Revista Argentina de Clínica Psicológica
2020, Vol. XXIX, N4, 115-121
DOI:10.24205/03276716.2020.813

Correlations of LINC00858 and miR-363-3p Expressions in The Serum with Clinicopathological Characteristics of Liver Cancer Patients

Chenhui Ma[a,b], Junye Wen[b*], XiaoYanFan[b], YichaoWang[a], Huaibin Guo[b], ChunCheng Wang[b], Wanxing Zhang[b*]

Abstract

Objective: To investigate the correlations of the expressions of long non-coding ribonucleic acid (lncRNA) long intergenic non‑protein coding RNA 858 (LINC00858) and micro RNA (miR)-363-3p in the serum with the clinicopathological characteristics and prognosis of liver cancer patients.

Methods: A total of 90 liver cancer patients admitted to and treated in our hospital from January 2017 to March 2019 were selected as liver cancer group, and 70 healthy people receiving physical examination in the same period were enrolled into control group. The expression levels of serum LINC00858 and miR-363-3p were detected using qRT-PCR. Then the liver cancer patients were assigned into LINC00858 high expression group (n=50), LINC00858 low expression group (n=40), miR-363-3p high expression group (n=30) and miR-363-3p low expression group (n=60) based on the average values of LINC00858 and miR-363-3p expression levels, and the correlations of LINC00858 and miR-363-3p expression levels with the clinicopathological characteristics of liver cancer patients were observed. The correlation between LINC00858 and miR-363-3p in the serum of liver cancer patients was analyzed by Pearson’s method. The receiver operating characteristic curves were plotted to analyze the diagnostic value of LINC00858 and miR-363-3p in liver cancer. All the patients were followed up for 2 years, and their 2-year survival was analyzed by Kaplan-Meier method.

Results: The expression level of serum LINC00858 was increased significantly (P<0.05), while that of miR-363-3p was decreased significantly (P<0.05) in liver cancer group compared with those in control group. LINC00858 was negatively correlated with miR-363-3p (r=-0.3946, P=0.0001), and the expression levels of LINC00858 and miR-363-3p had close relations to tumor thrombus, lymph node metastasis, tumor-node-metastasis (TNM) stage, differentiation degree and liver cirrhosis (P<0.05). As for LINC00858, the sensitivity was 65.56%, the specificity was 65.71%, the area under curve (AUC) was 0.673, the 95% confidence interval (CI) was 0.595-0.745, and the cutoff value was 1.18. The sensitivity, specificity, AUC, 95%CI and cutoff value of miR-363-3p were 83.33%, 37.14%, 0.597, 0.516-0.674 and 1.14, respectively. The survival rate of patients in LINC00858 high expression group was significantly lower than that in LINC00858 low expression group (P<0.05), but it was significantly higher in miR-363-3p high expression group than that in miR-363-3p low expression group (P<0.05).

Conclusion: Liver cancer patients have a high expression of LINC00858 and a low expression of miR-363-3p in the serum, LINC00858 and miR-363-3p are negatively correlated with each other, and they have close correlations with the TNM stage, tumor thrombus, differentiation degree, lymph node metastasis and other clinicopathological characteristics of patients, so they are conducive to the diagnosis of liver cancer and the evaluation of patient's prognosis.

Keywords: liver cancer, LINC00858, miR-363-3p, clinicopathological characteristic, prognosis.

a.North China university of science and technology, TangShan, China
b.Department of hepatobiliary, Hebei General Hospital, Shijiazhuang 050000, China
**Corresponding Author: Junye Wen, Wanxing Zhang*
Address: Department of hepatobiliary, Hebei General Hospital, Shijiazhuang 050000, China
Email: nari8249974@163.com

1. Introduction

Liver cancer, a widespread malignant tumor in China, is distinguished by a high mortality rate and recently a rise in its morbidity rate per year. At present, alpha fetoprotein is used as a key diagnostic and prognostic marker for liver cancer diagnoses in the clinic, but is comparatively poor in its sensitiveness and specificity. Studies have shown that the pathological production of long non-coding ribonucleic acids (lncRNAs) in liver cancer has a possible impact on disease diagnoses and therapies (Wang H. et al. 2010) (Shang R. et al. 2020) (Mao L.H. et al.20) (Yan D. et al. 2020). Study has shown that the long intergenic RNA 858 (LINC00858) nonprotein code lncRNA is widely expressed in gastric cancer, which can be considered as a major diagnostic indicator for gastric cancer patients (Ai W and others 2020). (Ai W. et al., 2020). Micro-RNA (miR)-363-3p is likely a target gene of LINC00858 according to the bioinformatics review. An earlier literature found that miR-363-3p is poor in bile-bladder cancer and can deter disease progression (Wang SH et al. 2016; Mahajan et al., Manthalkar et al., 2019; Gautam et al., 2019; Dhere & Dharmadhikari, 2019; Josephy et al., 2019). The goal of this research was therefore to examine serum lncRNA LINC00858 and miR-363-3p expressions in and their connection to the client's clinicopathological characteristics, and evaluate how they relate to the diagnosis of liver cancer and the prognosis of patients.

2. Materials and methods

General information

In general, from January 2017 to February 2019, 90% of the patients certainly diagnosed with liver cancer were treated as a category with liver cancer, including 54 male and 36 females aged 40-75, aged 58.62± 9.85 years. The average age was between January 2017 and February 2019. None of the patients has several malignant tumors problematic. 70 stable individuals were also included in the control group under physical inspection during the same time. There was a total of 50 men and 20 women aged 45-70 and (60.32± 10.11) years. The two subgroups (P>0.05), which were similar, had no statistically meaningful age-sex variations. The Ethical Committee of the hospital accepted this research and all patients were told of the analysis and signed their consent.

Methods

Blood sample collection

Early in the morning, each of the participants obtained fasted venous blood (5 mL) in both groups and then centrifuged at 4 ° C and 3000 r / min for around 10 minutes. The serum was then put into a tube and deposited in an ultra-low freezer.

Measurement of LINC00858 and miR-363-3p expression levels by qRT-PCR

A TRIzol reagent (TransGen Biotech Co., Ltd., Beijing) procedure was used to remove complete RNA from serum, with the NanoDrop 2000c ultra-micro-spectrophotometer being used to calculate RNA concentration. Then, a reverse transcription package was used to synthesize the overall RNA to cDNA [TIANGEN Biotech (Beijing) Co., Ltd.]. In-first for LINC00858: 5'-AGCTCCTTACACGTGGA-3, Reverse Premier: 5'-GTCCGTCATTGCAGCATCAGC-3,' Forward-Forward-First for miR-363-3p:5'-AATTGCACGTCATCGTCTGT-3, Reverse Primer: 5'-AGGCTCAGAATGCATGTC-3'; Forward-Forward-Forward for U6:5'-GCTCGCATCATATTTACT-3', Reverse-First: 5'-A-GGA Sangon Biotech (Shanghai) Co., Ltd has developed and synthesized primers. A qRT-PCR package was subsequently implemented to conduct PCR amplification [TIANGEN Biotech (Beijing) Co., Ltd]. LINC00858 and miR-363-3p are then measured using 2-normalCt approach and GAPDH as internal LINC00858 and U6 value as internal miR-363-3p index.

Follow-up

All the patients were followed up for 2 years mainly through telephone inquiries and out-patient reexamination, and the follow-up was terminated on January 13th, 2020. The survival time of the patients was recorded, and the survival rate was calculated.

2.1. Statistical analysis

Both data have been evaluated systematically by program SPSS21.0. The quantitative knowledge usually distributed was interpreted as the mean ± standard deviation (± s). The objective sample test administered the contrasts between two individuals, and between different categories, in a single method. analysis of variance. The numerical data is checked for μ2. Pearson 's approach has studied the association between LINC00858 and miR-363-3p in patients with liver cancer serum. In liver cancer, a

diagnostic significance of LINC00858 and miR-363-3p was analyzed utilizing recipient Operating Caracteristic (ROC) courves. Kaplan-Meier process evaluated the 2-year longevity. The statistically relevant P<0.05 was found.Results

2.2. Serum LINC00858 and miR-363-3p expression levels

The expression level of serum LINC00858 was increased significantly (P<0.05), while that of miR-363-3p was decreased significantly (P<0.05) in liver cancer group compared with those in control group (Table 1).

2.3 Correlation between serum LINC00858 and miR-363-3p expression levels

The association between LINC00858 and miR-363-3p in the serum of patients with liver cancer was tested by Pearson 's procedure, and the connection of LINC00858 to miR-363-3p was negative (r=-0.3946, and P=0.0001).

Table 1: **Serum LINC00858 and miR-363-3p expression levels ($\overline{x}$ ± s)**

Group	n	LINC00858	miR-363-3p
Control	70	1.02±0.28	1.00±0.32
Liver cancer	90	1.23±0.31*	0.86±0.26*
t		4.433	3.053
P		0.000	0.003

Compared with control group, *P<0.05.

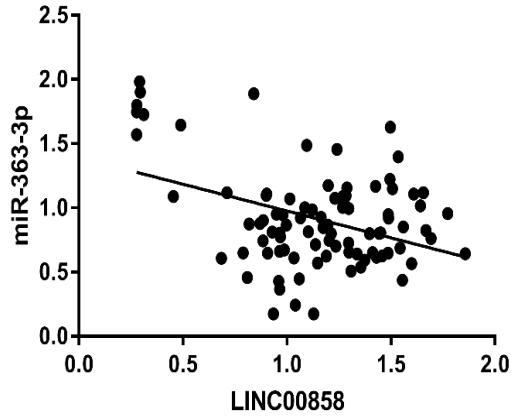

Figure 1: **Correlation between serum LINC00858 and miR-363-3p expression levels.**

2.4 Correlations of serum LINC00858 and miR-363-3p expressions with clinicopathological characteristics of liver cancer patients

Then, the patients with liver cancer were allocated the low-expression category of LINC00858 (n=50), LINC00858 (n=40), LINC00858 (LOS) (MIR)-363-3p (n=30, and MIR-363-3p (LOS) based on the average levels of expression of LINC00858 and MIR-363-3p and the association of LOS-363-3p with clinical characteristics o cancer patients were observed. The results manifested that the expression levels of LINC00858 and miR-363-3p displayed close relations to tumor thrombus, lymph node metastasis, tumor-node-metastasis (TNM) stage, differentiation degree and liver cirrhosis (P<0.05) (Table 2).

2.3. Diagnostic value of LINC00858 and miR-363-3p for liver cancer

The diagnostic value of LINC00858 and miR-The ROC curves were used to evaluate 363-3p in liver cancer. The findings show that LINC00858 had a sensitivity of 65.56 percent, a specimen of 65.71 percent, a region of 0.673 below curve (AUC), a trust interval of 0.595-0.745, of 95 percent (CI), a failure value of 1.18. Sensitivity, accuracy, AUC, 95% CI and mi-R-363-3p cutoffs were 83.33%, 37,14%, respectively, of 0.597, 0.516-0.674 and 1.14 (figure two).

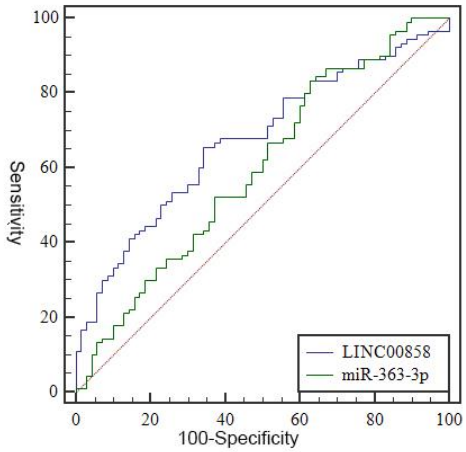

Figure 2: **Diagnostic value of LINC00858 and miR-363-3p for liver cancer.**

2.4. Correlations of serum LINC00858 and miR-363-3p expressions with prognosis

Kaplan-Meier 's study was used to assess the two-year survival in patients with liver cancer and showed that the survival rate in LINC00858 was 20.36% and in LINC00859 it was 52.30%. The high-expression group of LINC00858 was considerably below the degree of survival rate for the low-expression community (P<0.05). LINC00858 In comparison, patients with miR-363-3p in high expression community lived slightly more (59.68 percent vs.21.30 percent) (P<0.05) than patients in miR-363-3p (Figure 3).

Table 2: **Correlations of serum LINC00858 and miR-363-3p expressions with clinicopathological characteristics of liver cancer patients**

Clinicopathological characteristic	n	LINC00858		χ^2, P	miR-363-3p		χ^2, P
		High expression group (n=50)	Low expression group (n=40)		High expression group (n=30)	Low expression group (n=60)	
Age				0.538, 0.463			0.861, 0.353
<60 years	33	20	13		13	20	
≥60 years	57	30	27		17	40	
Gender				0.750, 0.386			0.000, 1.000
Male	54	32	22		18	36	
Female	36	18	18		12	24	
Tumor size (cm)				2.350, 0.125			1.469, 0.226
<5	53	33	20		15	38	
≥5	37	17	20		15	22	
Tumor thrombus				36.750 ,0.000			7.500, 0.006
Yes	54	44	10		24	30	
No	36	6	30		6	30	
Differentiation degree				29.770 ,0.000			8.882, 0.003
High	31	5	26		4	27	
Moderate-low	59	45	14		26	33	
Lymph node metastasis				36.699 ,0.000			35.839, 0.000
No	49	13	36		3	46	
Yes	41	37	4		27	14	
TNM stage				10.500 ,0.001			23.810, 0.000
Ⅰ~Ⅱ	63	28	35		11	52	
Ⅲ~Ⅳ	27	22	5		19	8	
Liver cirrhosis				42.438 ,0.000			34.128, 0.000
Yes	56	46	10		6	50	
No	34	4	30		24	10	

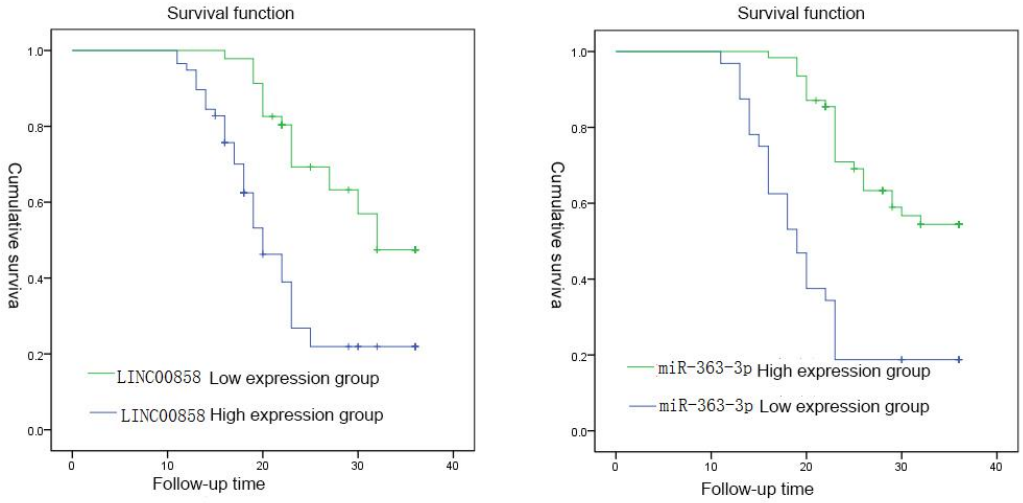

Figure 3: **Correlations of serum LINC00858 and miR-363-3p expressions with prognosis.**

4. Discussion

Pathological, pathology and laboratory tests control the testing approaches for Liver Cancer, although most patients are definitly detected at the advanced level. The quest for Serum Biomarkers with positive sensitivity and specificity is thus critical for the diagnosis and treatment of Liver Cancer. Studies suggest that lncRNAs are likely to be implicated in the production and prevalence of liver cancer through manipulation of miRNA expressions (Gao J. et al., 2020; Dong H. et al., 2020; Jiao Y. et al., 2020; Li J. et al., 2020). However, certain lncRNAs in liver have expressions cancer and their clinical significance have not been elaborated.

LINC00858 has improved expression in colorectal cancer and can encourage disease progression (Zhan W. et al. 2020; Xu T. et al. 2019; Sha Québec et al. 2019). (Sha Québec et al. 2019). LINC00858 is strongly expressed in lung cancer, and may promote the progression of lung cancer by the tracking of the molecular axis miR-3182 / MMP-2 (Xue M. et al., 2019). Furthermore, LINC00858 will control the molecular axis miR-139 / CDK14 to enable osteosarcoma to evolve and advance (Gu Z et al., 2018). According to the results, LINC00858 expression levels were surprisingly large in liver cancer patients, which indicates LINC00858 may play a crucial regulatory function in the occurrence of liver cancer, similar to the results above. Further analysis revealed that serum levels LINC00858 increased markedly along with thrombosis, metastasis of the lymph node, increased stage of TNM and differentiation, and the incidence of liver cirrhosis in patients, indicating that LINC00858 may be involved in liver cancer incidence and in the development of the disease. An analysis showed that miR-363-3p is poor in colon cancer and capable of reducing colon cancer incidence and metastasis (Dong J. et al. 2018).). With liver cancer, miR-363-3p has low expression, and up-regulated expression will restrict the development of hepatitis cancer (Wang J. et al., 2020). MiR-363-3p has reduced levels of prevalence and development of the disorder in pulmonary adenocarcinomas (Rong H. et al.2020). In comparison, miR-363-5p cuts down the intermittent and aggressive symptoms of NEDD9 and SOX4 non-small cell lung cancer (Chang J. et al, 2020). MiR-363-3p is down-regulated in colorectal cancer, which is involved in colorectal cancer growth which incidence (Xie J.J. et al.2019). The miR-363-3p was found in the serum of patients who suffered from liver cancer to be downregulated. In addition, certain patients with liver cancer were classified into the high-expression miR-363-3p community and the low-expression miR-363-3p community depending on the average value of the Mir 363-3ps degree of speech. The findings showed that the expression level of miR-363-3p has been closely connected with tumor thrombuses, metastasis of lymph nodes, TNM process, difference grade and liver cirrhosis;

that miR-363-3p may be involved in the occurrence and development of liver cancer. Meanwhile, the LINC00858 expression had a negative relation to miR-363-3p expression in the serum of liver cancer patients, implying that LINC00858 is likely to participate in the development and progression of liver cancer through negative regulation of miR-363-3p expression.

Herein, ROC curves were plotted to analyze the Serum LINC00858 and miR-363-3p diagnostic values for liver cancer were found to have 65,56%, 65,71%, 60,563%, 0,673 and 0,595-0,745 and 1,18, respectively, specificity, classification, CI, 95% and cutoff value of the LINC00858 diagnostic value. The sensitivity was 83.33% for miR-363-3p, the specimens were 37.14%, with AUC 0.597, 95% CI 0.516-0.674 and a cut-off value of 1,14. Both these findings suggest that LLINC00858 has a higher specificity than miR-363-3p when diagnosed with liver cancer, while miR-363-3p has a higher diagnostic sensitivity than LINC00858, which suggested that serum LINC00858 and miR-363-3p together may increase the precision of the early diagnosis of liver cancer. In addition, a Kaplan-Meier system examined the survival of 2-year patients with liver cancer, and the results indicated that high expressive LINC00858 displayed a slightly lower rate of survival than LINC00858, whereas miR-3633-3p displayed a distinctly higher rate of survival than the low-expression miR363-3p, indicating that the increased LINC00858e

Finally, in patients with Liver Cancer, the serum LINC00858 is significantly higher and serum miR-363-3p is substantially lower, with two variables being adversely associated together, strongly connected with the tumor thrombus, metastasis of the Lymph Node, stage TNM, degree of separation and hepatic circulation. Therefore, they can not only act as important biomarkers for the detection of liver cancer, but also as indexes for the identification of patients with liver cancer. However, in the case of incidence and growth, molecular pathways LINC00858 and miR-363-3p have to be investigated further.

Funding

The work was supported by Key Project of Medical Science Research in Hebei Province （20190382）.

References

Wang H, Huo X, Yang XR, et al. (2010). STAT3-mediated upregulation of lncRNA HOXD-AS1 as a ceRNA facilitates liver cancer metastasis by regulating SOX4. *Mol Cancer*, 16(1), 136-146.

Wang M, Dai B et al. Shang R. (2020). RNA SLC2A1-AS1 is a long non-coding controlling aerobic glycolysis and development of hepatocellular carcinoma by STAT3 / FOXm1 and GLUT1 inhibition. Oncol Mol, 16(1), 1–10.

Mao LH, Chen SY, Li XQ, et al. (2020). In order to facilitate development and invasion of hepatocellular carcinoma, the Lnc RNA-LALR1 re-regulates small nucleolar RNA SNORD72. Cultivation (Albany New York), 12(1), 1-12.

Jin F, Lin Y, Yan D. (2020). (2020). LncRNA HAND2-AS1 Impedes the development and movement of liver cancer cells via the re-regulatory SOCS5 in order to inactivate the JAK-STAT pathway. Radiopharm Cancer Biother, 35(2), 143-152.

Ai W, Li F, among Yu HH, and others (2020). Large non-coding RNA LINC00858 up-regulation is consistent with low gastric cancer pronostics. California, 4(1), 3182-12.

Wang SH, Zhang WJ, Wu XC, et al. (2016). The lncRNA MALAT1 acts as opposing endogenous RNA to control MCL-1 expression in gallbladder cancer by sponging miR-363-3p. Mol Med neuron, 20(12), 2299-2308.

Gao J, Dai C, Yu X, etc. Long noncodification RNA LINC00324 is pro-toriginal in the impact of the upregulation of fas ligand through the usage of PU box binding protein on the liver cancer stem cells. BEAUCHE, 3(1).

Yu M, et al. Dong H, Jian P, 2020. Silence with RNA-136-5p / WNK1 for long period stops the production of hepatocellular carcinoma from the center of the crosstalk. Bitch, 18(1), 1-10. Physiol.

Y, Jiao, Y, B, B, etc. (2020). The prognostic importance and possible role of lncRNA SNHG4 in liver cancer[J]. Rep Biosci, 40(1), 1-12.

Li J, W Guo, and others. (2019). Long non-encodation of RNA AUROKAS1, by controlling miR-142, miR-155, and miR-181, potentiates malignant hepatocellular carcinoma development. Sci Rep, 9(1), 1855-627.

Zhan W, Liao X and others (2020). Chen Z. The spungal miR-4766-5p to control PAK2 encourages colorectal cancer. Toxicol cell Biol, 4(1), 1-12.

Zhang L et al. (2019). (2019). Long non-coding function of RNA LINC00858 in colon cancer is tumor-promoting by HNF4α and WNK2 control. Dordr (Oncol Cell), 28(1), 1-13.

Chen L, Sha QK, Xi JZ, et al. (2019). Long-term non-coding RNA LINC00858 facilitates the growth, movement and invasion of cells, functioning as miR-22-3p ceRNA in the case of colorectal cancer. Nanomed Biotechnol Artif Cells, 47(1), 1057-1066.

M, M. Shi D, M. Xu, etc. (2019). The long non-coding RNA linc00858 promotes advancement of lung cancer through miR-3182 / MMP2 axis. Nanomed Biotechnol, Phys Cells, 47(1), 2091-2097.

Gu Z, Hou Z, Zheng L et al. The RNA LINC00858 long non-coding encouraged osteosarcoma by the miR-139-CDK14 axis controlled. Res commun BIOCHEM, 503(2), 1134-1140.

Geng J, Tan W., Dong J. (2018). (2013). The SphK2 targeting MiR-363-3p suppresses the development of the tumor and the metastasis of colorectal cancer. Pharmacother Biomed, 105(1), 922-931.

Lu L et al. Wang J (2020). LncRNA OIP5-AS1 interacts with miR-363-3p to aid development of hepatocellular carcinoma by up-regling SOX4. Ther, 10(1), 1-12.

Chen H (2020) and Wei X (2020). Long non-coding RNA XIST accelerates progression of lung adenocarcinoma by upregulating MDM2 expression through a miR-363-3p binding .. Cancer of Thorace, 11(3), 659-671.

Chang J, Gao F, Chu H and others (2020). miR-363-3p prevents migrations, invasions, and epithelium mesenchymal transformations in the non-small cell lung cancer by attacking NEDD9 and SOX4. Physiol's Unit, 235(2), 1808-1820.

Li WH and Xie JJ et al. (2019). Xie JJ, Li X. The sponging miR-363-3p in order to control EZH2 expression[J] facilitates colorectal growth of cancer. 33(2), 331-343; Biol Rule Homeost Workers.

Mahajan, K., Kandoria, A., Bhardwaj, R., Negi, P. C., Asotra, S., & Gupta, G. (2019). Clinical and coronary angiographic profile in women presenting with anginal chest pain: Results from a single-center prospective observational study. Journal of Natural Science, Biology and Medicine, 10(1), 60.

Manthalkar, P. S., & Peerapur, B. V. (2019). Demographic and clinical profile of patients infected with dengue virus serotypes 1, 2, and 3 in North Karnataka. Journal of Natural Science, Biology and Medicine, 10(2), 144.

Gautam, R. K., Singh, C. P., Saxena, R., & Rao, D. P. (2019). Synthesis And Studies Of Some Cis-Moo2 (Vi) Complexes With Nitrogen Donor Macrocyclic Ligands. European Chemical Bulletin, 8(12), 387-393.

Dhere, D. D., & Dharmadhikari, S. M. (2019). Chemical Analysis Of Pigment Produced By Haloalkalotolerent Bacteria Paracoccus Beibuensis SL2. European Chemical Bulletin, 8(12), 394-398.

Joseph, P. L., Bonsignore, A., Kunkel, G. F., Grace, S. L., Sockalingam, S., & Oh, P. (2019). Benefits and barriers to exercise among individuals with class III obesity. American journal of health behavior, 43(6), 1136-1147.