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Preventive Activity Of Ginger Against Acetaminophen-Induced Liver Cirrhosis In Mice Model

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ABSTRACT
Drug induced liver injury (DILI) is one of the causes of liver disease. Acetaminophen or APAP induced liver injury is the most common DILI where half of the people develop acute liver failure (ALF) accidentally in the event where APAP dose where just a little bit higher than recommended dose. Although there are so many treatment options for DILI, sudden occurrence of DILI or ALF is always risky. Therefore, safe and natural protection could solve the problem and save hundreds of lives. In this study, the effectiveness of ginger in case of sudden ALF or cirrhosis is tested where the ginger solution was inoculated at one-day intervals up to 21 days and thus it helped significantly to reduce the liver enzyme in mice compared to positive control and keep the liver enzyme quite identical considering negative control groups of mice. This study concluded that ginger could be considered as a possible protective agent against sudden occurrence of ALF.

Keywords:*Ginger, Acetaminophen, DILI, mice*

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Liver disease is a most common problem around the world where chronic liver disease and cirrhosis causes 2 million deaths worldwide (Mokdad, Lopez et al. 2014, Tapper and Parikh 2018). There are several causes of liver diseases where drug induced liver disease/injury (DILI) is one of them. DILI is usually known as adverse or unexpected harm that happens in liver caused by a drug during common use due to hepatotoxicity. This type of hepatotoxicity usually has two types one is intrinsic and another is idiosyncratic injury. The main example of intrinsic liver DILI is Acetaminophen or APAP or paracetamol hepatotoxicity which accounts half of the total acute liver failure (ALF) cases in USA as well as UK (Scotland) (Reuben, Tillman et al. 2016, Donnelly, Davidson et al. 2017). In this case, a good number of people develop ALF or Hepatotoxicity accidentally where the dose of APAA was slightly higher than the recommended dose. Other drugs also has hepatotoxicity activity although the severity of hepatotoxicity varies widely between each other . Also access use of drug is also a public health concern all over the world (Donnet, Lantéri-Minet et al. 2009, de Miguel-Díez, Carrasco-Garrido et al. 2011, Busfield 2015, Ali, Abbasi et al. 2020) which can cause serious health effect in people including DILI (Katarey and Verma 2016). The risk of DILI in every drug is estimated to be 1/10 or 10000 persons exposed where a study showed that it could 1/100 patients admitted in an internal medicine department (Meier, Cavallaro et al. 2005). There are several types of treatment available for the treatment of DILI or liver disease/injury (Tajiri and Shimizu 2008, Giordano, Rivas et al. 2014). There are several researchers tried various herbal for the treatment of the liver disease (Dhiman and Chawla 2005, Ghosh, Ghosh et al. 2011, Wei, Qiu et al. 2022). According to Singh D et al. some of the herbal drug has preventive capability against liver disease and we all know that preventive measurement is always better than a curative action (Singh, Cho et al. 2015). Ginger root is one the herbal product which shows protective activity against liver disease specially DILI as ginger root is protective against damage due to anti-oxidant as well as anti-lipid proactive activity (Halvorsen, Holte et al. 2002, Kim and Oppel 2002). Some researcher tested ginger root protective activity in mice as well as RAT (Lamfon 2011, AbdulazizBardi, Halabi et al. 2013) which were metalaxyl and ERZO induced liver hepatotoxicity or cirrhosis respectively. In this study, the main objective was to evaluate the protective role of ginger root against APAP induced liver toxicity or cirrhosis in Swiss Albino mice.

I. MATERIALS AND METHODS:

Animals: Twenty-four male Swiss albino mice (Musmusculus) were selected for this experiment. All mice were 8 to 10 weeks old, weighed approximately (40±5) gms, and were placed into six groups. Prior to the experiment's start by one week, the experiment's animals were housed in plastic cages at a constant room temperature (23±20 C) We maintained a standard rodent diet pellet feed which contains crude protein 20.93%, Crude fat 5.35%, Crude fiber 6.22%, Total Ash 7.20 % and 4-5% vitamin & minerals (Animal nutrition, DLS, Dhaka).

Preparation of ginger aqueous Extract: Ginger (Zingiberofficinale Roscoe) rhizome was purchased from the local market at Dinajpur, four-kilogram fresh ginger rhizome was cleaned, washed under running tap water, cut into small pieces, air dried and powdered.

Figure-1: 1&2) 1.2g Ginger power and the record sheet of weight machine during taking weight, 3&4) Dissolve it in Ethanol and filtration after mixing it and resting it 24 hours.

Ginger Extract preparation: Ginger solution was prepared as per the modified method of Fuhrman (Frondoza et al.) where ginger powder (1.2gm) was suspended in 3 ml of ethanol in a glass tube with stoppered and was mixed up 10 minutes vigorously for at least 10 minutes. The mixer was left at room temperature for 24 hours (Frondoza, Sohrabi et al. 2004) and the next day it mixed again for another 10 minutes and filtered. The next step was to add sterile saline to the solution to adjust the 100 ml volume, and the final concentration of ginger was 12 mg/ml.

Experiment design: Twenty-four albino mice were divided into six equal groups, each containing four animals. Group-1 mice given 10 mg/kg body weight ginger solution in the intraperitoneal region every 48 hours interval up to 21 days. The mice in groups 2 through 4 received 20 mg/kg, 40 mg/kg, and 80 mg/kg body weight, respectively, following the same sequence. Group-5 mice received normal saline (1 ml/kg body weight) at the same intervals and in the same patterns.. To be used as a control, group-6 mice received no medication at all.

Following Mossanen et al. method to make cirrhosis, all the mice except group 6 were kept fasted for 12 hours before injection of APAP at 12 mg/ml (300 mg/kg body weight) via intraperitonealrejoin on the 21st

day. After that all the mice were rendered unconscious (Anesthesia agent was ketamine HCl) to collect the blood (serum) for biochemical test (alanine transaminase or ALT and aspartate aminotransferase or AST).

Biochemical assays: Serum collection from blood through centrifugation at 3000 rpm for 5 minutes. The serum specimen then sent to Pathology unit, Medical Center, Jahangirnagar University to test ALT (alanine aminotransferase) and AST (aspartate aminotransferase) which were measured using fully automated Siemens dimension REXLTM with LM integrated chemistry system.

Statistical analysis: The result was expressed as mean ± SD of different groups. The intergroup one-way ANOVA was performed between Ginger experimental groups (group 1 to group 4) and positive control or saline group (Group 5). Similar experiments were done between ginger experimental groups and negative control (group 6) as well.

II. RESULT AND DISCUSSION

There were several in-vivo researches on the preventive effects of ginger in cases of liver damage or cirrhosis, but very few or none of the studies examined the protective effects of ginger in cases of Acetaminophen or DILI-induced liver cirrhosis (Lamfon 2011, AbdulazizBardi, Halabi et al. 2013, Badawi 2019). This study is also unique is case of ginger inoculation schedule or dosing in mice as the objective of this study to estimate the protective role of ginger considering previously presence of ginger chemicals in body whether other studies investigate inoculate the ginger along with cirrhosis creating agents (Lamfon 2011, AbdulazizBardi, Halabi et al. 2013, Badawi 2019).

The liver enzymes found significantly protective against APAP compared to saline group where saline group mice had no protection against APAP induced liver cirrhosis (Table- 1). Furthermore, there were no appreciable differences in the levels of liver enzymes between protective groups and the non-cirrhosis group or group 6 (Table-2);this suggests that ginger inoculation can be protective against any type of incidence or sudden occurrence that could cause cirrhosis or liver failure in the body as most DILI occurs suddenly where APAP dose is slightly higher than the recommended dose.. When compared to the non-cirrhosis group, the group 4 or 80 mg/kg ginger dose group mice displayed results that were nearly identical (Table 2).

The findings, which were remarkably comparable to those of other research, demonstrated that AST and ALT levels can be lowered by inoculating animals with a continuous dose of ginger at a particular level. (Lamfon 2011, AbdulazizBardi, Halabi et al. 2013, Badawi 2019). However, the outcome of this research demonstrated that taking ginger regularly can also aid to protect the body against the unanticipated or unexpected incidence of DILI. In contrast, several issues need to be addressed that these data may vary in the case of oral dose of ginger but according to the ginger study conducted by Badawi et al. the protective role ginger in oral dose is also statically significant (Badawi 2019). In addition, the herbal medicine or dietary supplement can cause some renal dysfunction in certain cases (IsnardBagnis, Deray et al. 2004) but according to Mehrdad et al. the ginger found safe in case of renal function (Mehrdad, Messripour et al. 2007). Despite having some limitations like lack of histopathological analysis or toxicity testing or ginger chemical concentration of mice blood of different groups, this study primarily proved that the continuous consumption or inoculation of ginger can be beneficial where it could save many lives who are at the risk of sudden liver failure or DILI.

	ALT					AST				
	Mean	Std Deviation	Lower limit	Upper limit	Significance	Mean	Std Deviation	Lower limit	Upper limit	Significance
Group 1	76.00	20.41	43.51	108.48		127.00	32.48	75.30	178.69	
Group 2	114.25	47.98	37.90	190.59		177.50	53.90	91.72	263.27	
Group 3	82.25	26.53	40.02	124.47	0.01	145.75	36.00	88.46	203.03	0.01
Group 4	58.00	16.99	30.96	85.03		104.50	19.22	73.90	135.09	
Group 5 - Saline	242.50	149.82	4.09	480.91		367.25	208.70	35.16	699.33	

Table 1: One way ANOVA between ginger experimental groups and positive control or saline group

	ALT	AST

	Mean	Std Deviation	Lower limit	Upper limit	Significance	Mean	Std Deviation	Lower limit	Upper limit	Significance
Group 1	76.00	20.41	43.51	108.48		127.00	32.48	75.30	178.69	
Group 2	114.25	47.98	37.90	190.59		177.50	53.90	91.72	263.27	
Group 3	82.25	26.53	40.02	124.47	0.07	145.75	36.00	88.46	203.03	0.05
Group 4	58.00	16.99	30.96	85.03		104.50	19.22	73.90	135.09	
Group 6-control	57.00	18.34	27.80	86.19		108.00	20.54	75.31	140.68	

Table 2: One way ANOVA between ginger experimental groups and negative control groups

III. AUTHORSHIP CONTRIBUTION STAEMENT

The authors confirm contribution to the paper as follows: study design and conception: Chowdhury Mohammad Ghalib; In-vivo experiment and data collection: Md. Faridul Islam, Md. Mohebul Arifin and Md.MahmudulHasan; Analysis and interpretation of results: Chowdhury Mohammad Ghalib, Md.MahmudulHasan, Mst.MisratMasumaParvez, SumonSarkar, Rakibul Islam, and Md.NiamulShahadat; Manuscript writing: Chowdhury Mohammad Ghalib and Md. Faridul Islam. All authors reviewed the result and approved the final version of the manuscript.

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