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Rate of Glucose Utilization by Blood Cells in Serum and Plasma Specimens With or Without Using Preservative

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ABSTRACT

Objective: This study aims to estimate and compare the time-course change in blood glucose levels by blood cells in serum, and plasma with or without preservatives, which may reflect the rate of glucose utilization by blood cells.

Method: This laboratory-based cross-sectional study was carried out using a blood specimen of 28 participants among which 14 were diagnosed with diabetes and 14 were non-diabetic. Fasting blood specimen was collected in a plain tube, Ethylene Diamine Tetra Acetic Acid (EDTA) tube, and EDTA+ Sodium Fluoride (NaF) tube. The test was performed by hourly estimation of glucose for 24 hours. Time-course changes in glucose levels in serum and plasma with or without NaF preservative were statistically compared using ANOVA test.

Result: Serum and EDTA plasma glucose levels decreased gradually after the 3rd hour to 24th hour in comparison to EDTA+NaF plasma ($p<0.05$). The rate of glucose utilization by blood cells was significantly higher in clotted blood and anticoagulated blood (EDTA) specimens in comparison with anticoagulated blood (EDTA) containing preservative (NaF) (($p<0.05$). In addition, decreased rate of glucose utilization was observed in hyperglycemic specimens compared to that of normoglycemic blood.

Conclusion: Higher rate of glucose utilization by blood cells observed in serum and EDTA plasma represents a pre-analytical error in a long-standing specimen. The use of preservative NaF with EDTA significantly prevents cellular glucose utilization and stabilize plasma glucose level. In contrast, this study also shows further insight into the reduced cellular metabolic rate of glucose utilization in diabetes mellitus.

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Abbreviations

EDTA, Ethylene Diamine Tetra Acetic Acid; NaF, Sodium Fluoride; MMIHS, Manmohan Memorial Institute of Health Sciences; MMTH, Manmohan Memorial Teaching Hospital; WBC, White blood cell; AACC, American Association for Clinical Chemistry.

Introduction

Glucose is one of the least stable metabolites in the blood which serves as the principal fuel of all tissues (1). Most energy for cellular activities is derived from glucose metabolism providing more than 70% of the energy in the human body which is important in maintaining the body's normal physiological functions (2). The cells in the blood utilize the glucose via the glycolytic process as a source of energy Thus, the level of glucose falls from the whole blood on standing over a period at ambient temperature (3-5). Depending upon the various factors such as glucose concentration, leukocytes count, and hematocrit level, the rate of utilization of glucose in the blood is reported to average 5-7% per hour (6-8). So, it is the most common preanalytical issue because glycolytic enzyme complexes present in the membrane of erythrocytes which utilize glucose by glycolysis leads to the reduction of glucose concentration (9-11).

Glucose can be measured in whole blood, serum, or plasma. To minimize this crucial pre-analytical issue, some potential solutions have been developed which include heparin, salt of Ethylene Diamine Tetra Acetic Acid (EDTA), oxalates, sodium fluoride (NaF), Citrate buffer, etc. (12). Sodium fluoride in addition to an anticoagulant potassium oxalate or EDTA is the commonest inhibitor for glucose measurement (5). Fluoride inhibits the glycolytic enzyme enolase involved in the eighth step of glycolysis and has some effects on glucose oxidase and glucose peroxidase enzymes as well as inhibits bacterial growth. While EDTA is the most common anticoagulant, it prevents the formation of fibrin by chelating the calcium needed for blood clotting and forms an insoluble calcium salt. Thus, EDTA has a high ability to prevent clotting by binding to $Ca2+$ in comparison with oxalates (2, 5, 13, 14). Moreover, EDTA also inhibits the activity of the glycolytic enzyme, 3-phosphoglycerate kinase (15).

In remote areas, blood needs to be transported from the site of collection to a laboratory for analysis. Blood samples are collected and kept for a longer period. In certain cases, when using an automated analyzer, there may be a waiting period before the analysis is carried out. These are the interferences of the possibility of immediate analysis. Under such conditions, it is important to recognize that the blood glucose values can be reduced than the actual value (16).

According to the guideline of the American Association for Clinical Chemistry (AACC), the sample is immediately placed into ice which inhibits glycolysis, but prompt cooling and processing of each blood sample in the cold is difficult to achieve in routine clinical practice. Therefore, preservatives are used to stabilize glucose during blood collection and processing procedures that are performed at room temperature (17, 18). Accurate and precise measurement of blood glucose is of great importance in the diagnosis and management of diabetes (19). There are two different methods of determining glucose level: the chemical method and the enzymatic method. The chemical method exploits the non-specific reducing property of glucose in reactions with an indicator substance, which concomitantly changes color on its reduction. Whereas, the enzymatic method has reached an advanced stage where the enzymes could be immobilized in electronic machines or devices for easier and faster analysis (20, 21).

This study aimed to measure serum and plasma glucose concentration and the rate of glucose utilization by blood cells using anticoagulant (EDTA) with or without preservative NaF at different storage periods at room temperature. This may contribute management of pre-analytical error to improve quality in the diagnosis of diabetes mellitus. Moreover, the study may also provide insight into the rate of cellular glucose utilization in hyperglycemia in comparison to the normoglycemic environment.

Methods

This analytical cross-sectional study was carried out in Manmohan Memorial Institute of Health Sciences (MMIHS), Kathmandu, Nepal, and Manmohan Memorial Teaching Hospital (MMTH), Kathmandu, Nepal. A total of 28 blood specimens were collected among which 14 were clinically diagnosed diabetic and 14 were non-diabetic individuals. Fasting blood samples were collected by venipuncture in plain, EDTA, and EDTA + NaF tube followed by hourly estimation of glucose for 24 hours. Hemolysed blood samples were excluded from the study. Fasting blood glucose concentration was estimated by the enzymatic method following the standard guideline provided by the reagent manufacturer (Human GmBh, Wiesbaden, Germany).

All tests were analyzed in Biolyzer 100 (Analytical, Germany, Semi-autoanalyser). The concentration of glucose was expressed in gm/dl. Internal quality control was performed daily while external quality control was performed quarterly for validation of the test.

Statistical analysis

All the data were collected and analyzed by SPSS version 23 (IBM corporation, Armonk, NY, USA) and Microsoft excel 2013. Mean comparison between serum and plasma glucose concentration was performed by one-way ANOVA test and Post-hoc (LSD) ANOVA test. Percentage glucose utilization by blood cells was performed by descriptive statistics. A p-value of less than 0.05 was considered statistically significant.

Result

A total of 28 patients among which 14 were clinically diagnosed diabetic and 14 were non-diabetic. The study included 18 males and 10 females whose ages ranged from 20 years to 67 years.

Comparison of serum and plasma glucose in normoglycemic blood

The glucose level in serum and plasma differed significantly from 2 hours ($p<0.05$) and Post Hoc LSD showed that the serum glucose values were significantly lower ($p<0.05$) than EDTA+NaF but there was no significant difference with EDTA plasma ($p=0.133$) at two hours. However, from the third hour, serum and EDTA plasma glucose values were significantly decreased ($p<0.05$) than EDTA+NaF plasma glucose values in normoglycemic blood (Table 1).

Comparison of serum and plasma glucose in hyperglycemic blood

The glucose level in serum and plasma differed significantly from four hours ($p<0.05$) and Post Hoc LSD showed that the serum glucose values were significantly lower ($p<0.05$) than EDTA+NaF but there was no significant difference with EDTA plasma ($p=0.205$) at four hours. However, from five hours serum and EDTA plasma glucose values were significantly decreased ($p<0.05$) than EDTA+NaF plasma glucose values in hyperglycemic blood (Table 2).

Percentage of glucose utilized by blood cells up to 12 hours in normoglycemic and hyperglycemic blood respectively

The rate at which the blood glucose decreases vary with serum and EDTA plasma with or without NaF. It was noticed in normoglycemic patients that, fluoride plasma showed the least fall in glucose level (17.8%), followed by serum (83.7%) and EDTA plasma (88.7%) which showed significant variation in the glucose level. A similar result was found in the hyperglycemic patients, with a rate of decrease in glucose (17.7%) in fluoride plasma and (66.9%) serum and (63.1%) fall in EDTA plasma after 12 hours of storage respectively (Figure 1 and 2).

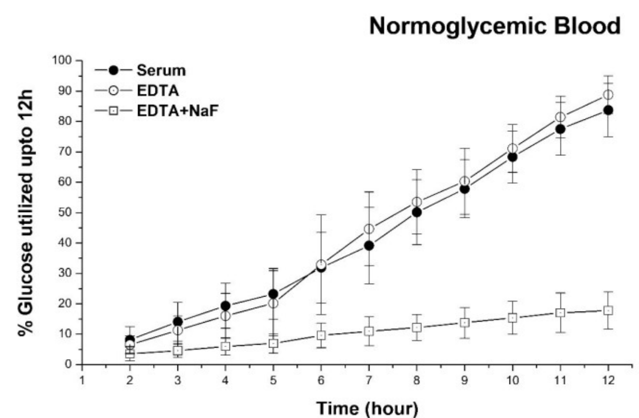

Figure 1. Percentage of glucose utilized by blood cells up to 12 hours in normoglycemic blood. EDTA, Ethylene Diamine Tetra acetic acid; NaF, Sodium fluoride.

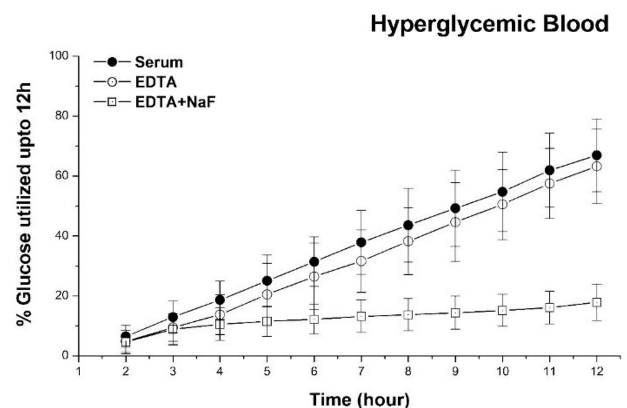

Figure 2. Percentage of glucose utilized by blood cells up to 12 hours in hyperglycemic blood. EDTA, Ethylene Diamine Tetra acetic acid; NaF, Sodium fluoride.

Table 1. Comparison of serum and plasma glucose level up to 24 hours by One Way ANOVA in normoglycemic blood

Time	Anticoagulants	Mean±SD	*p-value*	Post hoc(LSD)		
				Anticoagulants		*p-value*
1hour	Serum	79.72±8.73	0.367	EDTA+NaF	Serum	
	EDTA	81.91±9.51			EDTA	-
	EDTA+NaF	84.60±8.73				
2hour	Serum	73.16±8.01	0.049	EDTA+NaF	Serum	**0.015**
	EDTA	76.55±8.99			EDTA	0.133
	EDTA+NaF	81.72±9.69				
3hour	Serum	68.33±7.58	**0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	72.55±8.45			EDTA	**0.014**
	EDTA+NaF	80.78±9.29				
4hour	Serum	64.14±7.94	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	68.69±9.03			EDTA	**0.002**
	EDTA+NaF	79.60±9.28				
5hour	Serum	60.97±7.78	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	65.27±10.18			EDTA	**<0.001**
	EDTA+NaF	78.78±9.11				
6hour	Serum	54.02±9.81	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	54.46±12.62			EDTA	**<0.001**
	EDTA+NaF	76.35±7.61				
7hour	Serum	48.25±10.69	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	44.92±9.45			EDTA	**<0.001**
	EDTA+NaF	75.22±7.70				
8hour	Serum	39.72±9.66	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	37.76±8.45			EDTA	**<0.001**
	EDTA+NaF	74.21±7.82				
9hour	Serum	33.60±8.95	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	32.10±8.49			EDTA	**<0.001**
	EDTA+NaF	72.81±7.58				
10hour	Serum	25.36±8.27	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	23.76±7.48			EDTA	**<0.001**
	EDTA+NaF	71.51±8.24				
11hour	Serum	18.09±8.22	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	15.33±6.49			EDTA	**<0.001**
	EDTA+NaF	70.08±8.60				
12hour	Serum	13.06±7.92	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	9.16±5.49			EDTA	**<0.001**
	EDTA+NaF	69.41±7.98				
24hour	Serum	8.03±4.52	**<0.001**	EDTA+NaF	Serum	**<0.001**
	EDTA	5.22±2.54			EDTA	**<0.001**
	EDTA+NaF	67.63±7.64				

EDTA- Ethylene Diamine Tetra acetic acid; NaF- Sodium fluoride; SD- standard deviation

Table 2. Comparison of serum and plasma glucose level up to 24 hours by One Way ANOVA in hyperglycemic blood (N=14)

Time	Anticoagulants	Mean±SD	*P-value*	Post hoc(LSD)		
				Anticoagulants		*p-value*
1hour	**Serum**	122.24±11.30	0.588	**EDTA+NaF**	**Serum**	**-**
	EDTA	123.49±14.36			**EDTA**	
	EDTA+NaF	127.16±13.25				
2hour	**Serum**	114.45±13.08	0.454	**EDTA+NaF**	**Serum**	**-**
	EDTA	117.77±16.38			**EDTA**	
	EDTA+NaF	121.31±13.13				
3hour	**Serum**	106.56±13.24	0.215	**EDTA+NaF**	**Serum**	**-**
	EDTA	111.95±15.08			**EDTA**	
	EDTA+NaF	115.86±13.01				
4hour	**Serum**	99.74±14.43	**0.051**	**EDTA+NaF**	**Serum**	**0.015**
	EDTA	106.66±16.03			**EDTA**	0.205
	EDTA+NaF	113.82±13.57				
5hour	**Serum**	92.17±16.53	**0.010**	**EDTA+NaF**	**Serum**	**0.003**
	EDTA	98.69±20.38			**EDTA**	**0.038**
	EDTA+NaF	112.57±13.51				
6hour	**Serum**	84.20±14.83	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	91.42±21.33			**EDTA**	**0.003**
	EDTA+NaF	111.7±13.18				
7hour	**Serum**	76.40±17.31	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	85.05±19.85			**EDTA**	**<0.001**
	EDTA+NaF	110.41±13.58				
8hour	**Serum**	69.50±18.86	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	76.82±19.69			**EDTA**	**<0.001**
	EDTA+NaF	109.75±13.55				
9hour	**Serum**	62.55±19.08	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	69.30±22.71			**EDTA**	**<0.001**
	EDTA+NaF	108.95±13.76				
10hour	**Serum**	55.32±17.96	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	61.83±19.63			**EDTA**	**<0.001**
	EDTA+NaF	108.01±13.87				
11hour	**Serum**	47.20±18.46	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	53.32±19.44			**EDTA**	**<0.001**
	EDTA+NaF	106.76±13.76				
12hour	**Serum**	41.06±17.89	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	46.46±20.37			**EDTA**	**<0.001**
	EDTA+NaF	104.53±13.47				
24hour	**Serum**	26.75±15.66	**<0.001**	**EDTA+NaF**	**Serum**	**<0.001**
	EDTA	18.05±13.24			**EDTA**	**<0.001**
	EDTA+NaF	102.11±13.54				

EDTA- Ethylene Diamine Tetra acetic acid; NaF- Sodium fluoride; SD- standard deviation

Percentage of glucose utilized by blood cells in 24 hours

Figure 3 shows the utilization of glucose per day by blood cells in serum and EDTA plasma with or without NaF in both normoglycemic and hyperglycemic blood. It was noticed that the fasting blood glucose in serum, EDTA, and EDTA+NaF reduced at a mean percentage of 89.95%, 93.60%, and 19.95 per day respectively and in normoglycemic blood, it was reduced 78.64%, 85.85%, and 19.11% per day respectively in hyperglycemic blood.

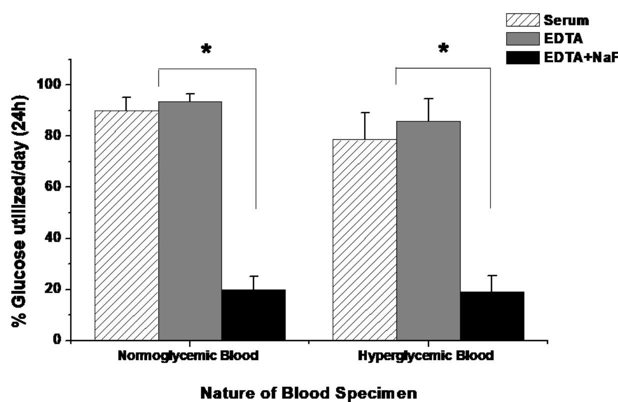

*Figure 3. Percentage of glucose utilized by blood cells in serum, EDTA, and EDTA+NaF up to 24 hours in normoglycemic and hyperglycemic blood. EDTA, Ethylene Diamine Tetra acetic acid; NaF, Sodium fluoride. Note: * indicates p-value less than 0.05.*

Percentage of glucose utilized by blood cells per hour

Figure 4 shows the rate of glucose utilized per hour by blood cells in the serum or EDTA plasma with or without NaF in both normoglycemic and hyperglycemic blood. It was noticed that the fasting blood glucose in serum, EDTA, and EDTA+NaF decreased at a mean percentage of 15.08%, 17.17%, and 1.76% per hour respectively in normoglycemic blood while 9.88%, 8.87%, and 1.75% per hour respectively in hyperglycemic blood.

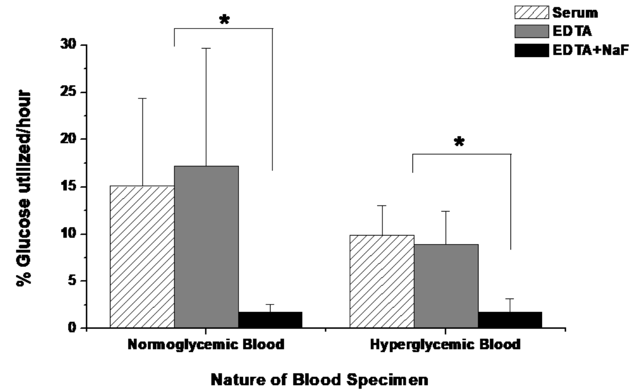

*Figure 4. Percentage of glucose utilized per hour by blood cells in serum, EDTA, and EDTA+NaF in normoglycemic and hyperglycemic blood. EDTA, Ethylene Diamine Tetra acetic acid; NaF, Sodium fluoride. Note: * indicates p-value less than 0.05.*

Discussion

Glucose, the most common blood constituent, is frequently estimated in laboratories because of the high prevalence of medical conditions that derange glucose homeostasis (22). Early diagnosis, successful treatment, and assessment of the risk of developing diabetes mellitus depend on the measurement of glucose concentration accurately (23, 24). Once the blood is drawn, the concentration of glucose will continue to decrease because of glycolysis, due to the presence of erythrocytes and white blood cells (WBCs) (25). Hence, the estimation of true blood glucose level is important not only for the diagnosis of diabetes at the earliest but also for the accurate identification of patients at high risk (26). The level of blood glucose can be strongly affected by the method of storage and handling of the blood samples between the time of collection and the time of analysis (27). Improper storage and handling of samples can generate improper results that may mislead the clinician into the wrong diagnosis (28). To overcome this crucial preanalytical error, some potential solutions have been developed which include the collection of blood samples in a tube containing heparin, salt of Ethylene Diamine Tetra Acetic Acid (EDTA), oxalates, sodium fluoride (NaF), Citrate buffer, etc. (12).

Anticoagulated blood is thought to be the best sample used for measuring fasting blood glucose as glucose is preserved in its naive state for a longer time when different anticoagulants are used for storage (2). In this study, an attempt was made to compare the changes in blood glucose level and percentage of glucose utilized by blood cells over 12 and 24 hours when anticoagulated blood (EDTA) with and without glycolytic inhibitor (NaF) and serum were used as specimens.

In our study when glucose concentration from the specimen with different anticoagulants was compared in the different time intervals, the three specimen's serum, EDTA plasma, and EDTA+NaF plasma showed a significant difference in glucose level after the third hour. The glucose level in EDTA+NaF plasma showed a significant difference with serum glucose at two hours while with both serum and EDTA plasma glucose thereafter. Additionally, the glucose level in EDTA+NaF plasma showed a significant difference with serum glucose at four hours while with both serum and EDTA plasma glucose after four hours in normoglycemic and hyperglycemic blood respectively. The result obtained by Nwangwu C. O. Spencer et al. showed a steady significant ($p < 0.05$) decrease in fasting blood glucose levels in the blood samples stored in all the anticoagulants under study (29). NaF along with anticoagulant inhibits the enolase enzyme in the glycolytic pathway (30). Thus, the conversion of 2-phosphoglycerate to phosphoenolpyruvate is stopped. So, the processes of inhibition of glycolysis take 2-4 hours to be initiated and arrest the utilization of blood glucose (31, 32). In our study, the mean concentration of plasma glucose estimated in EDTA was lowered than that measured in fluoride ($p < 0.05$). Therefore EDTA+NaF was found to be an appropriate anticoagulant for the estimation of glucose concentration. The study conducted by Nwangwu C. O. Spencer et al. showed the possibility of Sodium fluoride being a better anticoagulant for long-term storage of blood samples for glucose determinations, as the glucose concentration in the blood samples stored in it tends to be comparatively more stable (29).

Our study showed that glucose concentration decreased at the minimum rate in EDTA+NaF, followed by EDTA and clotted blood respectively. A similar study conducted by Hubert W. Vesper et al. in Atlanta that the glucose concentrations in EDTA blood and clotted blood decreased faster 50% within 8 hours and 90% after 24 hours (33) which is almost similar to our study. Additionally, EDTA changes the immediate environment of glycolytic enzymes, including the pH and ionic strength, thus making the environment more stable for glucose as compared to clotted blood (33). Our study also showed that the rate of decrease in the glucose level in normoglycemic blood is higher than that of hyperglycemic blood. According to Xiao-Jian Hu et al., the rate of glucose entry in hyperglycemic erythrocytes is only 77% of the normoglycemic erythrocytes. This could be due to the presence of compounds or macromolecules in the blood of these patients, which may include their medications. Furthermore, the possible reasons might be the alteration of phospholipid bilayers in diabetic erythrocyte membranes, change in GLUT1 content, abnormality of other proteins in the erythrocyte membranes, and the alteration of structure or conformation of GLUT1 in diabetic patients (14, 34).

This study has some limitations, in which we used a commercially available single concentration of anticoagulant, which may change actual results after a prolonged time of storage. We recommend using a different concentration of anticoagulant in further study. As well we could not measure the concentration of glucose immediately after collection.

Conclusion

Glucose level was found to be least stable when serum and EDTA plasma were used as a sample for glucose estimation. However, plasma from EDTA with glycolytic inhibitor (EDTA+NaF) was found to be the best sample as there was the least utilization of glucose level during a different time interval. Despite the use of any sample, there was a high decline in glucose level during storage. Thus, to get reliable results, glucose determination should be carried out immediately after the collection of a sample or within the shortest possible time. As well use of preservative NaF with EDTA significantly prevents cellular glucose utilization and stabilize plasma glucose level. Meanwhile, this study also shows further insight into the reduced cellular metabolic rate of glucose utilization in diabetes mellitus.

Declarations

Funding
Not applicable.

Conflicts of interest
Not applicable.

Authors' Contributions
MPB, PR, and AN - conceived the design of the study, reviewed literature, performed necessary interventions including laboratory investigations. SS- participated in data collection and laboratory procedures. SP, SS, and PR - analyzed the data. MPB, SP, and AN prepared the manuscript. All authors contributed toward drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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