxicity with previous literature (Elghareeb *et al.,* 2020) (Table. I).

Summary

Naringenin in combination with 5-FU treatment primarily mitigate some complications such as dyslipidemia through anti-oxidant and hypolipedemic property. More research is needed to determine the benefits of NG in reducing oxidative stress and its pathogenicity at different intervals.

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