RESEARCH PAPER

Evaluation of Chronic Unpredictable Mild Stress on Albino Rats WSR To Liver Function Test And Liver Biopsy

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ABSTRACT

Background - During the past three decades the number of deaths due to CVDs has increased from 15.2% to 28.1% in India. There are many dietary and lifestyle factors are responsible for this rise. In ancient Indian medical science, Ayurveda, it is mentioned that psychological causes like *Chinta* (worry), *Bhaya* (Fear/Anxiety), *manasik trass* (mental tension) are responsible for heart disease. There is sharp increase in cases of anxiety and depression due to change lifestyle in present era. The present study is a part of broader study which evaluated the role of anxiety as a factor in the development of heart disease. Concomitantly the role of psychological factor *Bhaya* (Anxiety) in the development of liver disease was also evaluated.

Aims And Objectives – To evaluate the role of Ayurvedic psychological factor such as *Bhaya* (Anxiety) in the development of liver disease.

Material & Methods - Chronic unpredictable mild stress (CUMS) is the most elegant model for evaluation of anxiety in the rats as this model possesses construct, predictive and face validity in rats. Hence, this model is used in the present study. In CUMS process, animals were subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety-like symptoms in humans and also cause cognition impairment.

Liver biochemical parameters like SGOT, SGPT, Albumin, Bilirubin, are measured to know the effect of stressors on liver health. And accordingly, they are evaluated in both normal and disease control rats. Liver biopsy was also done at the end of the study for further evaluation.

Observation - It is observed that CUMS had generated the anxiety in rats with no significant change in liver biochemical parameters.

Result & Conclusion – Anxiety did not cause any significant effect on the function of the liver in experimental rats of the present study.

KEYWORDS – CUMS, LFT, Stress, Anxiety

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INTRODUCTION

Mental stress is the complex negative cognitive and emotional body response to external environmental stressors that exceed an individual's ability to cope with these demands. [1]

Hence, the measurement, standardisation, and reproducibility of the mental stressors on one particular scale is difficult. Several stressors may be used for the study. Stressors may be perceived or real threats to an individual, which are evaluated by the brain according to previous experience and current life. Accordingly, there may be an alteration in his or her physiological homeostasis [2] [3] [4]

The brain activates physiologic hemodynamic, neuroendocrine, and immune changes through the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis in response to the mental stress. The physiological changes induced by stress prepare the individual for fight or flight. Hence, the risk of a cardiovascular event induced by mental stress depends on a combination of external challenge and an individual's ability to deal with the stress, based on genetics and early and adult life experiences. [5] [6]

There are several research studies, as mentioned in the review of literature, which have proved that mental stress has affected liver health in various ways. Chronic unpredictable mild stress (CUMS) is the most elegant model for evaluation of anxiety, as this model possesses construct, predictive and face validity in rats. In CUMS process, animals were subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety-like symptoms in humans and also cause cognitive impairment. [7]

CUMS protocol was performed in a separate room, but the normal animal was left unchallenged. During the 7 weeks, animals were submitted to 6 different stressors: **tilted cage** (45°), **food and water deprivation**, **restricted access to food**, **exposure to empty bottle**, **24 h wet cage** (200ml of water in 100g of sawdust bedding), **continuous illumination**. These stressors are randomly scheduled over a week period and are repeated to maintain the aspect of unpredictability. Liver biochemical parameters like bilirubin, SGOPT, SGPT, Proteins were measured to know

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the effect of stressors on liver health. Liver biopsy was also done at the end of the study.

REVIEW OF LITERATURE

2.1 Stress and Alteration In Physiology

As per the study conducted by lrich-Lai & Herman in 2009, Stress leads to alteration in homeostatic response. [8]
As per the study conducted by Cohen, Janicki-Deverts, & Miller in 2007, stress negatively affect the cardiovascular, psychiatric, endocrine, and cancerous disorders. [9] [10]
As per the study conducted by Koolhaas et.al; in the year 2011, during stress, unpredictable and uncontrollable environmental threats pose a challenge to the natural defensive regulatory mechanism of the body. [11]

As per the study conducted by Goldstein & Kopin, in 2007, stress creates pathology through the involvement of multiple systems; particularly the sympathetic nervous and adrenocortical system. [12]

2.2 Stress and Liver Pathology

As per the study conducted by Racanelli & Rehermann in the year 2006, liver receives digested food, microbial products, damaged cells and toxic metabolites through portal vein which can induce high immune response in liver. [13]

As per the study conducted by Liu, Wang, & Jiang, in the year 2017, stress can alter the immune tolerance process exhibited by the liver. [14]

As per the study conducted by Kunkel et al., in the year 2000 and Nagano, Nagase et.al, in 2004, stress worsens the clinical symptoms and alters the hepatic biochemistry in patients with chronic viral B and C type of hepatitis. [15] [16]
As per the study conducted by Fukudo, Suzuki et.al., in 1989, stress worsens the alcoholic hepatitis. [17]

As per the study conducted by Elwing et.al., in 2006, stress worsens the nonalcoholic steatohepatitis. [18]
And as per the study conducted by Srivastava & Boyer, in 2010, stress also affects the autoimmune hepatitis. [19]

In the animal study conducted by Chida, Sudo, Motomura, & Kubo, in the year 2004; stress was found as the direct causes of liver injury. [20]
Contributing factors to liver injury under stress conditions can be studied under the following headings.

2.3 Hypoxia-reoxygenation

Stress causes reduction in hepatic blood flow, which is mediated by the hypothalamus–adrenal medulla–epinephrine axis. [21]

Hypoxia in hepatic tissue leads to the production of reactive oxygen species (ROS), in the hepatic cell mitochondria, causing endoplasmic reticulum stress and necrosis of hepatic cells. [22] [23]

2.4 Over-activation of Kupffer cells and oxidative stress

Reperfusion of the blood flow, activates Kupffer cells and endothelial cells to produce ROS and to secrete various inflammatory cytokines. [24] [25]

Oxidative stress also leads to the over-production of proinflammatory cytokines which activates the inflammatory cells such as neutrophils, monocytes, and lymphocytes. These activated inflammatory cells produce more reactive oxygen species causing oxidative stress and hepatic necrosis. [26]

2.5 Influx of gut-derived LPS and norepinephrine

Psychological stress decreases intestinal blood flow by the release of stress hormones, called neuropeptide Y, mediated by the combined effect of sympathetic activation and parasympathetic suppression. [27]
The reduction and reperfusion of blood flow in the gut leads to the secretion of high levels of norepinephrine in the gut that enters the liver. [28]
Norepinephrine in the liver can induce Kupffer cells to secrete the inflammatory cytokine TNF-α, leading to hepatic necrosis. [29]

Under stress conditions, factors like hypothalamus-secreted CRF, neuron-released acetylcholine and glucocorticoids from the adrenal cortex increase the permeability of the intestinal canal and make the portal vein prone to an influx of LPS or other antigens. [30] [31] [32]

2.6 Over-production of stress hormones and activation of the sympathetic nerve

Animal study showed that administration norepinephrine led to increase the production of two proinflammatory cytokines, TNF-α and IL-6, by Kupffer cells and hepatocytes. [33]
As per the animal study conducted by Nair & Bonneau, in the year 2006, stress leads to the activation of hypothalamus, pituitary and adrenal axis causing release of stress hormones like glucocorticoids. [34]

RESEARCH QUESTION

Whether Ayurvedokta *Bhaya* (Anxiety) acts as an aetiological factor for development of liver disease

HYPOTHESIS

NULL HYPOTHESIS (H1)

Bhaya (Anxiety) acts as an aetiological factor for development of liver disease

ALTERNATE HYPOTHESIS (H0)

Bhaya (Anxiety) does not acts as an aetiological factor for development of liver disease.

AIMS & OBJECTIVES

The present study, aims to study the aetiological factor ***Bhaya* (Fear/Anxiety)** as the cause for the development of liver disease.

MATERIAL & METHODOLOGY

3.1 Study Design

Center of Study – Dept of Roga Nidana & Vikrutvigyana, Government Ayurvedic College, Nanded And National Testing Centre, Pune
Duration of Study – 18 months after approval of synopsis.

Animal required for the Study
Species/Common name - **Albino Rat**
Weight **- 200-250 g**
Gender – **Male and Female**
Number to be used - **12**

3.2 Study Population And Sampling

Groups:

Animals were divided into 2 groups.

Groups (n = 6)	**Treatment**
Normal Control	No treatment
Disease Control	Chronic unpredictable mild stress induction

3.3 Data Collection & Instrumentation

The animals were subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety-like symptoms in humans and also cause cognition impairment.
CUMS protocol is performed in separate room. During the 7 weeks, animals were subjected to 6 different stressors:
1] tilted cage (45°),
2] **Tail Clamping for 3 minutes**,
3] **Cold swimming for 5 minutes at 4°C**
4] **exposure to an empty bottle**,
5] **24 h wet cage**,
6] **continuous illumination**.
These stressors were randomly scheduled over a one-week period and were repeated to maintain the aspect of unpredictability. At the end, the animals were sacrificed, and blood was collected for biochemical analysis. The organ was measured, and the tissues of the liver were given for histopathological analysis.

3.4 Assessment Criteria

Serum bilirubin and SGOT and SGPT indicate liver tissue damage, whereas Albumin serves as the marker of the synthetic function of the liver.
The normal reference range of various biochemical parameters using the experimental method is predetermined from various studies. [35] [36]

1. The normal reference range of Total **Bilirubin** in rats is 0.5 to 1.5mg/dl. Level. The level above than the normal range is considered significant rise.
2. The normal reference range of **SGOT** in rats is 5 to 60 IU/L. Level. The level higher than the normal range is considered a significant rise.
3. The normal reference range of **SGPT** in rats is 5 to 65 IU/L. Level. The level higher than the normal range is considered a significant rise.
4. The normal reference range of **Albumin** in rats is 4.5 to 5.5 g/dl. Level. The level higher than the normal range is considered a significant rise.
5. The normal reference range of random blood sugar in rats is 140 mg/dl. Level. The level higher than the normal range is considered a significant rise.

3.5 SYSTEM AND MANAGEMENT

1. Species	Rats
2. Strain	Wistar
3. Source	APT Testing and Research Pvt Ltd, Pune
4. Sex	Male, Female
5. Body weight range	200 g to 250 g
6. Identification	By unique identification number marked by writing on cage tag and by corresponding colour body markings.
7. No. of animals	6 animals were tested per group
8. Acclimatisation	The rats were housed in their cages for five days prior to the start of dosing in the experimental room after veterinary examination.
Husbandry	
9. Environmental Conditions	Room temperature maintained between $22 \underline{+} 3^0$C, relative humidity 50-60 % and illumination cycle set to 12 hours light and 12 hours dark.
10. Accommodation	Three rats per cage housed in polypropylene cages with stainless steel grill top, facilities for food and water bottle, and bedding of clean paddy husk.
11. Diet	Pelleted feed supplied by Supplier.
12. Water	Potable water passed through 'Aquaguard' water filter was provided ad libitum in plastic bottles with stainless steel sipper tubes.

OBSERVATION & RESULT

The results were analysed for statistical significance by two-way ANOVA and t-test, and were expressed as Mean + SEM by using Graphpad Prism 9 version.

Table No. 1 – Bilirubin (mg/dl)

Date:07/Feb/2024				**T.Bill**
Group	**Animal No**	**Sex**	**Marking**	**mg/dl**

NC	1	M	1	0.4
	2	M	2	0.4
	3	M	3	0.4
	4	F	1	0.5
	5	F	2	0.4
	6	F	3	0.5
MEAN				0.4
SD				0.0
DC	7	M	1	0.6
	8	M	2	0.3
	9	M	3	0.3
	10	F	1	0.6
	11	F	2	0.6
	12	F	3	0.5
MEAN				0.5
SD				0.1

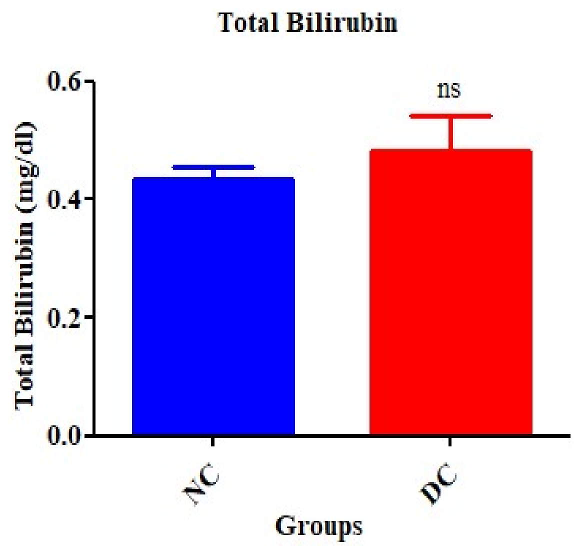


Table No. 2 – SGOT Value (IU/L)

Date:07/Feb/2024				SGOT
Group	Animal No	Sex	Marking	U/L
NC	1	M	1	54.0
	2	M	2	55.1
	3	M	3	52.4
	4	F	1	48.6
	5	F	2	51.5
	6	F	3	65.4
MEAN				54.5
SD				5.8
DC	7	M	1	104.8
	8	M	2	172.2
	9	M	3	123.3
	10	F	1	104.4
	11	F	2	112.4
	12	F	3	128.6
MEAN				124.3

SD				**25.4**

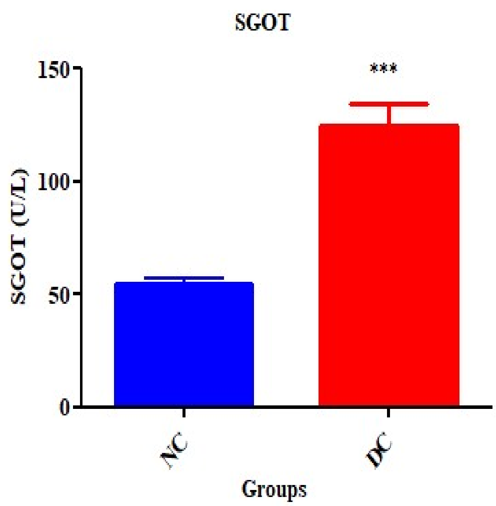


Table No. 3 – SGPT Values (IU/L)

Date:07/Feb/2024				**SGPT**
Group	**Animal No**	**Sex**	**Marking**	**U/L**
NC	**1**	**M**	**1**	64.2
	2	**M**	**2**	66.2
	3	**M**	**3**	57.9
	4	**F**	**1**	75.5
	5	**F**	**2**	47.7
	6	**F**	**3**	61.7
MEAN				**62.2**
SD				**9.2**
DC	**7**	**M**	**1**	102.0
	8	**M**	**2**	126.4
	9	**M**	**3**	111.0
	10	**F**	**1**	137.0
	11	**F**	**2**	127.0
	12	**F**	**3**	124.4
MEAN				**121.3**
SD				**12.6**

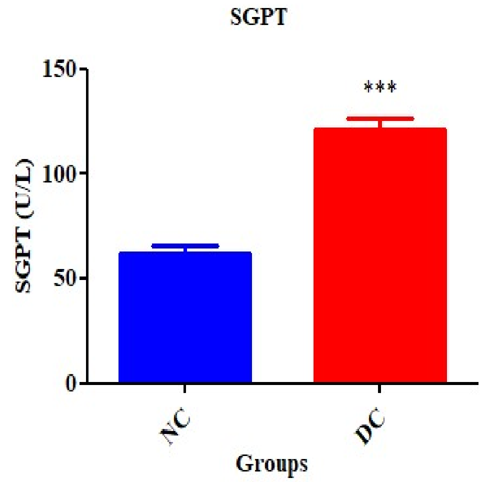


Table No. 4 – Albumin Values (g/dl)

Date:07/Feb/2024				ALB
Group	**Animal No**	**Sex**	**Marking**	**g/dl**
NC	1	M	1	4.6
	2	M	2	4.3
	3	M	3	3.8
	4	F	1	4.7
	5	F	2	4.7
	6	F	3	4.8
MEAN				**4.5**
SD				**0.4**
DC	7	M	1	4.1
	8	M	2	4.0
	9	M	3	2.2
	10	F	1	5.3
	11	F	2	5.3
	12	F	3	5.5
MEAN				**4.4**
SD				**1.2**

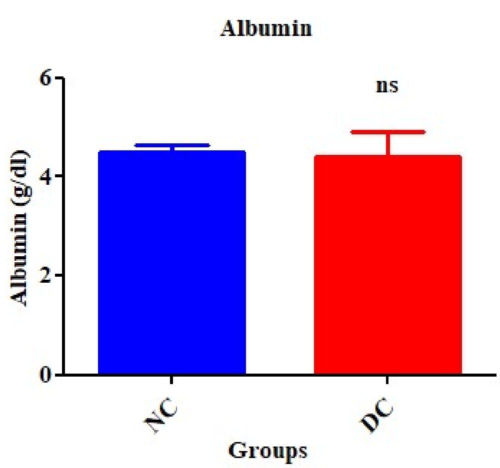


Table No. 5 – Glucose Value (mg/dl)

Date:07/Feb/2024	Glucose

Group	Animal No	Sex	Marking	mg/dl
NC	1	M	1	57.6
	2	M	2	70.0
	3	M	3	64.2
	4	F	1	40.9
	5	F	2	83.1
	6	F	3	74.5
MEAN				65.0
SD				14.7
DC	7	M	1	78.6
	8	M	2	157.7
	9	M	3	105.9
	10	F	1	167.3
	11	F	2	175.8
	12	F	3	161.4
MEAN				141.1
SD				39.3

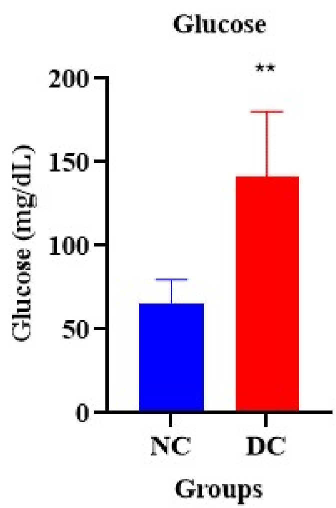
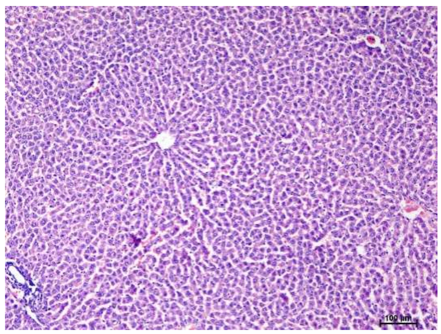


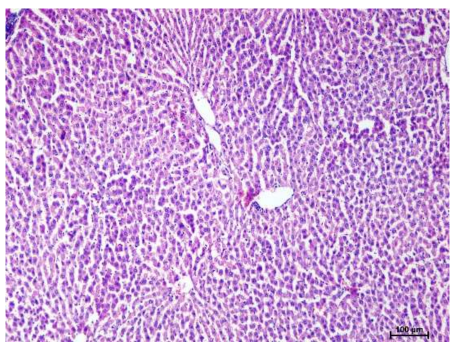
Table No. 6 – Histopathology of Liver

Histopathology Report of Toxicity Study			
Sr. N.	**Group /Slide Code**	**Histopathological observations 2. Liver**	**Overall Pathological Grade**
1	**NC-1M**	Normal hepatic parenchyma with normal histomorphology of hepatocytes with intact cellular features. The hepatocytes were arranged in hepatic strands around central vein. Hepatocytes appeared polygonal to round in shape with presence of round nucleus and intact cell borders. Absence of any metabolic or pathological cellular lesions in the liver.	**NAD**
2	**NC-2F**	Normal hepatic parenchyma with normal histomorphology of hepatocytes with intact cellular features. The hepatocytes were arranged in hepatic strands around central vein. Hepatocytes appeared polygonal to round in shape with presence of round nucleus and intact cell borders.	**NAD**

		Absence of any metabolic or pathological cellular lesions in the liver.	
3	**DC_3M**	Mild degenerative changes in the hepatic parenchyma with focal areas of cellular swelling and congested vasculature and focal areas of hemorrhages interstitial in hepatic parenchyma. Focal areas with granular cytoplasmic changes and loss of nucleus were noted.	**Mild (+2)**
4	**DC-4F**	Mild degenerative changes in the hepatic parenchyma with focal areas of cellular swelling and congested vasculature and focal areas of hemorrhages interstitial in hepatic parenchyma. Focal areas with granular cytoplasmic changes and loss of nucleus were noted.	**Mild (+2)**



Liver Biopsy – NCM



Liver Biopsy - DCM

DISCUSSION

Serum bilirubin and SGOT and SGPT indicates liver tissue damage whereas Albumin serves as the marker of the synthetic function of the river.

1. The normal reference range of Total **Bilirubin** in rats is 0.5 to 1.5mg/dl. Level. The level above than the normal range is considered significant rise.

The mean Total bilirubin in NC is 0.4 mg/dl whereas in DC group it is 0.5 mg/dl with standard deviation of 0.1 mg/dl which indicates slight increase in bilirubin value after subjecting the rats to the stressors but not significant.

2. The normal reference range of **SGOT** in rats is 5 to 60 IU/L. Level. The level higher than the normal range will be considered significant rise.

The mean SGOT in NC is 54.5 mg/dl whereas in DC group it is 124.3 mg/dl with standard deviation of 25.4 mg/dl which indicates slight increase in SGPT levels after subjecting the rats to the stressors but not significant.

3. The normal reference range of **SGPT** in rats is 5 to 65 IU/L. Level. The level higher than the normal range is considered significant rise.

The mean SGPT in NC is 62.2 mg/dl whereas in DC group it is 121.3 mg/dl with standard deviation of 12.6 mg/dl which indicates slight increase in SGPT levels after subjecting the rats to the stressors but not significant.

4. The normal reference range of **Albumin** in rats is 4.5 to 5.5 g/dl. Level. The level higher than the normal range is considered significant rise. The mean Albumin level in NC is 4.5 mg/dl whereas in DC group it is 4.4 mg/dl with standard deviation of 1.2 mg/dl which indicates slight decrease in protein levels after subjecting the rats to the stressors but not significant.

The normal reference range of random blood sugar in rats is 140 mg/dl. Level. The level higher than the normal range is considered significant rise. The mean Blood sugar in NC is 60.0 mg/dl whereas in DC group it is 141.1 mg/dl with standard deviation of 39.3 mg/dl which indicates slight increase in sugar levels after subjecting the rats to the stressors but not significant.

Liver biopsy report

Mild degenerative changes in the hepatic parenchyma with focal areas of cellular swelling and congested vasculature and focal areas of hemorrhages interstitial in hepatic parenchyma. Focal areas with granular cytoplasmic changes and loss of nucleus were noted. Findings in NC group was unremarkable.

SUMMARY & CONCLUSION

- In the DC group, levels of SGPT, SGOT, were slightly elevated as compared to the NC group but not significant.
- There was slight increase in sr. Bilirubin values in DC group as compared to NC group but not significant.
- There was slight decrease in protein levels in DC group after subjecting the rats to the stressors as compared to NC group but not significant.
- Histopathology of liver tissue showed no abnormalities in NC group. While in DC group mild degenerative changes in the hepatic parenchyma with focal areas of cellular swelling and congested vasculature and focal areas of hemorrhages interstitial in hepatic parenchyma was seen. Focal areas with granular cytoplasmic changes and loss of nucleus were also noted.
- The overall effect of stressors on liver function test was insignificant although minor degree of alteration was seen in DC group of animals. Hence, it can be stated that anxiety did not cause any significant effect on the function of liver in experimental rats of the present study.

Declarations

- **Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
- **Conflict of Interest:** None.

- **Ethical Approval:** - The research study was approved by the Institutional Ethics Committee of Government Ayurvedic College, Nanded (letter No.OW/IEC/685 dated 26-04-2022) as well as by National testing laboratory, APT Research Foundation, Pune (IAEC approval No. 32/2122 dated 26-02-2022). Guidelines set by national research council governing the care and use of laboratory animals were followed.
- **Use of AI in preparation of Manuscript :** - No help of AI is taken for preparing the manuscript.

REFERENCES

1. Cohen S., Tyrrell D.A.J., Smith A.P. Psychological Stress and Susceptibility to the Common Cold. N. Engl. J. Med. 1991; 325:606-612. doi: 10.1056/NEJM199108293250903.
2. Liu T.-K., Chen Y.-P., Hou Z.-Y., Wang C.-C., Chou J.-H. Non-invasive evaluation of mental stress using by a refined rough set technique based on biomedical signals. Artif. Intell. Med. 2014; 61:97–103. doi: 10.1016/ j. artmed.2014.05.001.
3. Katmah R., Al-Shargie F., Tariq U., Babiloni F., Al-Mughairbi F., Al-Nashash H. A Review on Mental Stress Assessment Methods Using EEG Signals. Sensors. 2021;21:5043. doi: 10.3390/s21155043.
4. Burg M.M., Vashist A., Soufer R. Mental stress ischemia: Present status and future goals. J. Nucl. Cardiol. 2005; 12:523-529. doi: 10.1016/ j. nuclcard.2005.06.085.
5. Brotman D.J., Golden S.H., Wittstein I.S. The cardiovascular toll of stress. Lancet. 2007; 370:1089-1100. doi: 10.1016/S0140-6736(07) 61305-1.
6. Steptoe A., Kivimäki M. Stress and cardiovascular disease. Nat. Rev. Cardiol. 2012; 9:360-370. doi: 10.1038/nrcardio.2012.45.
7. Lisa Pangemanan, Irwanto, Margarita M Maramis, Psychological dominant stressor modification to an animal model of depression with chronic unpredictable mild stress Vet World, 2023 Mar 24;16(3):595-600. doi: 10.14202/vetworld.2023.595-600.
8. Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. Nature Reviews Neuroscience, 10(6), 397–409. 10.1038/nrn2647 [DOI] [PMC free article] [PubMed] [Google Scholar]
9. Cohen, S. , Janicki-Deverts, D. , & Miller, G. E. (2007). Psychological stress and disease. JAMA, 298(14), 1685–1687. 10.1001/jama.298.14.1685 [DOI] [PubMed] [Google Scholar]
10. Reiche, E. M. V., Nunes, S. O. V., & Morimoto, H. K. (2004). Stress, depression, the immune system, and cancer. The Lancet. Oncology, 5(10), 617–625. 10.1016/S1470-2045(04)01597-9 [DOI] [PubMed] [Google Scholar]
11. Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., … Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. Neuroscience and Biobehavioral Reviews, 35(5), 1291–1301. 10.1016/j.neubiorev.2011.02.003 [DOI] [PubMed] [Google Scholar]
12. Goldstein, D. S., & Kopin, I. J. (2007). Evolution of concepts of stress. Stress, 10(2), 109–120. 10.1080/10253890701288935 [DOI] [PubMed] [Google Scholar]
13. Racanelli, V., & Rehermann, B. (2006). The liver as an immunological organ. Hepatology, 43(S1), S54–S62. 10.1002/hep.21060 [DOI] [PubMed] [Google Scholar]
14. Liu, Y.-Z., Wang, Y.-X., & Jiang, C.-L. (2017). Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience, 11, 316 10.3389/fnhum.2017.00316 [DOI] [PMC free article] [PubMed] [Google Scholar]
15. Kunkel, E. J., Kim, J. S., Hann, H. W., Oyesanmi, O., Menefee, L. A., Field, H. L., … Myers, R. E. (2000). Depression in Korean immigrants with hepatitis B and related liver diseases. Psychosomatics, 41(6),

472–480. 10.1176/appi.psy.41.6.472 [DOI] [PubMed] [Google Scholar]
16. Nagano, J. , Nagase, S. , Sudo, N. , & Kubo, C. (2004). Psychosocial stress, personality, and the severity of chronic hepatitis C. Psychosomatics, 45(2), 100–106. 10.1176/appi.psy.45.2.100 [DOI] [PubMed] [Google Scholar]
17. Fukudo, S., Suzuki, J., Tanaka, Y., Iwahashi, S., & Nomura, T. (1989). Impact of stress on alcoholic liver injury; a histopathological study. Journal of Psychosomatic Research, 33(4), 515–521. 10.1016/0022-3999(89)90013-5 [DOI] [PubMed] [Google Scholar]
18. Elwing, J. E., Lustman, P. J., Wang, H. L., & Clouse, R. E. (2006). Depression, anxiety, and nonalcoholic steatohepatitis. Psychosomatic Medicine, 68(4), 563–569. 10.1097/01.psy.0000221276.17823.df [DOI] [PubMed] [Google Scholar]
19. Srivastava, S., & Boyer, J. L. (2010). Psychological stress is associated with relapse in type 1 autoimmune hepatitis. Liver International, 30(10), 1439–1447. 10.1111/j.1478-3231.2010.02333.x [DOI] [PMC free article] [PubMed] [Google Scholar]
20. Chida, Y., Sudo, N., Motomura, Y., & Kubo, C. (2004). Electric foot-shock stress drives TNF-alpha production in the liver of IL-6-deficient mice. Neuro-immuno Modulation, 11(6), 419–424. 10.1159/000080153 [DOI] [PubMed] [Google Scholar]
21. Chida, Y., Sudo, N., & Kubo, C. (2006). Does stress exacerbate liver diseases? Journal of Gastroenterology and Hepatology, 21(1 Pt 2), 202–208. 10.1111/j.1440-1746.2006.04110.x [DOI] [PubMed] [Google Scholar]
22. Chandel, N. S., McClintock, D. S., Feliciano, C. E., Wood, T. M., Melendez, J. A., Rodriguez, A. M., & Schumacker, P. T. (2000). Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1α during hypoxia a mechanism of O_2 sensing. Journal of Biological Chemistry, 275(33), 25130–25138. 10.1074/jbc.M001914200 [DOI] [PubMed] [Google Scholar]
23. Xu, C. (2005). Endoplasmic reticulum stress: Cell life and death decisions. Journal of Clinical Investigation, 115(10), 2656–2664. 10.1172/JCI26373 [DOI] [PMC free article] [PubMed] [Google Scholar]
24. Carden, D. L., & Granger, D. N. (2000). Pathophysiology of ischaemia–reperfusion injury. The Journal of Pathology, 190(3), 255–266. 10.1002/(SICI)1096-9896(200002)190:3<255:AID-PATH526>3.0.CO;2-6 [DOI] [PubMed] [Google Scholar]
25. Teoh, N. C., & Farrell, G. C. (2003). Hepatic ischemia reperfusion injury: Pathogenic mechanisms and basis for hepatoprotection. Journal of Gastroenterology and Hepatology, 18(8), 891–902. 10.1046/j.1440-1746.2003.03056.x [DOI] [PubMed] [Google Scholar]
26. Mittal, M., Siddiqui, M. R., Tran, K., Reddy, S. P., & Malik, A. B. (2014). Reactive oxygen species in inflammation and tissue injury. Antioxidants & Redox Signaling, 20(7), 1126–1167. 10.1089/ars.2012.5149 [DOI] [PMC free article] [PubMed] [Google Scholar]
27. Matheson, P. J. , Wilson, M. A. , & Garrison, R. N. (2000). Regulation of intestinal blood flow. The Journal of Surgical Research, 93(1), 182–196. 10.1006/jsre.2000.5862 [DOI] [PubMed] [Google Scholar]
28. Aneman, A. , Medbak, S. , Watson, D. , & Haglind, E. (1996). Met-enkephalin and catecholamine release during feline intestinal ischemia-reperfusion. Shock, 5(6), 434–439. 10.1097/00024382-199606000-00008 [DOI] [PubMed] [Google Scholar]
29. Zhou, M. , Yang, S. , Koo, D. J. , Ornan, D. A. , Chaudry, I. H. , & Wang, P. (2001). The role of Kupffer cell alpha(2)-adrenoceptors in norepinephrine-induced TNF-alpha production. Biochimica Et Biophysica Acta, 1537(1), 49–57. [DOI] [PubMed] [Google Scholar]
30. Castagliuolo, I., Lamont, J. T., Qiu, B., Fleming, S. M., Bhaskar, K. R., Nikulasson, S. T., Pothoulakis, C. (1996). Acute stress causes mucin release from rat colon: Role of corticotropin releasing factor and mast cells. The American Journal of Physiology, 271(5 Pt 1), G884–892. 10.1152/ajpgi.1996.271.5.G884 [DOI] [PubMed] [Google Scholar]
31. Meddings, J. B., & Swain, M. G. (2000). Environmental stress-induced gastrointestinal permeability is mediated by endogenous glucocorticoids in the rat. Gastroenterology, 119(4), 1019–1028. 10.1053/gast.2000.18152 [DOI] [PubMed] [Google Scholar]
32. Santos, J., Saunders, P. R., Hanssen, N. P., Yang, P. C., Yates, D., Groot, J. A., & Perdue, M. H. (1999). Corticotropin-releasing hormone mimics stress-induced colonic epithelial pathophysiology in the rat. The American Journal of Physiology, 277(2 Pt 1), G391–399. 10.1152/ajpgi.1999.277.2.G391 [DOI] [PubMed] [Google Scholar]
33. Jung, B. D., Kimura, K., Kitamura, H., Makondo, K., Okita, K. , Kawasaki, M., & Saito, M. (2000). Norepinephrine stimulates interleukin-6 mRNA expression in primary cultured rat hepatocytes. Journal of Biochemistry, 127(2), 205–209. 10.1093/oxfordjournals.jbchem.a022596 [DOI] [PubMed] [Google Scholar]
34. Nair, A., & Bonneau, R. H. (2006). Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. Journal of Neuroimmunology, 171(1–2), 72–85. 10.1016/j.jneuroim.2005.09.012 [DOI] [PubMed] [Google Scholar]
35. Patel S, Patel S, Kotadiya A, Patel S, Shrimali B, Joshi N, Patel T, Trivedi H, Patel J, Joharapurkar A, Jain M. Age-related changes in hematological and biochemical profiles of Wistar rats. Lab Anim Res.

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36. Sex-specific reference intervals for Wistar albino rats: hematology and clinical biochemistryR. Vigneshwar1*, A. Arivuchelvan1, P. Mekala1 and K. Imayarasi2
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