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Ameliorating Effect of Aqueous Ginger Extract And Exercise On Insulin Resistance in Fructose Induced Type 2 Diabetic Rats Through Upregulation of Serum Sirtuin-1

[1,2]Seher Naeem, [2]Muniza Saeed, [1]Jawaria Ilyas, [3]Asma Ashraf, [4]Madiha Akram, [5]Ruqaiyya Nazir

ABSTRACT

Introduction: The mounting prevalence of type 2 diabetes mellitus (T2DM) in developing countries calls for an immediate need to find novel treatment strategies that not only target its underlying pathological process but are also safe and cost effective.

Aims&Objectives: To determine the effect of ginger supplementation, exercise and their combination on insulin resistance (IR) and levels of serum sirtuin 1 (SIRT1) in fructose induced type 2 diabetic rat model.

Material&Methods: This randomized controlled trial was conducted at animal laboratory of Postgraduate Medical Institute Lahore, Pakistan, from January 2021 to June 2021, in which thirty rats were randomly allocated to five groups with six rats in each.Rats belonging to group1 (Normal Control) were given normal rat chow diet. Diabetes was induced in groups 2, 3 and 4 by administering 25% fructose diet, following which, group 2 was reserved as diabetic/positive control (PC) and continued to receive 25 %fructose diet only. Animals of group 3 received aqueous ginger extract (GE), group 4 underwent swimming exercise (EX) and group 5 received their combination (GE+EX) for 8 weeks. Aqueous ginger extract was prepared in the Pharmacology lab at PGMI where 50 gm of fresh ginger was blended with 75ml of 0.9% NaCl and filtered thrice. The obtained filtrate was centrifuged at a speed of 2000 rpm for ten minutes. The clear supernatant fraction was made to reach 100 ml mark using NaCl resulting in a concentration of 500 mg/ml which was used for oral administration. Data was entered and analyzed using SPSS version 26, a p-value of ≤ 0.05 was considered significant.

Results: The results of the current study showed development of T2DM with 25% fructose supplementation in PC group, resulting in significantly high level of IR along with a significant reduction in levels of serum SIRT1. Aqueousginger extract group as well as the exercise group, both individually showed a significant reduction in IR as compared to the diabetic group and this was associated with significantly increased level of serum SIRT1 ($p<0.05$). However, most pronounced effect was seen in the combination group having lowest level of IR associated with a statistically significant increase in SIRT1 levels ($p<0.05$).

Conclusion: Aqueous ginger extract supplementation and exercise training, alone and in combination have the potential to significantly ameliorate IR in T2DM through its positive influence on serum SIRT1.However, the combination group has the most pronounced effect reflecting a potential synergistic effect of both interventions. Ginger supplementation and exercise may be introduced as safer, cost effective and natural adjunct to anti diabetic drugs hence lowering their potentially harmful side effects.

Keywords: Type 2 Diabetes Mellitus, Insulin Resistance (IR), Ginger, Exercise, SIRT1.

INTRODUCTION

Diabetes Mellitus (DM) is a multi-faceted metabolic and hormonal disease typically identified by abnormal glucose level in blood[1].Globally, about 1 in 11 adults have been estimated to have DM; 90% being Type 2 diabetic. As many as 537 million people arediagnosed with diabetes globally with a total prevalence of 11.5% mainly in low to middle income countries like Pakistan[2].The conventional anti diabetic drug regimen that is prescribed health professionals may be categorized as insulin secretagogues (e.g., sulphonyl urea sand meglitinides), insulin sensitisers (e.g., biguanides and thiazolidinediones), alpha-glucosidase inhibitors and incretin-based therapies (e.g., glucagon-like peptide-1 receptor agonists and dipeptyl peptidase-4 inhibitors). However, these synthetic drugs carry several constraints due to their serious side effects such as hypoglycemic coma, risk of anemia, lactic acidosis, hepatic and renal dysfunction[3]. This has

1. [1]Department of Physiology, CMH Lahore Medical College & Institute of Dentistry Lahore.
2. [2]Department of Physiology, Postgraduate Medical Institute Lahore.
3. [3]Department of Physiology, Continental Medical College, Lahore.
4. [4]Department of Physiology, Pak Red Crescent Medical College, Dina Nath, Pakistan.
5. [5]Department of Physiology, Islamic International Medical College, Rawalpindi.

Correspondance:
Dr. Seher Naeem, *FCPS-II Trainee/Senior Demonstrator, Department of Physiology, CMH Lahore Medical College & Institute of Dentistry Lahore.*
Email: sahar_awais@cmhlahore.edu.pk

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lead to a considerable interest in alternative treatments especially conventional herbal therapy[4]. In this regard, Ginger (*Zingiber officinale*) is a commonly consumed medicinal herb used to treat a range of disorders. Research has demonstrated beneficial effects of ginger extract on serum glucose and IR[5] which may be attributed to its polyphenol rich bioactive ingredients that include gingerols, shogaols,quercetin and flavonoids[6].

Sirtuins belong to the silent information regulator 2 (SIRT) family, which consist of NAD+ dependent deacetylases and ADP-ribosyltransferases. SIRT1, is the most extensively explored and well-characterized member of this family. It is located mainly in the cell nucleus and is extensively found in various body tissues; the liver, leukocytes, skeletal muscle, pancreas, adipose tissues and brain. SIRT1 aptly up-regulates glucose metabolism via its deacetylase activity.[7]The function of SIRT1 is to modulate and control glucose metabolism via its direct and indirect effects on insulin signaling pathways hence reducing IR in T2DM[8]. Low SIRT1 activity is linked to the pathogenesis of T2DM and IR. Therefore, interventions that raise SIRT1 activity may prove favorable in amelioration and control of IR and T2DM. Dietary polyphenols, (such as those present in ginger) and physical exercise, by stimulation of SIRT1 activity may therefore lead to reduced insulin resistance (IR) in T2DM.[8] There is limited data on effect of ginger supplementation and exercise training on level of SIRT1 and insulin resistance.

In the present study we proposed to bridge this knowledge gap and hence elucidate the underlying mechanism by which ginger supplementation and exercise bring about their beneficial effects on IR by analyzing their impact on levels of serum SIRT1. The aim was also to determine their potential synergism if it exists. This would give credence to their use as safe and natural adjunct to anti diabetic drugs and hence reduce their potentially harmful side effects leading to an improved quality of life for T2DM patients.

MATERIAL AND METHODS

This randomized controlled trial was carried out at Postgraduate Medical Institute (PGMI), Lahore from January 2021 to June 2021, after the approval of synopsis from Ethical Committee of PGMI (Ref. No. 00-19-S-2019). Animals were treated in accordance with the ethical principles and guidelinesas laid down by World Medical Association (WMA) declaration of Helsinki. The sample size was calculated using HOMA-IR values in the following formula[9]whereby n was calculated to be 6.

$$n = \frac{\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_o - \mu a)^2}$$

Animals

Sprague-Dawley rats, weighing between 150-180 grams, were kept in the Animal House at PGMI, Lahore. They were acclimatized for one week with free supply of rat chow and water. Room temperature was maintained at 26±2°C with natural 12 hour day and night cycle.

Induction of diabetes

Special diet consisting of 25% fructose (purchased from Sigma-Aldrich Company, USA) combined with 75% normal rat chow (weight/weight) was prepared[10] in the animal house of PGMI.A total of 2 kg diet was freshly prepared after every 4 days and allowed to dry in form of pellets.

Average baseline fasting blood glucose (FBG) value of all rats was found to be 72mg/dl (using a portable glucometer, manufactured by Code-free, Korea)at day 0. The fructose based pellets were fed to rats *ad libitum* for a duration of 4 weeks and FBG levels were monitored weekly. Rats having FBG concentration above 126 mg/dl at the end of 4 weeks were labeled as diabetic.[11]

Aqueous Ginger Extract preparation

Aqueous ginger extract was prepared in Pharmacology Laboratory at PGMI, Lahore, according to the guidelines established by literature.[12] Fresh ginger roots were bought from a local commercial source and peeled. Fifty grams of ginger (weighed on an electronic scale) was cut into small pieces. A homogenized mixture was obtained by blending it with 75ml of 0.9% NaCl along with some crushed ice.This mixture was sieved three times using muslin cloth and the resultant filtrate was centrifuged at a speed of 2000 rpm for duration of ten minutes. The clear supernatant portion was collected and made to reach 100 ml mark using NaCl (Fig-1) resulting in final concentration of 500 mg/ml of aqueous ginger extract. Rats were given 500 mg ginger extract/kg body weight per oral (using syringe–dosing technique) once daily, for a total span of 8 weeks. The chosen dosage of 500mg ginger extract/kg body weight has previously been found to be effective and non-toxic in rats.[10,13]Rats were weighed on a weekly basis and the dose was adjusted accordingly.

Swimming Exercise Protocol

Rats were made to swim in a water tank[14] (80 cm length/100 cm height/40 cm water depth) with temperature maintained at 35 ± 1°C. In order to habituate, rats were initially trained to swim for 10 minutes, with daily increments of 10 minutes, until a swimming period of half an hour was attained. This duration of swimming was maintained for next 8 weeks.[15] At the end of each exercise session, animals were dried and kept in a warm environment (Fig-2).

Sample Size:

Thirty rats were randomly divided into five groups by lottery method, each containing six rats.

Inclusion Criteria:

Male Sprague-Dawley rats, 6 weeks of age, weighing 180-200g.

Exclusion Criteria:

Rats apparently inactive or not well (having symptomatic illness/anomaly) at the time of selection. Rats that did not develop diabetes after four weeks of fructose administration.

Animal Grouping And Procedure:

Rats belonging to group1 (Normal Control) were given normal rat chow diet. 25% fructose diet was given to group 2, 3, 4 and 5 for four weeks to induce diabetes as mentioned earlier. Following successful induction of diabetes, group 2 was maintained as diabetic (Positive) Control and continued to receive 25 %fructose diet. Animals of group 3 received aqueous ginger extract (GE), group 4 underwent swimming exercise (EX) and group 5 received their combination (GE+EX) for 8 weeks.

Measurement Of Serum Parameters:

Cardiac puncture was performed on overnight fasted animals to collect blood samples. FBG measurement was carried using commercially available kit based on the glucose oxidase method. Fasting serum insulin (FSI) and serum SIRT1 was measured by ELISA kit (Bioassay Technology Laboratory, China - catalogue # E0707Ra and E1214Ra respectively). IR value of each rat was calculated using the HOMA-IR index formula. Insulin resistance (IR) of each rat was calculated using the HOMA-IR index formula [fasting serum glucose (mg/dL) × fasting serum insulin (μU/mL)/405]..[16]

Statistical Analysis:

Data wasexpressed as median(IQR) applying SPSS 26. Kruskal-Wallis and Mann Whitney-U test was employed to assess the difference among study groups and pair wise comparisons respectively. To determine the correlation between HOMA-IR and SIRT1, Spearman correlation test was used. P-value ≤0.05 was deemed as statistically significant.

RESULTS

A significant difference ($p = 0.003$) among all study groups was seen with regard to HOMA-IR whereby the diabetic rats displayed highest value of IR. All three intervention groups showed a significant reduction in IR ($p = 0.003$) while the combination group showed the most pronounced effect (Table-1). Pair wise comparison also showed significant reduction in IR ($p=0.004$) by all three intervention groups when compared to diabetic (PC) group (Table-2, Fig-3). Serum SIRT1 also showed a highly significant difference ($p < 0.001$) among all study groups. Least level of SIRT1 was seen in the diabetic group whereas all three intervention groups showed improved level with the combination group showing the highest increase (Table-1). Pair wise comparison also revealed highest increase of serum SIRT1 in the combination group as compared to diabetic group (Table-2, Fig-4).Spearman correlation test showed a highly significant negative correlation between HOMA-IR and levels of serum SIRT1 (rho = -0.665, $p < 0.001$***). Straight line fit plot exhibits the trend followed by HOMA-IR with serum SIRT1 (Fig-5).

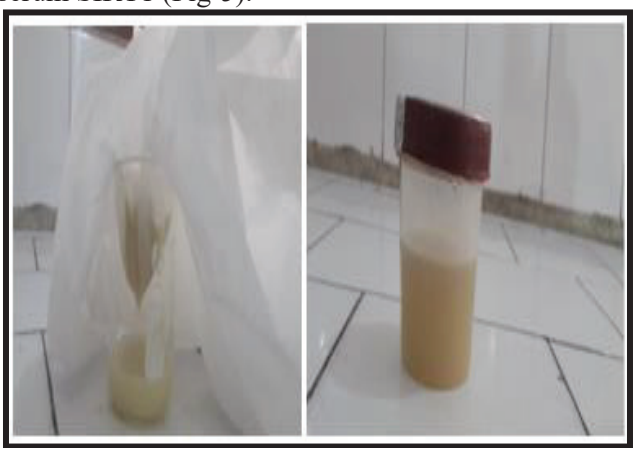

Fig-1: Aqueous Ginger Extract Preparation

Fig-2: Swimming Exercise

Groups	HOMA-IR			Serum SIRT1		
	Median (Inter-quartile range)	Mean Ranks	P-value	Median (Inter-quartile range)	Mean Ranks	P-value
NC n=6	0.43 (0.23-0.63)	11.08	0.003 **	2.85 (2.40-3.35)	27.00	<0.001 ***
PC n=6	1.64 (1.60-1.70)	27.50		0.35 (0.30-0.40)	4.00	
GE n=6	0.51 (0.38-0.80)	16.50		0.50 (0.40-0.63)	10.50	
EX n=6	0.35 (0.28-0.70)	12.33		0.60 (0.56-0.70)	14.25	
GE+EX n=6	0.34 (0.31-0.37)	10.08		1.75 (1.15-2.23)	21.75	

Table-1:HOMA-IR And SIRT1 Levels {Median (IQR)} And Mean Ranks Of Rats In All Study Groups At End Of 12 Weeks Study Period By Kruskal Wallis Test

*p ≤ 0.05 significant,
**p ≤ 0.01 highly significant,
***p ≤ 0.001 very highly significant
n = no. of rats in a group
NC= Normal Control, PC = Positive Control (Diabetic),
GE = Ginger Extract,
EX = Exercise, GE+EX = Ginger Extract & Exercise

Groups		HOMA-IR		Serum SIRT1	
		Mean Ranks	P-value	Mean Ranks	P-value
NC n=6	PC	3.5-9.5	0.004**	9.50-3.50	0.003**
	GE	5.5-7.5	0.337	9.50-3.50	0.004**
	EX	6.0-7.0	0.630	9.50-3.50	0.004**
	GE+EX	6.58-6.42	0.936	9.0-4.0	0.016*
PC n=6	GE	9.50=3.50	0.004**	4.0-9.0	0 .012*
	EX	9.50 -3.50	0.004**	3.50-9.50	0 .003**
	GE+EX	9.50-3.50	0.004**	3.50-9.50	0.003**
GE n=6	EX	7.50-5.50	0.336	4.92-8.08	0.115
	GE+EX	8.50-4.50	0.054	3.58-9.42	0.005**
EX n=6	GE+EX	6.83-6.17	0.748	3.67-9.33	0.006**

Table-2:Comparison Of HOMA-IR And Serum SIRT1 Among The Groups By Mann Whitney U Test At The End Of 12 Weeks Study Period.

Significant *P< 0.05, vs. Diabetic group, Highly Significant **P < 0.01, vs. Diabetic group
NC = Negative Control, PC = Positive Control, GE = Ginger Extract Group
EX = Exercise Group, GE+EX = Ginger Extract + Exercise Group

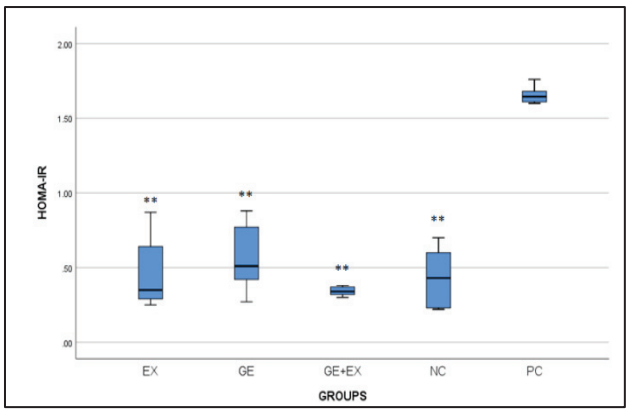

Fig-3: HOMA-IR Levels {Median (IQR)} Of Rats Of All Study Groups At The End Of 12 Weeks Study Period.

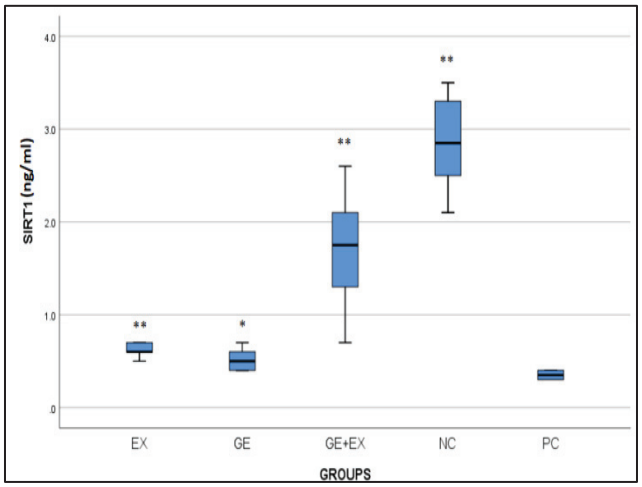

Fig-4: Serum SIRT1 Levels {Median (IQR)} of rats of all study groups at the end of 12 weeks study period.

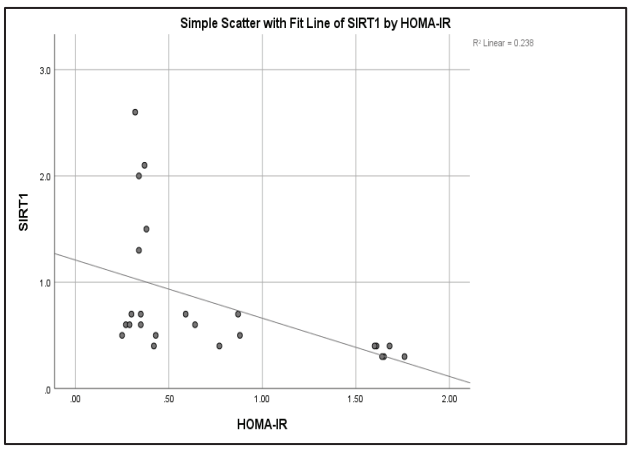

Fig-5: Correlation between HOMA-IR and serum SIRT1 in T2DM rats at the end of 12 weeks of study.

DISCUSSION

The current study showed that the diabetic (PC) group developed significantly high levels of IR linked with significantly lower levels of serum SIRT1 as compared to all other groups. On the

contrary, all three treatment groups exhibited a significant decrease in IR as compared to PC group and this was linked with significant increase in levels of serum SIRT1.However, most profound reduction in IR was displayed by the combination group which was also associated by a statistically significant increase in serum SIRT1.

The diabetic group developed a significant raise in IR ($p = 0.004$) as compared to NC group. These findings are in accordance with previous literature which state that long term consumption of increased amount of fructose has detrimental effects on body's ability to respond to normal circulating levels of insulin and also on glucose homeostasis.[17,18]The mechanisms for development of IR in response to high fructose feeding in experimental animals include increased lipolysis in adipose tissue and inhibition of FFA esterification leading to increased circulating FFA concentrations hence aggravating IR. It also causes direct impairment of insulin signaling pathways in the liver by reduced expression of insulin receptor substrate 2 (IRS2) or an increase in protein-tyrosine phosphatase 1B (PTP1B) activity, the negative modulator of insulin activity.[19]Serum SIRT1 levels of the diabetic group were found to be significantly reduced ($p = 0.003$) as compared tonormal group. This finding is supported by another study that demonstrated a decrease in expression of SIRT1 in muscle biopsies obtained from subjects with T2DM. This outcome was likely due to post-transcriptional modifications as no differences in SIRT1 mRNA levels were observed between the healthy controls and T2DM patients.[20]Sirtuins are particularly sensitive to environmental (diet/lifestyle) or metabolic (obesity/diabetes) insults at mRNA and protein levels in insulin-responsive organs. These post transcriptional insults lead to synthesis of dysfunctional SIRT1 protein consequently resulting in blunted SIRT1 activity in these tissues[21].

TheGE group demonstrated a significant improvement in IR as compared to diabetic group ($p = 0.004$) with median value close to that of normal. These results are in line with a former study who discovered that treatment of diabetic rats with 200 mg/kg of ginger extract for 8 weeks caused a significant decline in blood glucose[22]. They further showed that the effect of ginger treatment was parallel to that of glibenclamide (a conventional hypoglycemic medicine). The underlying mechanism for these positive effects are reported to be the result of its primary bioactive ingredients, mainly, the polyphenols[5,23]. Serum SIRT1 levels of GE group in the current study were found to be significantly raised as compared to diabetic (PC) group ($p = 0.012$). These results are reinforced by similar study that suggests that dietary polyphenols can significantly increase SIRT1 activity. To this effect, it was seen that quercetin (a potent polyphenol) reduced oxidative damage by increasing SIRT1 expression in streptozotocin-induced diabetic rats[24]. The underlying mechanism of increased SIRT1 expression is the activation (via phosphorylation) of adenosine monophosphate activated protein kinase (AMPK) enzyme by polyphenolic components present in ginger resulting in downstream activation of SIRT1; activation of AMPK leads to a raised nicotinamide adenine dinucleotide (NAD+) level and NAD+/NADH ratio. This raised NAD+/NADH ratio serves as an improved substrate for SIRT1 synthesis and activity.[25]

Swimming exercise also successfully lowered HOMA IR in T2DM rats as there was a significant difference when compared to diabetic group ($p = 0.004$). These results harmonize with Rahimi et al., 2021in their meta analyses which concluded that exercise significantly lowered fasting glucose, insulin and IR level as compared to diabetic control patients.[26] Likewise, a significant increase in serum SIRT1 level of swimming exercise group ($p = 0.003$) is supported by a study whereby swimming exercise training significantly increased SIRT1 gene and protein expression in high fructose diet induced diabetic rat group as opposed to diabetic control group. An improvement in pancreatic β-cells and oxidative stress injuries was also observed;SIRT1 preserves insulin secretion by deacetylating forkhead box 1 protein (FoxO1) and minimizes the death of β-cells. Moreover, SIRT1 enhances the expression of Mn-SOD (a mitochondria-specific isoform of superoxide dismutase) and in this way reduces mitochondrial oxidative injuries.[27]

The combination group (GE+EX) demonstrated a highly significant reduction ($p = 0.004$***) in HOMA-IR.Lambert et al., 2018 corroborate the findings of current study and indicate that combination of polyphenol supplementation with exercise training produces an additive beneficial effect on reducing IR.[28] Similarly, serumSIRT1 level of**c**ombination group, was found to be significantly raised not just in comparison to diabetic group ($p = 0.003$) but also in comparison to ginger ($p = 0.005$) and exercise ($p = 0.006$) groups, suggesting a substantial synergistic effect. Ricordi et al., 2021 have outlined the potential complementary role of polyphenol supplementation and exercise training stating that supplementation of SIRT1 activating substances could be of valuable help when performing regular exercise[29].The

AMPK signaling pathway is common to both exercise and polyphenols, which explains their additive effect and leads to the presumption that some polyphenols act like "exercise-mimetics"[30,31].

The current study also examined the correlation between serum SIRT1 and HOMA-IR. A highly significant inverse relationship between the two variables ($P<0.001$) was found. These results conform to that of Mariani et al., 2018 who also found a significant inverse correlation between plasma SIRT1 and IR, with the highest levels measured in participants with lowest HOMA IR and extremely reduced visceral fat content.[32]

Limitations

Advance evaluation methods such as gene expression and western blot could not be employed in the current study. More satisfying results for SIRT1 gene expression could be obtained by utilizing these methods to gain deeper insight into the molecular mechanisms involved in the reduction of HOMA IR by GE and Exercise.

CONCLUSION

In the light of the results procured in present study, it may be deduced that aqueous ginger extract supplementation and exercise training, alone and in combination significantly improve IR in T2DM with the most pronounced effect seen in the combination group. This positive influence is associated with an up regulation and restoration of levels of serum SIRT1. Moreover, the use of ginger supplementation (as a SIRT1 activator substance)and exercise may be introduced as a safe and natural adjunct to anti diabetic drugs hence lowering their potentially harmful side effects.T2DM patients who suffer from co-morbidities that restrict body movements (e.g. joint or musculoskeletal disorders) may adopt ginger supplementation alone to produce a significant reduction in IR.

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The Authors:

Dr. Seher Naeem,
FCPS-II Trainee/Senior Demonstrator,
Department of Physiology,
CMH Lahore Medical College & Institute of Dentistry Lahore

Dr. Muniza Saeed,
Professor,
Department of Physiology,
Postgraduate Medical Institute, Lahore.

Dr. Jawaria Ilyas,
Assistant Professor,
Department of Physiology,
CMH, Lahore Medical College & Institute of Dentistry Lahore.

Dr. Asma Ashraf,
Senior Demonstrator,
Department of Physiology,
Continental Medical College, Lahore

Dr. Madiha Akram,
Senior Demonstrator,
Department of Physiology,
Pak Red Crescent Medical College, Dina Nath,
Pakistan.

Dr. Ruqaiyya Nazir,
PhD Scholar/Demonstrator,
Department of Physiology,
Islamic International Medical College,
Rawalpindi.

Authorship:

S.N: Conceptualization, Methodology, Writing-Original draft
M.S: Supervision
J.I: Review
A.A: Review
M.A: Data Collection
R.N: Data Collection & Analysis