EJMCM

EUROPEAN JOURNAL OF MOLECULAR & CLINICAL MEDICINE

ISSN 2515-8260

www.egmcm.com

editor@egmcm.com

European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 03, 2020

Risk Factors For The Progression Of Non-Alcoholic Fatty Liver Disease And The State Of Intestinal Microflora In Overweight And Obese Patients

Botir T. Daminov[1], Umida Sh. Usmanova[2], Bahromkhon A. Alavi[3], Gozal N. Sobirova[4]

[1]MD, Rector of the Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.
[2]MD, assistant of the Department of Faculty Internal Medicine, Tashkent Pediatric Medical Institute. Tashkent, Uzbekistan.
[3]MD, professor assistant of The Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation, Tashkent, Uzbekistan.
[4]MD, professor assistant of The Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation, Tashkent, Uzbekistan.

E-mail: [1]mail@tashpmi.uz, [2]sherzod999@mail.ru, [3]info@tsdi.uz, [4]info@tsdi.uz

ABSTRACT

Recently, the growth of non-alcoholic fatty liver disease has been actively discussed in domestic and foreign literature. In Uzbekistan, the incidence of non-alcoholic fatty liver disease increased from 27.0% in 2007 to 37.1% in 2014 and ranked first among liver diseases.

KEY WORDS: non-alcoholic fatty liver disease, non-alcoholic fatty hepatosis and non-alcoholic steatohepatitis, BMI, intestinal microflora.

1. INTRODUCTION

The concept of non-alcoholic fatty liver disease includes two morphological forms of the disease with different prognosis: non-alcoholic fatty hepatosis and non-alcoholic steatohepatitis [18,5,6]. The severity of non-alcoholic steatohepatitis is highly variable, including fibrosis, cirrhosis, and hepatocellular carcinoma [1.18]. Non-alcoholic fatty liver disease is 20–86 cases per 1000 person-years according to the level of liver feces and / or ultrasound (ultrasound) data and 34 cases per 1000 cases per year according to PMR [14], according to other sources. The prevalence of non-alcoholic fatty liver disease among the adult population ranges from 17 to 46% [3.17].

According to the Russian study DIREG 2, non-alcoholic fatty liver disease was diagnosed in 37.3% (n = 50 145 people): USA - in 75.6% of patients, non-alcoholic steatohepatitis - in 24.4%, while 80.5% of patients had BMI. > 27 kg / m2, abdominal obesity (AO) - 67.2% [2.8]. According to a pooled meta-analysis (based on 21 cohort studies), obesity is associated with a 3.5-fold increase in the risk of non-alcoholic fatty liver disease [3,4,20]. In recent years, there has been an alarming trend towards an increase in non-alcoholic fatty liver disease among children [19], in about 3% of the entire child population and in 53% of obese children [9]. To clarify the classification of children with and without non-alcoholic steatohepatitis, a special histological scale has been developed for non-

alcoholic fatty liver disease in children - Pediatric NAFLD Histological Score, PNHS [18,11].

We decided to consider the relationship between intestinal microbiocenosis and non-alcoholic fatty liver disease, since disorders of human intestinal microbiocenosis occupy the third place in the structure of gastroenterological pathology [20]. Normal intestinal microflora supports all physiological functions of the host [12], with a beneficial effect on its health. At the same time, changes in the composition of the intestinal microflora (dysbiosis) can contribute to the development of diseases such as obesity, type 2 diabetes mellitus, inflammatory bowel diseases, and cardiovascular diseases [7]. To date, the results of controlled trials for the treatment of non-alcoholic fatty liver disease are not fully understood. There are no treatment standards, the recommendations are flexible and can be individual in each case [5], which prompted the study of the intestinal microflora in patients with non-alcoholic fatty liver disease, since the treatment includes the elimination of risk factors [5], 10,18] drugs that do not affect on the intestinal microflora.

Purpose - to conduct a comparative analysis of the lipid sector and intestinal microflora in patients with non-alcoholic fatty liver disease.

2. MATERIALS AND METHODS

The study was conducted at the Republican Specialized Scientific and Practical Medical Center for therapy and medical rehabilitation.

The study is based on data from 60 patients, of which 30 patients (group 1) with non-alcoholic fatty liver disease without diabetes mellitus, 30 patients (group 2) with type 2 diabetes mellitus and 20 healthy individuals (control group) without clinical and instrumental diagnostic signs of non-alcoholic fatty liver disease.

The age gradation of patients varied from 29 to 77 years, of which 18 were men and 42 were women.

Table 1. Patient distribution according to age and gender

Age	Patients with non-alcoholic fatty liver disease			
	Men	%	Women	%
31-40	3	5	5	8,3
41-50	2	3,3	8	13,3
over 51	13	21,7	29	48
Total	18	30	42	70

The peak incidence of non-alcoholic fatty liver disease occurs in the age period over 50 (69.7%), that is, at an older age.

Patients with metabolic syndrome have the highest risk of developing non-alcoholic fatty liver disease [5, 6].

Based on this, we examined the anthropometric parameters: body weight, height, waist, hips, BMI calculation and waist / hip ratio.

Table 2. BMI of examined patients with non-alcoholic fatty liver disease, (M ± m)

Parameters	BMI	Abdominal obesity
1 – group (p- 30)	29,5±1,26	106,3±4,2
2 - group (p- 30)	33,7±1,22*	110,5±1,7

Note: * - the difference is significant compared with SG (p <0.05)

The study did not include: patients with hepatitis of viral, alcoholic and drug etiology, cumulative diseases, cardiac liver fibrosis, liver cirrhosis, chronic renal failure, stage II, III circulatory failure, organic colon disease.

Verification of the diagnosis of hypertension was based on ultrasound parameters characteristic of fatty hepatosis, in the absence of other causes of changes in the sound conduction of the liver with normal or moderately elevated levels of ALT, bilirubin, alkaline phosphatase and GGTP. In the presence of ultrasound liver changes characteristic of fatty hepatosis and an increase in cytolysis (more than 2N), bilirubin, alkaline phosphatase and GGTP, the diagnosis of non-alcoholic steatohepatitis was established. The diagnosis of diabetes mellitus was established after consulting an endocrinologist with confirmed laboratory tests (blood glucose, impaired glucose and glycohemoglobin tolerance).

Examination of patients with non-alcoholic fatty liver disease included clinical, laboratory, instrumental, physicochemical and immunological methods. The general plan of the patient's examination for the diagnosis of non-alcoholic fatty liver disease included: a general blood test, a biochemical blood test (ALT, ASAT, GGTP, ALP, total bilirubin), a study of the lipid profile (cholesterol, TG, LDL, HDL), microbiological examination.

Sowing feces to consider the microflora of the colon was performed 2 times. The fabric for the study was fecal tests collected instantly after the act of defecation.

Ultrasound examination of the stomach organs was performed for all patients utilizing the ALOCA device (Japan) employing a sensor with a recurrence of 3.5 MG in genuine mode. Specific attention was paid to the state of the hepatobiliary framework. The sizes of the liver, echogenicity of the liver parenchyma, and the perceivability of the vascular design were assessed.

3. RESULTS

The nearness of an increment within the echogenicity of the changed parenchyma of the liver, accompanied by the acoustic impact of attenuation of ultrasound within the profound layers of the parenchyma, was too echosonographic. The structure of the liver parenchyma remained homogeneous. In this case, the shape of the organ was not abused, the forms remained smooth, the edge was sharp. In patients with non-alcoholic greasy liver illness, the foremost common diffuse shape of fatty infiltration was 37 individuals (61.7% of cases), in which there was a uniform increment in echogenicity over the whole surface of the liver, a central shape was recognized in as it were 7 patients (11.7%) and nearby shape in 16 people (26.7%).

In this way, in patients with non-alcoholic greasy liver illness, the nearness of greasy infiltration, presented most frequently within the shape of a diffuse shape, is famous. Too, in most patients, hypomotor-type gallbladder dyskinesia was watched, went with by a feeling of largeness within the right hypochondrium of changing degrees of concentrated, as well as the nearness of dyspeptic signs and abdominal-pain syndromes, showed by throbbing torment or distress within the right hypochondrium without a clear connection with nourishment

admissions. In expansion, the endless lion's share of patients appeared expanded weakness and asthenic disorder.

Ponders of biochemical parameters of blood serum characterizing the state of cytolytic and cholestatic pointers of hepatocytes, we conducted independently in bunches 1 and 2. Ponders have shown that, in patients, there was an increment within the markers of "cytolysis" of AlAT (cytoplasmic enzyme, present in huge amounts within the liver) by 2.8 and 3, 3 times (p <0.05) and AcAT (mitochondrial enzyme present in expansive sums within the heart, liver, skeletal muscles and kidneys) 2.9 and 3.8 times, respectively (p <0.05). In spite of the reality that AlAT could be a more particular marker of hepatocyte harm than AcAT due to its predominant localization within the liver parenchyma, a unmistakable highlight of patients with nonalcoholic greasy liver infection is an increment within the AST / ALT coefficient..

The entire bilirubin was expanded, but it was not statistically noteworthy. The GGTP record was increased within the 1st bunch of patients by 100% (p <0.05), and within the 2nd bunch 2.4 times (p <0.05). The alkaline phosphatase record (a marker of cholestasis) was expanded in patients with non-alcoholic fatty liver illness in both bunches 4.0 and 4.0 times, separately, compared with sound individuals, significantly.

Table 3. Indicators of biochemical parameters of blood serum of patients with non-alcoholic fatty liver disease (M ± m)

Indicators	**AlAT, U / L**	**AsAT, U / L**	**Bilirubin, µmol / l**	**ShF, Unit / l**	**GGTP, Unit / l**
Healthy	19,3± 3,3	15, 2± 4,4	9, 2± 0,51	79 ,7± 10,2	39,73± 7,3
1 group	55, 8± 6,62*	44, 0± 6,98*	21,02± 1,17*	317,9± 25,34*	79,78± 16,18*
2 group	62,7± 7,86*	58, 4± 9,05*	22, 04± 2,62*	377, 1± 31, 46*	95, 95± 19, 08*

Note: * - the difference is significant compared with healthy individuals (p <0.05)

Table 4. Lipid spectrum of blood serum of patients with non-alcoholic fatty liver disease

Parameters	**Healthy**	**1 group**	**2 group**
Total cholesterol, mmol / l	5,97 ± 0	5,82±0,24	6,13±0,41
triglycerides, mmol / l	3,01 ± 0,32	2,74±0,34	3,26±0,32
HDL, mmol / l	1,02 ± 0,12	1,17±0,12*	0,86±0,04*
LDL, mmol / l	3,33 ± 0,23	3,41±0,30	3,19±0,16
VLDL, mmol / l	0,63 ± 0,04	0,62±0,10*	0,94±0,05*
Atherogenic index	5,24 ± 0,58	4,72±0,27*	5,76±0,37*

Note: * - the difference is statistically significant compared between 1 and 2 gr. (p <0.05-0.001)

HDL *- high density lipoprotein cholesterol,* ***LDL*** *- low density lipoprotein cholesterol,* ***VLDL*** *- very low density lipoprotein cholesterol*

In this way, the considers conducted in this area appeared that the course of non-

alcoholic greasy liver disease is went with by impeded serum lipid range, which is communicated by a diminish in HDL and an increment in LDL and TG. The awkwardness of the lipid range was corresponding to the severity of the infection and was altogether higher in patients. Non-alcoholic greasy liver illness with the presence of T2DM. Within the 2nd bunch, the values were somewhat higher: the level of TG was significantly higher, but no significant differences were found within the level of HDL cholesterol diminished to diagnostically noteworthy deviations characteristic of non-alcoholic fatty liver malady. All patients showed a 1.5–2-fold increment within the cholesterol of cholesterol, which is ordinary for hypertriglyceridemia. The most articulated deviations of this pointer were watched in patients of the 2nd gather. LDL cholesterol was more reliable with the target level overwhelmingly. The atherogenicity index significantly surpassed the reasonable values in all inspected, but basically ($p < 0.01$) in patients of the 2nd gather.

The nearness and degree of dysbiotic changes within the huge digestive system in patients Non-alcoholic fatty liver disease was analyzed taking into consideration the information of clinical and microbiological studies. Studies appeared that of all 60 patients inspected with non-alcoholic greasy liver malady, dysbiosis was watched in 57 (95%) patients. So, dysbiosis of the 1st degree was recognized in 15%, patients of the 2nd degree - in 36.6% of patients, 3 degrees - in 40% and 4 degrees in 5%.
The table presents information on the recurrence of discovery of intestinal dysbiosis in patients. Nonalcoholic greasy liver infection of the gotten comes about is obvious, intestinal microflora clutters were more pronounced in patients of bunch 2 with the nearness of T2DM. In gather 1, there was predominantly dysbacteriosis of 2 degrees 13 (43.3%) additionally 1 degree 5 (16, 7%) 3 degrees 9 (30%) patients. In patients of gather 2, dysbiosis of 2 and 3 degrees 13 (43, 3%) and 11 (36.6%), separately, were predominantly watched. It ought to be famous that 2 (6.7%) patients had review 4 dysbiosis.

Table 5. The degree of dysbiosis in patients with non-alcoholic fatty liver disease

	Normal flora	**I**	**II**	**III**	**IV**
Group 1	3 (10%)	5 (16, 7%)	13 (43, 3%)	9 (30%)	-
Group 2	-	4 (13,3%)	13 (43,3%)	11 (36, 7%)	2 (6,7%)

A study of the composition of the intestinal microflora in patients with dysbacteriosis Non-alcoholic fatty liver illness appeared that the most prominent number of associations, both positive and negative, their strength and noteworthiness level with other microorganisms colonizing the colon, was characteristic of bacterioiods. So, there was a positive relationship between the concentration of bacteroids, on the one hand, and bifidobacteria ($r = 0.54$; $p < 0.01$) and lactobacilli ($r = 0.60$; $p < 0.01$), on the other, additionally between the substance of bifidobacteria and lactobacilli ($r = 0.34$; $p < 0.05$), which may be due to the presence of common components for controlling their numbers.

Hence, in all patients with non-alcoholic greasy liver malady, infringement of the intestinal microbiocenosis were identified overwhelmingly of the 2nd degree and 3rd degree. In expansion, the most pronounced intestinal microflora clutters were recorded in patients

with non-alcoholic greasy liver disease with the nearness of T2DM. A relationship investigation of the connections between the files of intestinal microbiocenosis in patients with non-alcoholic greasy liver illness uncovered that the greatest number of associations, their quality and importance level with other microorganisms colonizing the colon was characteristic of bacterioiods. In common, the combination of non-alcoholic greasy liver disease and 1 and 2 degrees of dysbiosis is characterized by torment within the right hypochondrium, for the 3rd and 4th degrees - torment within the umbilical locale, as well as a combination of torments of diverse localization. The recurrence of discovery of torment around the navel can be utilized to distinguish a more pronounced degree of dysbiosis.

4. CONCLUSION

Non-alcoholic greasy liver infection involves a noteworthy put within the structure of the incidence of the gastrointestinal tract. Non-alcoholic greasy liver infection is almost 20-40% agreeing to the literature [13]. In spite of certain propels in pharmacotherapy of this pathology, one of the most issues is the non-specificity of the clinical appearances of the introductory organize. Non-alcoholic greasy liver infection is the stage of hepatic steatosis, which can cause awkward treatment and infection progression.

According to considers, it was found that patients with non-alcoholic greasy liver infection noted the presence of greasy penetration, displayed most regularly within the frame of a diffuse frame. Moreover, the larger part of patients showed hypomotor-type dyskinesia of the gallbladder, went with by a feeling of heaviness in the proper hypochondrium of shifting degrees of concentrated.

When examining the biochemical parameters of blood serum, it was uncovered that in patients with non-alcoholic greasy liver infection, a noteworthy increment within the levels of "cytolysis" and "cholestasis" in the blood serum, as well as a infringement of the lipid range of the blood serum, which is communicated by a diminish in HDL and an increment within the LDL and TG pool . Biochemical awkwardness was proportional to the seriousness of the malady and was altogether higher in patients. Non-alcoholic fat liver disease with the nearness of T2DM.

Thinks about of the intestinal microflora appeared that in all patients with non-alcoholic greasy liver disease, infringement of the intestinal microbiocenosis were transcendently of the 2nd degree. In addition, the most articulated intestinal microflora disarranges were recorded in patients with non-alcoholic fatty liver infection with the nearness of T2DM.

REFERENCES

[1] Kant, N., Saralch, S., & Singh, H. (2011). Ponderomotive self-focusing of a short laser pulse under a plasma density ramp. *Nukleonika*, *56*, 149-153.

[2] Patyar, S., & Patyar, R. R. (2015). Correlation between sleep duration and risk of stroke. *Journal of Stroke and Cerebrovascular Diseases*, *24*(5), 905-911.

[3] Khamparia, A., & Pandey, B. (2015). Knowledge and intelligent computing methods in e-learning. *International Journal of technology enhanced learning*, *7*(3), 221-242.

[4] Singh, A., Lin, Y., Quraishi, M. A., Olasunkanmi, L. O., Fayemi, O. E., Sasikumar, Y., ... & Kabanda, M. M. (2015). Porphyrins as corrosion inhibitors for N80 Steel in 3.5% NaCl solution: Electrochemical, quantum chemical, QSAR and Monte Carlo simulations studies. *Molecules*, *20*(8), 15122-15146.

[5] Singh, S., Kumar, V., Upadhyay, N., Singh, J., Singla, S., & Datta, S. (2017). Efficient biodegradation of acephate by Pseudomonas pseudoalcaligenes PS-5 in the presence

and absence of heavy metal ions [Cu (II) and Fe (III)], and humic acid. *3 Biotech*, *7*(4), 262.

[6] Mia, M., Singh, G., Gupta, M. K., & Sharma, V. S. (2018). Influence of Ranque-Hilsch vortex tube and nitrogen gas assisted MQL in precision turning of Al 6061-T6. *Precision Engineering*, *53*, 289-299.

[7] Prakash, C., Singh, S., Pabla, B. S., & Uddin, M. S. (2018). Synthesis, characterization, corrosion and bioactivity investigation of nano-HA coating deposited on biodegradable Mg-Zn-Mn alloy. *Surface and Coatings Technology*, *346*, 9-18.

[8] Feng, X., Sureda, A., Jafari, S., Memariani, Z., Tewari, D., Annunziata, G., ... & Sychrová, A. (2019). Berberine in cardiovascular and metabolic diseases: from mechanisms to therapeutics. *Theranostics*, *9*(7), 1923.

[9] Bashir, S., Sharma, V., Lgaz, H., Chung, I. M., Singh, A., & Kumar, A. (2018). The inhibition action of analgin on the corrosion of mild steel in acidic medium: A combined theoretical and experimental approach. *Journal of Molecular Liquids*, *263*, 454-462.

[10] Sidhu, G. K., Singh, S., Kumar, V., Dhanjal, D. S., Datta, S., & Singh, J. (2019). Toxicity, monitoring and biodegradation of organophosphate pesticides: a review. *Critical Reviews in Environmental Science and Technology*, *49*(13), 1135-1187.

[11] Nanda, V., & Kant, N. (2014). Enhanced relativistic self-focusing of Hermite-cosh-Gaussian laser beam in plasma under density transition. *Physics of Plasmas*, *21*(4), 042101.

[12] Kotla, N. G., Gulati, M., Singh, S. K., & Shivapooja, A. (2014). Facts, fallacies and future of dissolution testing of polysaccharide based colon-specific drug delivery. *Journal of Controlled Release*, *178*, 55-62.

[13] Farooq, R., & Shankar, R. (2016). Role of structural equation modeling in scale development. *Journal of Advances in Management Research*.

[14] Singh, S., Ramakrishna, S., & Gupta, M. K. (2017). Towards zero waste manufacturing: A multidisciplinary review. *Journal of cleaner production*, *168*, 1230-1243.

[15] Mahla, S. K., Dhir, A., Gill, K. J., Cho, H. M., Lim, H. C., & Chauhan, B. S. (2018). Influence of EGR on the simultaneous reduction of NOx-smoke emissions trade-off under CNG-biodiesel dual fuel engine. *Energy*, *152*, 303-312.

[16] Nanda, V., Kant, N., & Wani, M. A. (2013). Self-focusing of a Hermite-cosh Gaussian laser beam in a magnetoplasma with ramp density profile. *Physics of Plasmas*, *20*(11), 113109.

[17] Kaur, P., Singh, S. K., Garg, V., Gulati, M., & Vaidya, Y. (2015). Optimization of spray drying process for formulation of solid dispersion containing polypeptide-k powder through quality by design approach. *Powder Technology*, *284*, 1-11.

[18] Sharma, D., & Saharan, B. S. (2016). Functional characterization of biomedical potential of biosurfactant produced by Lactobacillus helveticus. *Biotechnology Reports*, *11*, 27-35.

[19] Wani, A. B., Chadar, H., Wani, A. H., Singh, S., & Upadhyay, N. (2017). Salicylic acid to decrease plant stress. *Environmental Chemistry Letters*, *15*(1), 101-123.

[20] Mishra, V., Patil, A., Thakur, S., & Kesharwani, P. (2018). Carbon dots: emerging theranostic nanoarchitectures. *Drug discovery today*, *23*(6), 1219-1232.

[21] Kumar, V., Pitale, S. S., Mishra, V., Nagpure, I. M., Biggs, M. M., Ntwaeaborwa, O. M., & Swart, H. C. (2010). Luminescence investigations of Ce3+ doped CaS nanophosphors. *Journal of alloys and compounds*, *492*(1-2), L8-L12.

[22] Pudake, R. N., Swaminathan, S., Sahu, B. B., Leandro, L. F., & Bhattacharyya, M. K. (2013). Investigation of the Fusariumvirguliformefvtox1 mutants revealed that the

FvTox1 toxin is involved in foliar sudden death syndrome development in soybean. *Current genetics*, *59*(3), 107-117.

[23] Kapoor, B., Singh, S. K., Gulati, M., Gupta, R., & Vaidya, Y. (2014). Application of liposomes in treatment of rheumatoid arthritis: quo vadis. *The scientific world Journal*, *2014*.

[24] Haldhar, R., Prasad, D., & Saxena, A. (2018). Myristica fragrans extract as an eco-friendly corrosion inhibitor for mild steel in 0.5 M H2SO4 solution. *Journal of Environmental Chemical Engineering*, *6*(2), 2290-2301.

[25] Bordoloi, N., Sharma, A., Nautiyal, H., & Goel, V. (2018). An intense review on the latest advancements of Earth Air Heat Exchangers. *Renewable and Sustainable Energy Reviews*, *89*, 261-280.

[26] Sharma, P., Mehta, M., Dhanjal, D. S., Kaur, S., Gupta, G., Singh, H., ... & Chellappan, D. K. (2019). Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. *Chemico-biological interactions*, *309*, 108720.

[27] Goga, G., Chauhan, B. S., Mahla, S. K., & Cho, H. M. (2019). Performance and emission characteristics of diesel engine fueled with rice bran biodiesel and n-butanol. *Energy Reports*, *5*, 78-83.

[28] Umashankar, M. S., Sachdeva, R. K., & Gulati, M. (2010). Aquasomes: a promising carrier for peptides and protein delivery. *Nanomedicine: Nanotechnology, Biology and Medicine*, *6*(3), 419-426.

[29] Sharma, A., Shree, V., & Nautiyal, H. (2012). Life cycle environmental assessment of an educational building in Northern India: A case study. *Sustainable Cities and Society*, *4*, 22-28.

[30] Kaur, T., Kumar, S., Bhat, B. H., Want, B., & Srivastava, A. K. (2015). Effect on dielectric, magnetic, optical and structural properties of Nd–Co substituted barium hexaferrite nanoparticles. *Applied Physics A*, *119*(4), 1531-1540.

[31] Datta, S., Singh, J., Singh, S., & Singh, J. (2016). Earthworms, pesticides and sustainable agriculture: a review. *Environmental Science and Pollution Research*, *23*(9), 8227-8243.

[32] Vij, S., & Bedi, H. S. (2016). Are subjective business performance measures justified?. *International Journal of Productivity and Performance Management*.

[33] Chawla, R., & Sharma, S. (2017). Molecular dynamics simulation of carbon nanotube pull-out from polyethylene matrix. *Composites Science and Technology*, *144*, 169-177.

[34] Prakash, C., & Uddin, M. S. (2017). Surface modification of β-phase Ti implant by hydroaxyapatite mixed electric discharge machining to enhance the corrosion resistance and in-vitro bioactivity. *Surface and Coatings Technology*, *326*, 134-145.

[35] Saxena, A., Prasad, D., & Haldhar, R. (2018). Investigation of corrosion inhibition effect and adsorption activities of Cuscuta reflexa extract for mild steel in 0.5 M H2SO4. *Bioelectrochemistry*, *124*, 156-164.

[36] Prabhakar, P. K., Kumar, A., & Doble, M. (2014). Combination therapy: a new strategy to manage diabetes and its complications. *Phytomedicine*, *21*(2), 123-130.

[37] Wheeler, K. C., Jena, M. K., Pradhan, B. S., Nayak, N., Das, S., Hsu, C. D., ... & Nayak, N. R. (2018). VEGF may contribute to macrophage recruitment and M2 polarization in the decidua. *PLoS One*, *13*(1), e0191040.

[38] Singh, A., Lin, Y., Ansari, K. R., Quraishi, M. A., Ebenso, E. E., Chen, S., & Liu, W. (2015). Electrochemical and surface studies of some Porphines as corrosion inhibitor for J55 steel in sweet corrosion environment. *Applied Surface Science*, *359*, 331-339.

[39] Gill, J. P. K., Sethi, N., Mohan, A., Datta, S., & Girdhar, M. (2018). Glyphosate toxicity for animals. *Environmental Chemistry Letters*, *16*(2), 401-426.

[40] Kumar, V., Singh, S., Singh, J., & Upadhyay, N. (2015). Potential of plant growth promoting traits by bacteria isolated from heavy metal contaminated soils. *Bulletin of environmental contamination and toxicology*, *94*(6), 807-814.

[41] Patel, S. (2012). Potential of fruit and vegetable wastes as novel biosorbents: summarizing the recent studies. *Reviews in Environmental Science and Bio/Technology*, *11*(4), 365-380.

[42] Srivastava, G., Das, C. K., Das, A., Singh, S. K., Roy, M., Kim, H., ... & Philip, D. (2014). Seed treatment with iron pyrite (FeS 2) nanoparticles increases the production of spinach. *RSC Advances*, *4*(102), 58495-58504.

[43] Nagpal, R., Behare, P. V., Kumar, M., Mohania, D., Yadav, M., Jain, S., ... & Henry, C. J. K. (2012). Milk, milk products, and disease free health: an updated overview. *Critical reviews in food science and nutrition*, *52*(4), 321-333.

[44] Vaid, S. K., Kumar, B., Sharma, A., Shukla, A. K., & Srivastava, P. C. (2014). Effect of Zn solubilizing bacteria on growth promotion and Zn nutrition of rice. *Journal of soil science and plant nutrition*, *14*(4), 889-910.

[45] Lin, Y., Singh, A., Ebenso, E. E., Wu, Y., Zhu, C., & Zhu, H. (2015). Effect of poly (methyl methacrylate-co-N-vinyl-2-pyrrolidone) polymer on J55 steel corrosion in 3.5% NaCl solution saturated with CO2. *Journal of the Taiwan Institute of Chemical Engineers*, *46*, 214-222.

[46] Mahesh, K. V., Singh, S. K., & Gulati, M. (2014). A comparative study of top-down and bottom-up approaches for the preparation of nanosuspensions of glipizide. *Powder technology*, *256*, 436-449.

[47] Singh, G., Gupta, M. K., Mia, M., & Sharma, V. S. (2018). Modeling and optimization of tool wear in MQL-assisted milling of Inconel 718 superalloy using evolutionary techniques. *The International Journal of Advanced Manufacturing Technology*, *97*(1-4), 481-494.

[48] Chauhan, C. C., Kagdi, A. R., Jotania, R. B., Upadhyay, A., Sandhu, C. S., Shirsath, S. E., & Meena, S. S. (2018). Structural, magnetic and dielectric properties of Co-Zr substituted M-type calcium hexagonal ferrite nanoparticles in the presence of α-Fe2O3 phase. *Ceramics International*, *44*(15), 17812-17823.

[49] Sharma, A., Shahzad, B., Kumar, V., Kohli, S. K., Sidhu, G. P. S., Bali, A. S., ... & Zheng, B. (2019). Phytohormones regulate accumulation of osmolytes under abiotic stress. *Biomolecules*, *9*(7), 285.

[50] Balakumar, P., Chakkarwar, V. A., Kumar, V., Jain, A., Reddy, J., & Singh, M. (2008). Experimental models for nephropathy. *Journal of the Renin-Angiotensin-Aldosterone System*, *9*(4), 189-195.

[51] Singh, A., Lin, Y., Liu, W., Kuanhai, D., Pan, J., Huang, B., ... & Zeng, D. (2014). A study on the inhibition of N80 steel in 3.5% NaCl solution saturated with CO2 by fruit extract of Gingko biloba. *Journal of the Taiwan Institute of Chemical Engineers*, *45*(4), 1918-1926.

[52] Kaur, T., Kaur, B., Bhat, B. H., Kumar, S., & Srivastava, A. K. (2015). Effect of calcination temperature on microstructure, dielectric, magnetic and optical properties of Ba0. 7La0. 3Fe11. 7Co0. 3O19 hexaferrites. *Physica B: Condensed Matter*, *456*, 206-212.

[53] Singh, P., Singh, A., & Quraishi, M. A. (2016). Thiopyrimidine derivatives as new and effective corrosion inhibitors for mild steel in hydrochloric acid: Electrochemical and quantum chemical studies. *Journal of the Taiwan Institute of Chemical Engineers*, *60*, 588-601.

[54] Anand, A., Patience, A. A., Sharma, N., & Khurana, N. (2017). The present and future of pharmacotherapy of Alzheimer's disease: A comprehensive review. *European journal of pharmacology*, *815*, 364-375.

[55] Saxena, A., Prasad, D., Haldhar, R., Singh, G., & Kumar, A. (2018). Use of Sida cordifolia extract as green corrosion inhibitor for mild steel in 0.5 M H2SO4. *Journal of environmental chemical engineering*, *6*(1), 694-700.

[56] Ahmadi, M. H., Ghazvini, M., Sadeghzadeh, M., Alhuyi Nazari, M., Kumar, R., Naeimi, A., & Ming, T. (2018). Solar power technology for electricity generation: A critical review. *Energy Science & Engineering*, *6*(5), 340-361.

[57] Kant, N., Wani, M. A., & Kumar, A. (2012). Self-focusing of Hermite–Gaussian laser beams in plasma under plasma density ramp. *Optics Communications*, *285*(21-22), 4483-4487.

[58] Gupta, V. K., Sethi, B., Upadhyay, N., Kumar, S., Singh, R., & Singh, L. P. (2011). Iron (III) selective electrode based on S-methyl N-(methylcarbamoyloxy) thioacetimidate as a sensing material. *Int. J. Electrochem. Sci*, *6*, 650-663.

[59] Mehta, C. M., Srivastava, R., Arora, S., & Sharma, A. K. (2016). Impact assessment of silver nanoparticles on plant growth and soil bacterial diversity. *3 Biotech*, *6*(2), 254.

[60] Gupta, V. K., Guo, C., Canever, M., Yim, H. R., Sraw, G. K., & Liu, M. (2014). Institutional environment for entrepreneurship in rapidly emerging major economies: the case of Brazil, China, India, and Korea. *International Entrepreneurship and Management Journal*, *10*(2), 367-384.

[61] Singh, A., Lin, Y., Obot, I. B., Ebenso, E. E., Ansari, K. R., & Quraishi, M. A. (2015). Corrosion mitigation of J55 steel in 3.5% NaCl solution by a macrocyclic inhibitor. *Applied Surface Science*, *356*, 341-347.

[62] Ansari, K. R., Quraishi, M. A., Singh, A., Ramkumar, S., & Obote, I. B. (2016). Corrosion inhibition of N80 steel in 15% HCl by pyrazolone derivatives: electrochemical, surface and quantum chemical studies. *RSC advances*, *6*(29), 24130-24141.

[63] Jnawali, P., Kumar, V., & Tanwar, B. (2016). Celiac disease: Overview and considerations for development of gluten-free foods. *Food Science and Human Wellness*, *5*(4), 169-176.

[64] Saggu, S., Sakeran, M. I., Zidan, N., Tousson, E., Mohan, A., & Rehman, H. (2014). Ameliorating effect of chicory (Chichorium intybus L.) fruit extract against 4-tert-octylphenol induced liver injury and oxidative stress in male rats. *Food and chemical toxicology*, *72*, 138-146.

[65] Bhatia, A., Singh, B., Raza, K., Wadhwa, S., & Katare, O. P. (2013). Tamoxifen-loaded lecithin organogel (LO) for topical application: development, optimization and characterization. *International Journal of Pharmaceutics*, *444*(1-2), 47-59.

[66] Singh, A., Lin, Y., Liu, W., Yu, S., Pan, J., Ren, C., & Kuanhai, D. (2014). Plant derived cationic dye as an effective corrosion inhibitor for 7075 aluminum alloy in 3.5% NaCl solution. *Journal of Industrial and Engineering Chemistry*, *20*(6), 4276-4285.

[67] Raza, K., Thotakura, N., Kumar, P., Joshi, M., Bhushan, S., Bhatia, A., ... & Katare, O. P. (2015). C60-fullerenes for delivery of docetaxel to breast cancer cells: a promising approach for enhanced efficacy and better pharmacokinetic profile. *International journal of pharmaceutics*, *495*(1), 551-559.

[68] Prabhakar, P. K., Prasad, R., Ali, S., & Doble, M. (2013). Synergistic interaction of ferulic acid with commercial hypoglycemic drugs in streptozotocin induced diabetic rats. *Phytomedicine*, *20*(6), 488-494.

[69] Chaudhary, A., & Singh, S. S. (2012, September). Lung cancer detection on CT images by using image processing. In *2012 International Conference on Computing Sciences* (pp. 142-146). IEEE.

[70] Mishra, V., Bansal, K. K., Verma, A., Yadav, N., Thakur, S., Sudhakar, K., & Rosenholm, J. M. (2018). Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. *Pharmaceutics*, *10*(4), 191.

[71] Singh, A. (2012). Hydroxyapatite, a biomaterial: its chemical synthesis, characterization and study of biocompatibility prepared from shell of garden snail, Helix aspersa. *Bulletin of Materials Science*, *35*(6), 1031-1038.

[72] Arora, S., & Anand, P. (2019). Binary butterfly optimization approaches for feature selection. *Expert Systems with Applications*, *116*, 147-160.

[73] Chhikara, N., Kushwaha, K., Sharma, P., Gat, Y., & Panghal, A. (2019). Bioactive compounds of beetroot and utilization in food processing industry: A critical review. *Food Chemistry*, *272*, 192-200.

[74] Singh, S., Kumar, V., Chauhan, A., Datta, S., Wani, A. B., Singh, N., & Singh, J. (2018). Toxicity, degradation and analysis of the herbicide atrazine. *Environmental chemistry letters*, *16*(1), 211-237.

[75] Baranwal, T., & Pateriya, P. K. (2016, January). Development of IoT based smart security and monitoring devices for agriculture. In *2016 6th International Conference-Cloud System and Big Data Engineering (Confluence)* (pp. 597-602). IEEE.

[76] Trukhanov, S. V., Trukhanov, A. V., Salem, M. M., Trukhanova, E. L., Panina, L. V., Kostishyn, V. G., ... & Sivakov, V. (2018). Preparation and investigation of structure, magnetic and dielectric properties of (BaFe11. 9Al0. 1O19) 1-x-(BaTiO3) x bicomponent ceramics. *Ceramics International*, *44*(17), 21295-21302.

[77] Singh, S., Singh, N., Kumar, V., Datta, S., Wani, A. B., Singh, D., ... & Singh, J. (2016). Toxicity, monitoring and biodegradation of the fungicide carbendazim. *Environmental chemistry letters*, *14*(3), 317-329.

[78] Bhyan, B., Jangra, S., Kaur, M., & Singh, H. (2011). Orally fast dissolving films: innovations in formulation and technology. *Int J Pharm Sci Rev Res*, *9*(2), 9-15.

[79] Saxena, A., Prasad, D., Haldhar, R., Singh, G., & Kumar, A. (2018). Use of Saraca ashoka extract as green corrosion inhibitor for mild steel in 0.5 M H2SO4. *Journal of Molecular Liquids*, *258*, 89-97.

[80] Panghal, A., Janghu, S., Virkar, K., Gat, Y., Kumar, V., & Chhikara, N. (2018). Potential non-dairy probiotic products–A healthy approach. *Food bioscience*, *21*, 80-89.

[81] Kumar, D., Agarwal, G., Tripathi, B., Vyas, D., & Kulshrestha, V. (2009). Characterization of PbS nanoparticles synthesized by chemical bath deposition. *Journal of Alloys and Compounds*, *484*(1-2), 463-466.

[82] Ansari, K. R., Quraishi, M. A., & Singh, A. (2015). Corrosion inhibition of mild steel in hydrochloric acid by some pyridine derivatives: an experimental and quantum chemical study. *Journal of Industrial and Engineering Chemistry*, *25*, 89-98.

[83] Singh, P. S., Singh, T., & Kaur, P. (2008). Variation of energy absorption buildup factors with incident photon energy and penetration depth for some commonly used solvents. *Annals of Nuclear Energy*, *35*(6), 1093-1097.

[84] Ansari, K. R., Quraishi, M. A., & Singh, A. (2015). Isatin derivatives as a non-toxic corrosion inhibitor for mild steel in 20% H2SO4. *Corrosion Science*, *95*, 62-70.

[85] Singh, A., Lin, Y., Ebenso, E. E., Liu, W., Pan, J., & Huang, B. (2015). Gingko biloba fruit extract as an eco-friendly corrosion inhibitor for J55 steel in CO2 saturated 3.5% NaCl solution. *Journal of Industrial and Engineering Chemistry*, *24*, 219-228.

[86] Dey, A., Bhattacharya, R., Mukherjee, A., & Pandey, D. K. (2017). Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. *Biotechnology Advances*, *35*(2), 178-216.
[87] Ansari, K. R., Quraishi, M. A., & Singh, A. (2015). Pyridine derivatives as corrosion inhibitors for N80 steel in 15% HCl: Electrochemical, surface and quantum chemical studies. *Measurement*, *76*, 136-147.
[88] Patel, S. (2012). Threats, management and envisaged utilizations of aquatic weed Eichhornia crassipes: an overview. *Reviews in Environmental Science and Bio/Technology*, *11*(3), 249-259.
[89] Mia, M., Gupta, M. K., Singh, G., Królczyk, G., & Pimenov, D. Y. (2018). An approach to cleaner production for machining hardened steel using different cooling-lubrication conditions. *Journal of Cleaner Production*, *187*, 1069-1081.
[90] Kondrateva T.S. Biopharmaceutical studies of children's suppositories with phosphothiamine. Pharmacy.-Moscow, 1990.-No.5.-P.14-15.
[91] Maksudova F.Kh., Karieva E.S., Tursunova M.Kh. Study of the pharmacological properties of the combined gel of sodium diclofenac and benzketozone ./Infection, immunity and pharmacologists I.- Tashkent.-2015.-№5.C.160-163 /
[92] Maksudova F. Kh., Karieva E. S. In vitro equivalence evaluationce of dic-
lofenac sodium generic medicinal preparation. // Pharmacy, a scientific and practical journal, special issue, St. Petersburg, 2016, pp. 461-464.
[93] Piotrovsky V.K. Model and model-independent methods for describing pharmacokinetics: advantages, disadvantages and interrelation. // Antibiotics and medical biotechnology. -Moscow, 1997.-№7.P.492-497.
[94] Kukes V.G., Sychev D.A. Clinical pharmacology. 5th ed ., Moscow, 2017, p. 478.
[95] Tillaeva U. M., Azizov U. M. Development of a methodology for isolating the amount of fensulcal determination from a biological object. Materials of the scientific-practical conference "Actual issues of education, science and production in pharmacy. Tashkent, 2009.-P.172 .
[96] Tillaeva U.M. Standardization and quality control of fensulcal in soft dosage forms. // Authors' dissertation for the study of the academician of the candidate of pharmaceuticals. Sciences . Tashkent. 2011.23 s.
[97] Golovkin V.A. On the importance of pharmacokinetics modeling for increasing the efficiency of biopharmaceutical research. // Optimization of drug supply and ways to increase the effectiveness of pharmaceutical science : Sat. Tez.dokl.-Kharkov, 1986.-P.61-62.
[98] Stefanova A.V. Preclinical studies of medicines. Kiev. -2002. -650 p.
[99] Ivashkin V.T., Maevskaya M.V., Pavlov Ch.S., Tikhonov I.N. et al. Clinical recommendations for the diagnosis and treatment of non-alcoholic fatty liver disease of the Russian Society for the Study of the Liver and the Russian Gastroenterological Association. Ros Zhurn gastroenterol hepatol coloproctol. 2016; 26 (2): 1–20 [Ivashkin V.T., Mayevskaya M.V., Pavlov Ch.S., Tikhonov I.N. et al. Diagnostics and treatment of non-alcoholic fatty liver disease: clinical guidelines of the Russian Scientific Liver Society and the Russian gastroenterological association. Rus J Gastroenterol Gepatol Koloproktol. 2016; 26 (2): 1–20 (In Rus.)].
[100] Ivashkin V.T., Drapkina O.M., Maev I.V., Trukhmanov A.S. et al. The prevalence of nonalcoholic fatty liver disease in patients with outpatient practice in the Russian Federation: the results of the DIREG 2 study. Ros journal gastroenterol hepatol coloproctol. 2015; 6: 31–41 [Ivashkin V.T., Drapkina O.M., Mayev I.V., Trukhmanov A.S. et al. Prevalence of nonalcoholic fatty liver disease in out-patients of the Russian

Federation: DIREG 2 study results. Rus J Gastroenterol Gepatol Koloproktol. 2015; 6: 31–41 (In Rus.)].

[101] Vernon G., Baranova A., Younossi Z.M. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011; 34: 274–85.

[102] Li L., Liu D. W., Yan H.Y. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. Obes rev. 2016; 17 (6): 510–9.

[103] N.I. Volkova, M.I. Porkishyan. Therapeutic archive 02.2017god., Pp. 91-97

[104] N.A. Toktagulova Vestnik KRSU 2019, Volume 19.№ 5 67-72 pp.

[105] Wang Z., Klipfell E., Bennett B.J., Koeth R., Levison B.S., Dugar B. et al. Gut microflora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472 (7341): 57-63.

[106] Fedorova T. E., Efimenko N. V., Kaysinova A. S. Spa therapy of non-alcoholic fatty liver disease using drinking mineral waters of the Essentuki type // Problems of balneology, physiotherapy and physiotherapy. 2012; 6: 21-23.

[107] Alisi A, Cianfarani S, Manco M, Agostoni C, Nobili V (2011) Nonalcoholic fatty liver disease and metabolic syndrome in adolescents: pathogenetic role of genetic background and intrauterine environment // Ann Med. 2012 Feb; 44 (1): 29-40

[108] Du J, Ma YY, Yu CH, Li YM. Effect of pentoxifylline on nonalcoholic fatty liver disease: A meta-analysis // World J Gastroenetol 2014; 20 (2): 569-577.

[109] Alkhouri N, De Vito R, Alisi A, Yerian L, Lopez R, Feldstein AE, et al. Development and validation of a new histological score for pediatric nonalcoholic fatty liver disease. J Hepatol 2012; 57: 1312–1318.

[110] Bindels LB, Delzenne NM, Cani PD et al. Towards a more comprehensive concept for prebiotics. Nat Rev Gastroenterol Hepatol 2015; 12: 303-310.

[111] Dugan C. E., Aguilar D., Park Y. K., Lee J. Y., Fernandez M. L. Dairy consumption lowers systemic inflammation and liver enzymes in typically low-dairy consumers with clinical characteristics of metabolic syndrome // J Am Coll Nutr. 2016; 35: 255–261. Marchesini G, Mazzotti A. NAFLD incidence and remission: only a matter of weight gain and weight loss? J Hepatol 2015; 62: 15-17.

[112] Karimov M.M., Saatov Z.Z., Sobirova G.N. Digestive diseases // Guide for doctors. - Tashkent, 2015.S. 1-279.

[113] Nishide T, Ikeda K, Kawamura Y et al. Clinicopathological improvement of non-alcoholic steatohepatitis associated with weight loss during a 14-year follow-up period // Liver Int 2007; 27: 1422-1427.

[114] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Non-alcoholic fatty liver disease in lean individuals in the United States. Medicine 2012; 91: 319–327.

[115] Clinical recommendations of the EASL – EASD – EASO for diagnosis and treatment of nonalcoholic fatty liver disease. Journal of Hepatology 2016 Volume 64 1388–1402

[116] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. ClinGastroenterolHepatol 2015; 13: 643–654, e641 – e649; quiz e639 – e640.

[117] Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013; 5: 1544-1560.

[118] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine 2012; 91:319–327.