Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 8 Issue 5 May 2025

Short Communication

Melatonin as a Future Prospective Therapy for Nonalcoholic Fatty Liver Disease by Targeting Hepatic Ferroptosis: A Short Communication'

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Received: April 10, 2025

Published: April 29, 2025

Abstract

Non-alcoholic fatty liver disease (NAFLD) portrays an escalating public health botheration with its prevalence along with an incidence escalating worldwide till6-35% in adults population. Earlier we reviewedhow Vitamin D, its receptors, allyl isothiocyanate, combination, of L-Carnitine (LC), Nicotinamide Ribose (NR), sodium dependent astragaloside IV and apical bile acid transporter (ASBT) or volixibat and silybin, probiotics and synbiotics, astragaloside IV, various prospective agents like Obeticholic Acid (OCA) etc, targeting gut microbiota. Of these other than silybin, probiotics and synbiotics, none of are getting used in clinical scenario. Thus need for generating innovative therapeutic targes for treating NAFLD/non alcoholic steatohepapititis (NASH), exists. Recent studies have pointed that ferroptosis, iron based cell demise has been tobe implicated in generating NAFLD. Additionally, Melatonin (Mel) displayed plausible advantages in avoidance of generation and of liver diseases. Here we have illustrated how Mel might be efficacious in the NAFLD treatment in a mouse model byhampering hepatic ferroptosis. Regarding mechanistic modes , MT2, however not MT1 was implicated in the actions of Mel . Moreover, Mel therapy hampered HFD or erastin activated ER stress and activated protein kinase A (PKA)/IRE1 signaling pathway. Coexpression of phosphorylated (p)- PKA and p-IRE1 got escalated by MT2 antagonist. Hampering agents of PKA and IRE1 respectively led to improvement of hepatic ferroptosis and activation of cyclic adenosine mono phosphate (cAMP)/IRE1 possessed the capacity of reverting Mel's actions on ferroptosis. Thereby pointing that exogenous Mel hampers hepatic ferroptosis in NAFLD by attenuating ERstress via MT2/ cAMP/PKA)/IRE1 pathway , that validates Mel attractive candidate agent therapy of hepatic ferroptosis in NAFLD. However in future human studies need to validate this.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD); Hepatic Ferroptosis; Melatonin (Mel); MT2; ER Stress

Introduction

Earlier we reviewed the etiopathogenesis (EP) of Non Alcoholic Fatty Acid Liver Disease (NAFLD) , non alcoholic steatohepapititis (NASH), along with its propagation to hepatocellular carcinoma (HCC) in addition to their therapies exhaustivelyon Vitamin D and its receptor in addition to allyl isothiocyanate (AITC, Like L-Carnitine (LC), Nicotinamide Ribose (NR) combination, as well as Apical Sodium dependent bile acid transporter (ASBT) or volixibat and silybin, probiotics and synbiotics, astragaloside IV, various prospective agents like Obeticholic Acid (OCA)etc, part of targeting gut microbiota etc [1-15]. Recently we comprehensively reviewed thepart of ''Combined use of cell death mechanisms as plausible therapeutic targets with canonical therapies for Breast Cancer concentrating on ferroptosis and cuproptosis apart from rest of cell [16]. Here we further highlight how targeting ferroptosis might become future prospective treatment.

Non alcoholic fatty liver disease (NAFLD) portrays an escalating public health botheration. The epidemiology as well as demographic characteristics simulate that of prevalence of obesity [17], in addition to its prevalence is escalating at a problematic rate specifically 34% currently in case of Asia [18], along with an incidence of 6-35% in reference to adults population worldwide [19]. The initiation of NAFLD takes place in the form of simple steatosis which might progress to non alcoholic steatohepapititis (NASH), along with ultimately towards fibrosis in addition to cirrhosis. At present, there is no availability of efficacious drug treatment for NAFLD. Scientific researchers need to work on the lacunae in knowledge for diminishing the risk load of NAFLD [20]. A significant kind of generation is that apart from cell demise kinds for instance apoptosis, necrosis as well as charring might be implicated in NAFLD correlated hepatocytotoxicity.

An accrual of inimical quantities of lipid peroxides stimulates the recently isolated kind of cell demise labelled as ferroptosis that control cell demise via an iron based way [21]. Iron metabolism conditions in addition to lipid peroxidation portray basically the major properties of ferroptosis [6]. The mechanistic modes in the controlling of ferroptosis implicate variable pathway for instance p53 pathway ii) glutamine pathway iii)Kelch-like-epichlorohydrin (ECH)-associated protein 1 (KEAP1))/nuclear factor erythroid-2-related factor-2 ((Nrf2) pathway [22]. In the last 2 decades the part of ferroptosis in the initiation of NAFLD has been highlighted . Hepatocyte ferroptosis might be detrimental for NAFLD by escalating the probability of hepatocytes getting swollen, inflammation as well as fibrosis, therefore escalating the rate of propagation of NAFLD to NASH [23,24]. Thereby hampering ferroptosis might work in the form of therapeutic target for NAFLD.

Ferroptosis is associated with endoplasmic reticulum (ER) stress. ER signaling activation has been displayed to modulate ferroptosis [25]. In the meantime the aberrant accrual of iron would further stimulate unfolded protein responses (UPR) , which gets followed by activation of ER stress. Of the three canonical molecular branches of UPR, inositol requiring enzyme (IRE1) portrays the maximum preserved ERstress sensor . Dimerization followed by autophosphorylation of IRE1 takes place subsequent to ERstress, which activates its kinase in addition to endoribonuclease actions [26]. Protein kinase R-like endoplasmic reticulum kinase (PERK) portrays one further canonical ERstress pathway. The importance of ERstress modulated byPERK in ERstress in ferroptosis has been well demonstrated [27], whereas modulated part of IRE1 continue to be uncharted. In toto greater requirement exists for evaluation of the association amongst hepatic ferroptosis along with ERstress in NAFLD.

Melatonin (Mel alias N- acetyl 5-methoxy-tryptamine) represents a robust antioxidant, has evoked considerable attention in view of its myriad of physiological actions in case of mammals, type1A (MT1) as well as type1B (MT2) membrane receptors are the major mechanistic modes through which Mel acts [28]. Scientific researchers have endorsed that Mel is a substantially good ferroptosis hampering agent, hampering ferroptosis in hippocampus [29], in addition to lungs [30]. The influence of Mel on hepatic ferroptosis has not been considerably evaluated. Earlier studies on the association amongst Mel along with NAFLD have been restricted. Taking into account that Mel aids in repression of oxidative stress (OS) in the liver. Guan., *et al*. [30], posited that Mel associated with hepatic ferroptosis in NAFLD. They generated a mouse model NAFLD stimulated by long term feeding of high fat diet (HFD). They observed that Mel therapy attenuated global metabolic abberations as well as hampered the propagation of NAFLD in mice (Figure 1).

Of greater significance, supplementation of Mel significantly resulted in improvement of HFD stimulated iron homeostasis abnormalities in the liver, inclusive of iron burden in addition to ferritin transportation abberations. Additionally, Mel abrogated HFD stimulated hepatic lipid peroxidation. The restorative part of exogenous Mel on hepatocyte ferroptosis was further found in case of palmitic acid (PA) or erastin treated HepG2cells (Figure 2).

For evaluating if Mel possessed the capacity of improving hepatic ferroptosis in NAFLD, Guan., *et al.* [30], initially explored iron homeostasis in the liver. Prussian blue iron staining consistently illustrated that the intracellular iron ions in the liver (blue or brown positive areas) were escalated by HFD. Nevertheless, intervening using Mel avoided the accrual of hepatic iron ions (Figure 3A-C). Subsequently, iron ions transportation was assessed. Mel reverted HFD-induced escalated protein quantities of transferrin recep-

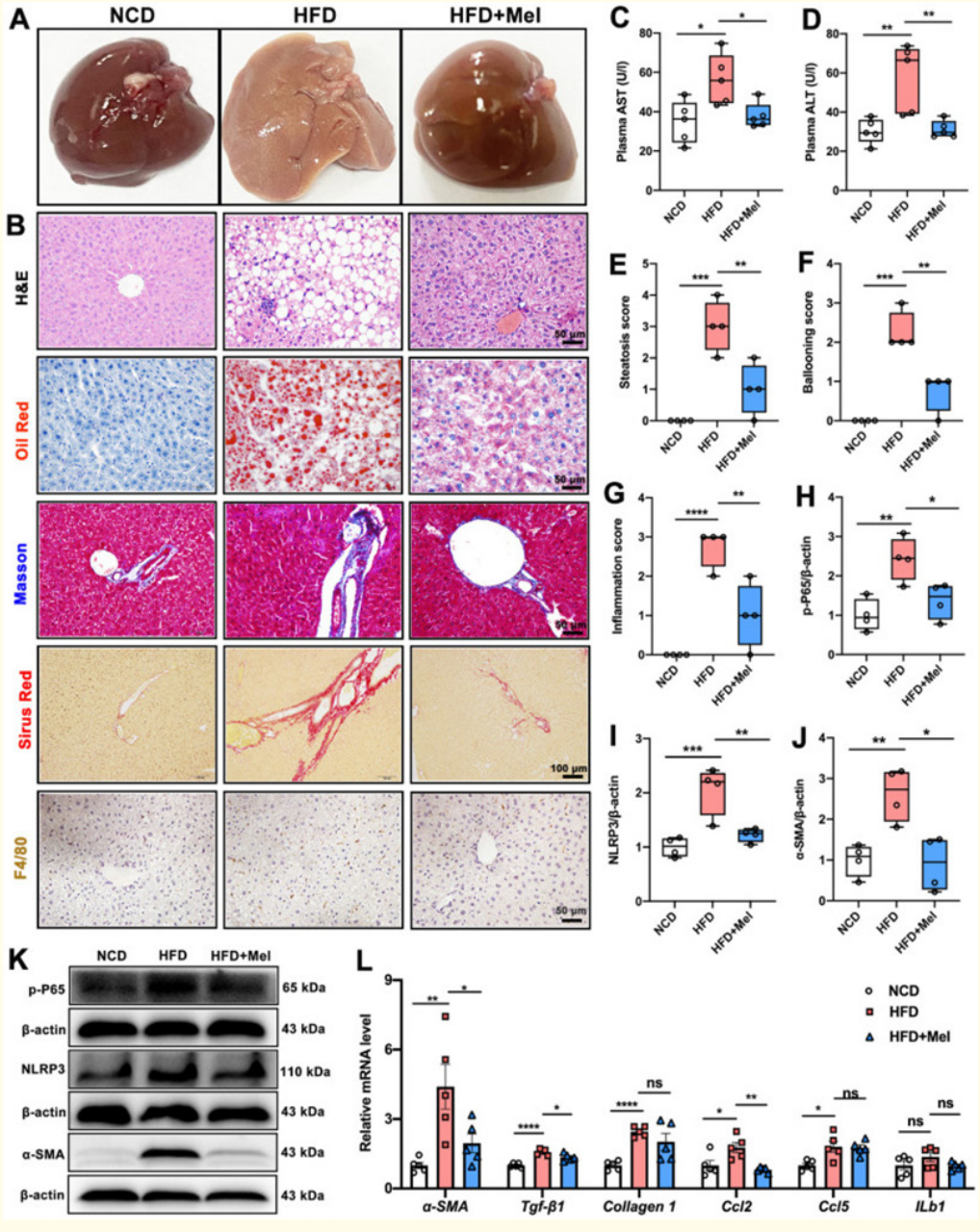

Figure 1: Courtesy reference no-31-The Mel inhibited the progression of NAFLD in mice induced by long-term HFD feeding. (A) Liver image. (B) Histology analysis including H&E (scale: 50 μm), Oil Red (scale: 50 μm), Masson (scale: 50 μm), Sirius Red (scale: 100 μm), and F4/80 IHC staining (scale: 50 μm). (C) Plasma AST (n = 5). (D) Plasma ALT (n = 5). (E) Steatosis score (n = 4). (F) Ballooning score (n = 4). (G) Inflammation score (n = 4). (H-K) Relative protein levels of p-P65, NLRP3, and α-SMA (n = 4). (L) Relative mRNA levels of *α-SMA, Tgf-β1, Collagen1, Ccl2, Ccl5*, and ILb1 (n = 5). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. *p < 0. 05, **p < 0. 01, ***p < 0. 001, and ****p < 0. 0001.

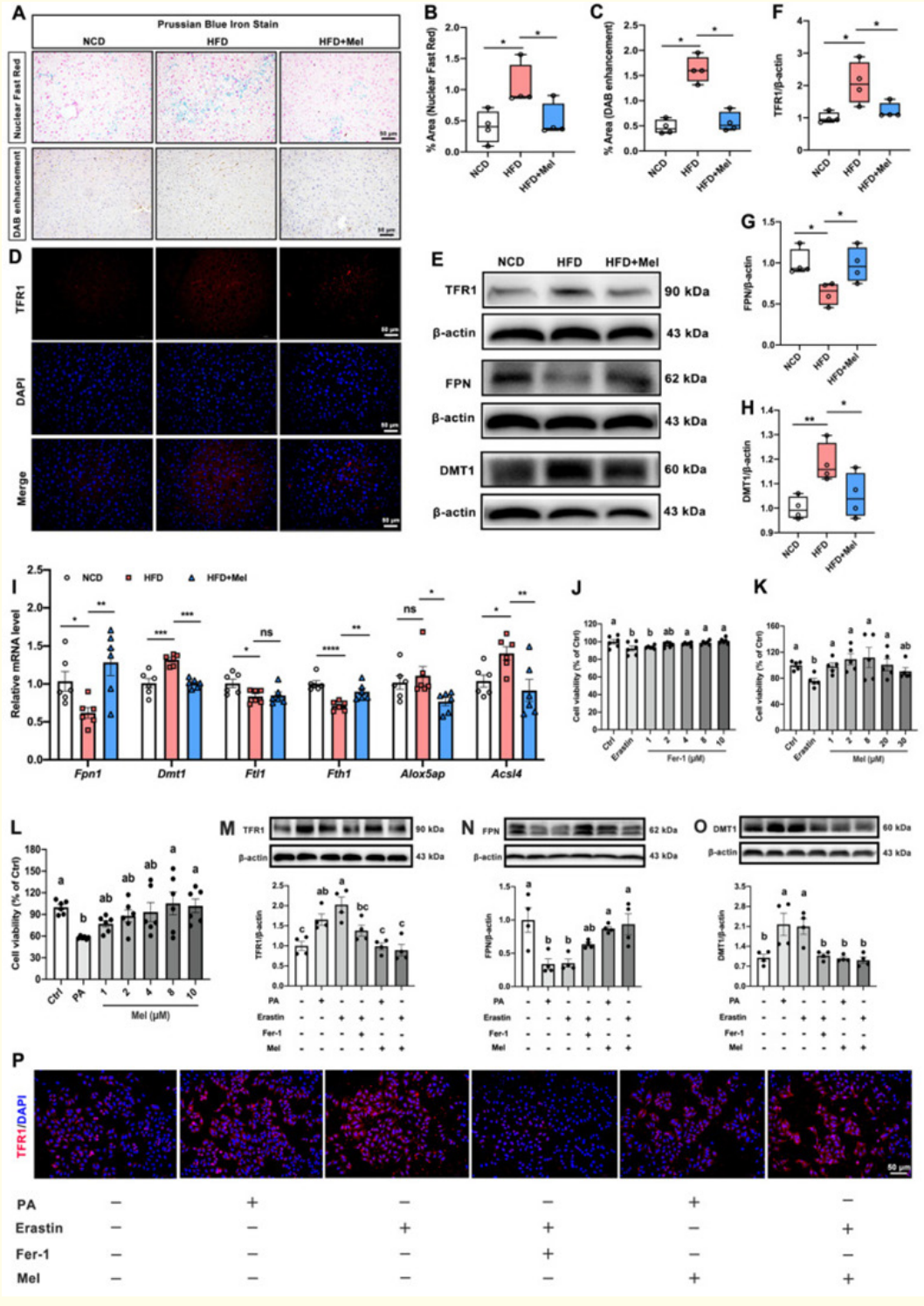

Figure 2: Courtesy reference no-31-Mel alleviated hepatic iron homeostasis dysregulation in NAFLD. (A) Prussian blue iron staining (scale: 50 μm). (B) % area of Prussian blue staining with Nuclear Fast Red (n = 4). (C) % area of Prussian blue staining with DAB enhancement (n = 4). (D) Immunofluorescence analysis of TFR1 in the liver (scale: 50 μm). (E-H) Relative protein levels of TFR1, FPN, and DMT1 in the liver (n = 4). (I) Relative mRNA levels of *Fpn1, Dmt1, Ftl1, Fth1, Alox5ap*, and *Acsl4* in the liver (n = 6). (J-L) Cell viability (% of Ctrl) (n = 5-6). (M-O) Relative protein levels of TFR1, FPN, and DMT1 in HepG2 cells (n = 4). (P) Immunofluorescence analysis of TFR1 in HepG2 cells (scale: 50 μm). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. Values without the same superscript letter were significantly different ($p < 0.05$); those with the same letter do not differ significantly ($p \geq 0.05$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

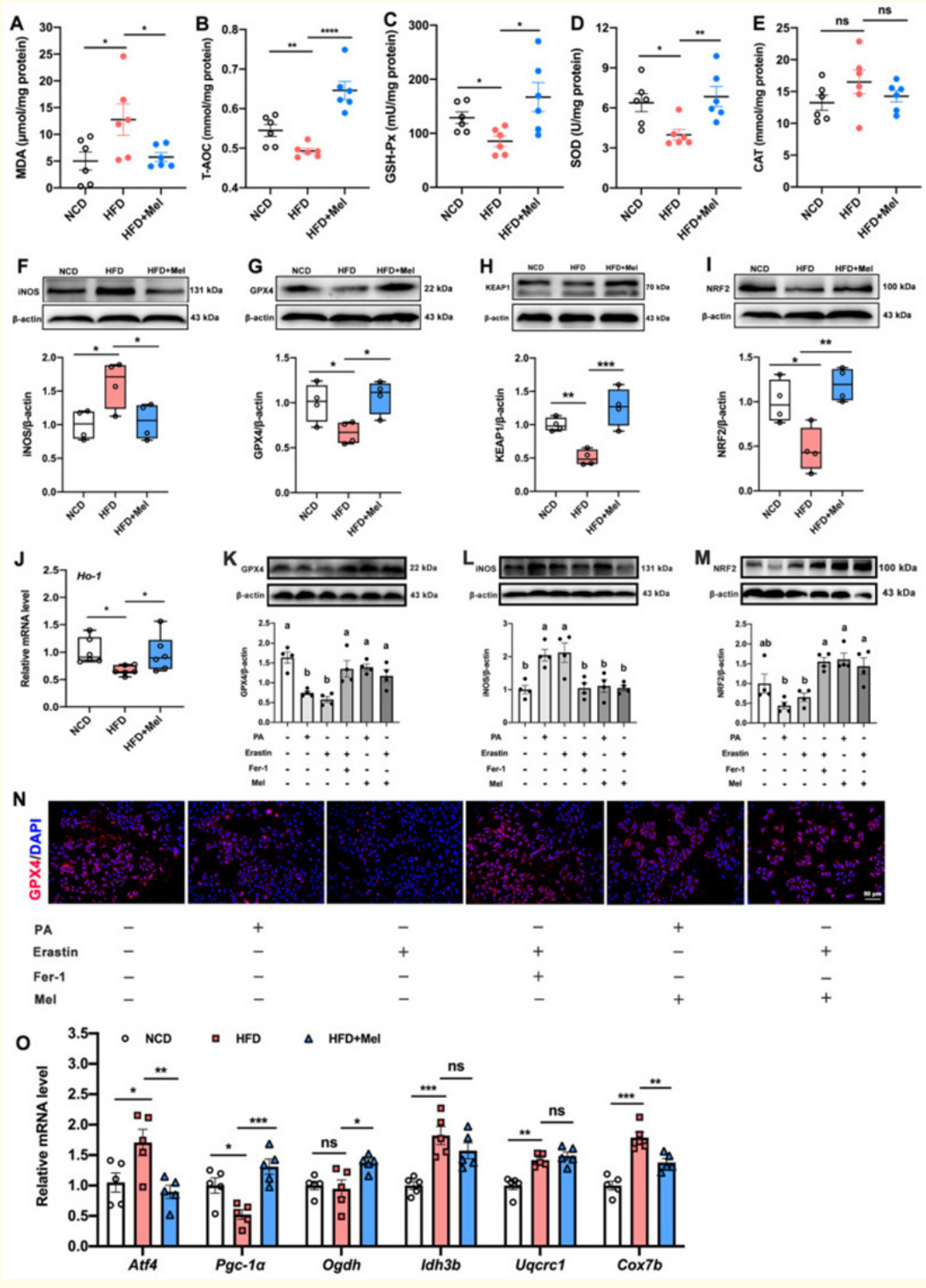

Figure 3: Courtesy reference no-31-Mel alleviated hepatic lipid peroxidation and mitochondrial dysfunction in NAFLD. (A-E) The levels of MDA, T-AOC, GSH-Px, SOD, and CAT in the liver (n = 6). (F-I) Relative protein levels of iNOS, GPX4, KEAP1, and NRF2 in the liver (n = 4). (J) Relative mRNA levels of Ho-1 in the liver (n = 6). (K-M) Relative protein levels of GPX4, iNOS, and NRF2 in HepG2 cells (n = 4). (N) Immunofluorescence analysis of GPX4 in HepG2 cells (scale: 50 μm). (O) Relative mRNA levels of *Atf4, Pgc-1α, Odgh, Idh3b, Uqcrc1*, and *Cox7b* in the liver (n = 5). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. Values without the same superscript letter were significantly different ($p < 0.05$); those with the same letter do not differ significantly ($p \geq 0.05$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

tor 1 (TFR1, Figure 3D-F) as well as divalent metal transporter 1 (DMT1, Figure 3E, H) in addition to diminished in ferroportin (FPN, Figure 3E, G) protein in the liver. Additionally, Mel recuperated hepatic mRNA quantities of *Fpn1*, *Dmt1*, ferritin heavy chain 1 (Fth1), along with acyl-CoA synthetase long-chain family member 4 (*Acsl4*) (Figure 3I) (Figure 3).

Furthermore, they grew HepG2 cells as well as exposed them to Erastin (1 μM)/palmitic acid (PA, 250 μM) with/without Mel (1 μM)/Ferrostatin-1 (Fer-1, 2 μM) for greater evaluation of the working of Mel in avoidance of ferroptosis hepatocytes. Fer-1 in addition to Mel possessed the capacity of protecting Erastin-/PA-induced cell death in hepatocytes (Figure 3J-L). Intriguingly, PA had the capacity of simulating the actions of Erastin, stimulating an escalation of TFR1 along with DMT1 as well as a diminished quantities of FPN proteins significantly in HepG2 cells. Conversely Mel pretreatment had the capacity of portraying the actions of Fer-1, recuperating iron transporter abnormalities brought on by PA in addition to Erastin (Figure 3M-P). Such outcomes pointed that Mel possessed the capacity of alleviating hepatic iron homeostasis along with thereby resulting in improvement of iron overload.

One more hallmark of ferroptosis is lipid peroxidation. In contrast to NCD, HFD possessed substantially greater quantities of malondialdehyde (MDA) (Figure 4A) as well as lower quantities of total- antioxidant capacity (T-AOC) (Figure 4B), glutathione peroxidase (GSH-Px), (Figure 4C), in addition to superoxide dismutase (SOD), (Figure 4D) in the liver. Nevertheless, such alterations got reverted by Mel supplementation. Apart from that, Mel drastically diminished the HFD-stimulated escalation of iNOS, as well as reduced GPX4, KEAP1, NRF2, along with Ho-1 in the liver (Figure 4F-J). *In vitro* studies were commensurate in corroborating Mel treatment was capable of improving PA-/Erastin stimulated - lipid peroxidation in hepatocytes (Figure 4K-N). In view of the lipid peroxidation event is correlated with mitochondrial impairment, they further explored a cascade of genes involved in mitochondrial working. Mitochondrial oxidative gene (activating transcription factor 4 ATF4]), mitochondrial oxidative phosphorylation gene (Cox7b, [cytochrome c oxidase subunit VIIb]), in addition to mitochondrial biogeneration gene (Pgc-1α peroxisome proliferator-activated receptor-γ coactivator-1α]) were significantly restored by Mel treatment (Figure 4O) (see Figure 4).

Membrane receptors MT1 or MT2 are presumed to be the major mechanistic modess through which Mel works . The manner displayed in Figure 5A, MT1 as well as MT2 were broadly expressed on the liver cell membrane. There was no statistically significant variation amongst MT1 expression (Figure 5B, C). Mel was nevertheless capable of restoring the HFD- diminished MT2 protein quantity (Figure 5B, D). In agreement with the *in vivo* observations, PA, Erastin, or Mel therapy had no action on the protein quantity of MT1 (Figure 5E). Conversely, Mel pretreatment counteracted the diminished MT2 stimulated by Erastin (Figure 5F). Thereby, Mel's defense against hepatic ferroptosis might be based greater on MT2 in contrast to MT1. Additionally, for excluding MT1 involvement , they further treated HepG2 cells with an MT1 hamperor (Luzindole). The manner anticipated, Luzindole was not capable of blocking Mel's action on PA stimulated - alterations in GPX4, FPN, TFR1, KEAP1, in addition to NRF2 (Figure 5G-L). However, 4P-PDOT pretreatment abolished Mel's relieving impact on Erastin-stimulated induced ferroptosis (Figure 5M-S). Thereby, Mel might result in improvementof hepatic ferroptosis via MT2 (see Figure 5).

MT2 portrays a G- protein coupled receptor (GPCR). PKA is a cAMP based protein kinase that phosphorylated IRE1 at the Ser743 region.

In reference to mechanistic modes , MT2, however not MT1 was implicated in the actions of Mel.

Hepatocyte ER stress is plausiblly implicated in ferroptosis in the liver. Subsequently , they evaluated the action of ER stress on hepatic ferroptosis along with the part of Mel in it. The germane mRNA expression quantities of X-box binding protein 1 (XBP1), spliced XBP1 (XBP1s), as well as prototypical XBP1- UPR target genes (dnaJ heat shock protein family member B9 [Dnajb9], er-degradation-enhancing α-mannosidase-like protein 1 [Edem1], SEC61 transposon α1 subunit [Sec61a1], bound immunoglobulin [Bip], as well as CCAAT/enhancer-binding protein homologous protein [Chop]) were significantly upregulated in the liver induced by HFD, whereas Mel possessed the capacity of restoring them to the NCD quantities (Figure 6A). Akin to that, Mel was capable of reverting the expression of GRP78 Bip, p-PKA, along with p-IRE1 proteins escalated by HFD (Figure 6B-E). Such outcomes pointed that the ER stress pathway was activated in NAFLD, as well as Mel possessed the capacity of easing it (see Figure 6).

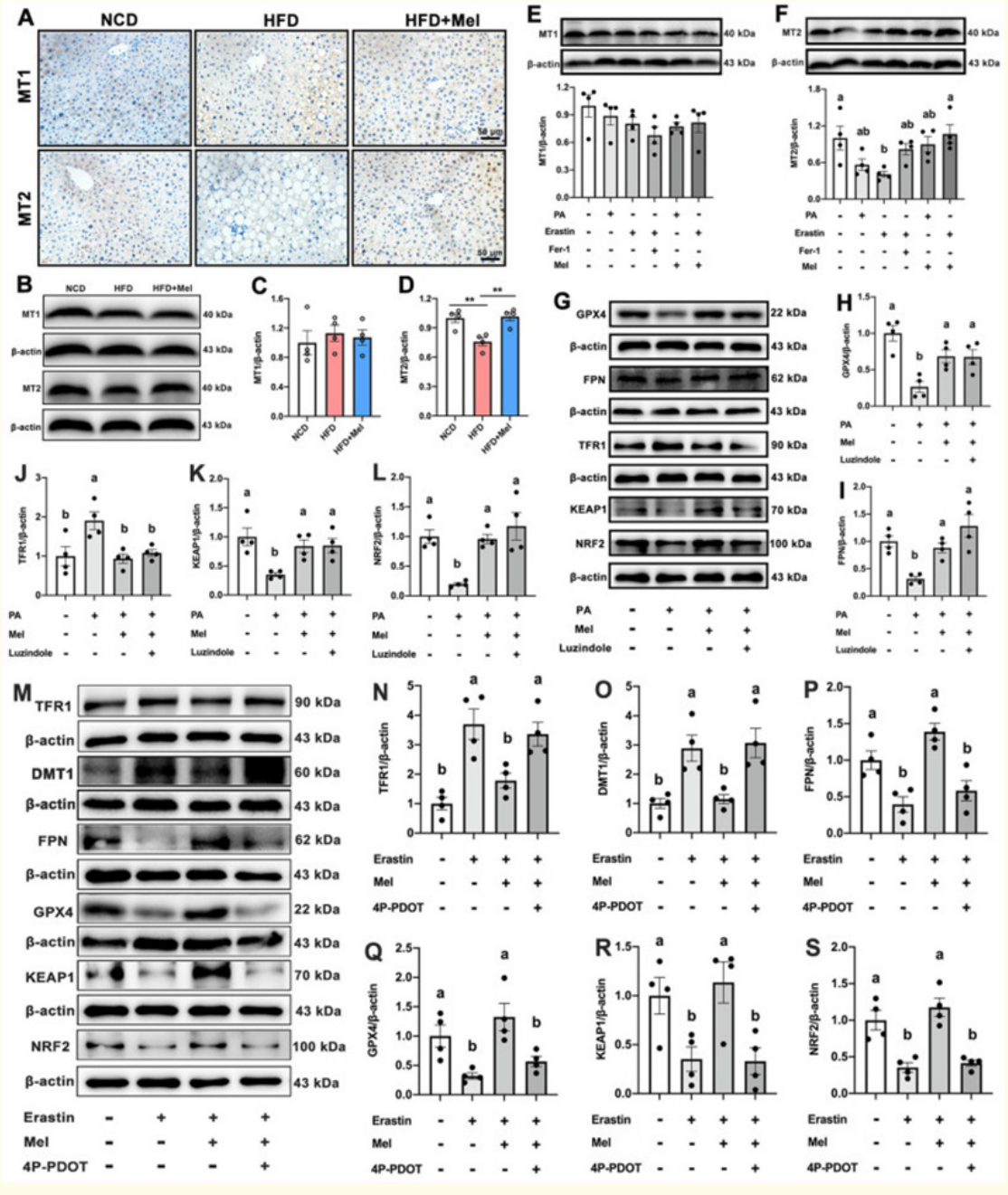

Figure 4: Courtesy reference no-31-Mel improved hepatic ferroptosis through MT2. (A) IHC analysis of MT1 and MT2 in the liver (scale: 50 μm). (B-D) Relative protein levels of MT1 and MT2 in the liver (n = 4). (E-F) Relative protein levels of MT1 and MT2 in HepG2 cells (n = 4). (G-L) Relative protein levels of *GPX4, FPN, TFR1, KEAP1*, and *NRF2* in *HepG2* cells treated with PA, Mel, or Luzindole (n = 4). (M-S) Relative protein levels of *TFR1, DMT1, FPN, GPX4, KEAP1,* and *NRF2* in *HepG2* cells treated with Erastin, Mel, or 4P-PDOT (n = 4). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. Values without the same superscript letter were significantly different ($p < 0.05$); those with the same letter do not differ significantly ($p \geq 0.05$). **$p < 0.01$.

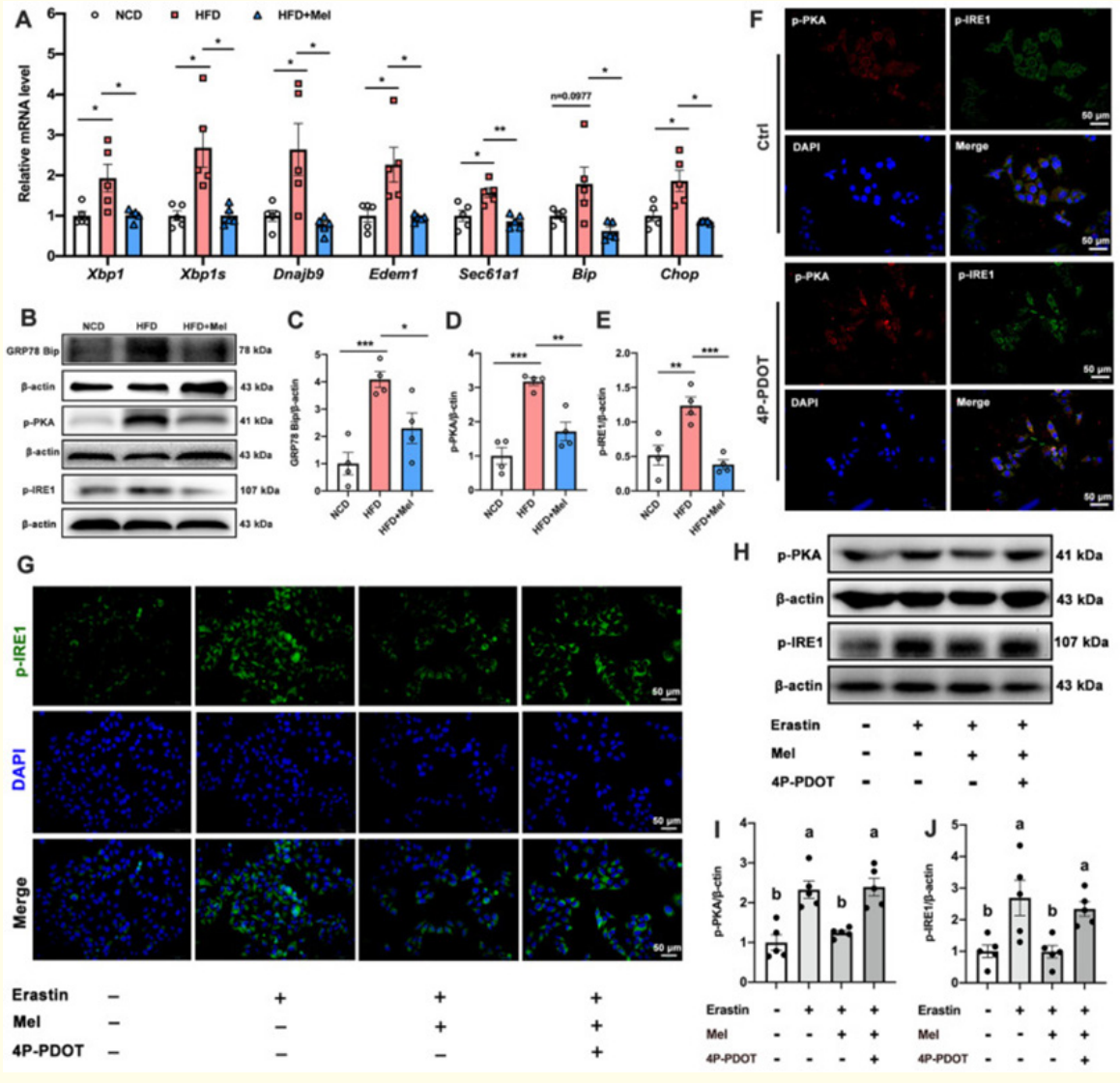

Figure 5: Courtesy reference no-31-Courtesy reference no-16-Mel/MT2 inhibited hepatic ER stress induced by HFD or Erastin. (A) Relative mRNA levels of *Xbp1, Xbp1s, Dnajb9, Edem1, Sec61a1, Bip,* and Chop in the liver (n = 5). (B-E) Relative protein levels of GRP78 Bip, p-PKA, and p-IRE1 in the liver (n = 4). (F) Co-expression of p-PKA (red), p-IER1 (green), and DAPI (blue) in HepG2 cells treated with or without 4p-PDOT (scale: 50 μm). (G) Immunofluorescence analysis of p-IER1 in HepG2 cells (scale: 50 μm). (H-J) Relative protein levels of p-PKA and p-IRE1 in HepG2 cells (n = 5). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. Values without the same superscript letter were significantly different ($p < 0.05$); those with the same letter do not differ significantly ($p \geq 0.05$). *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

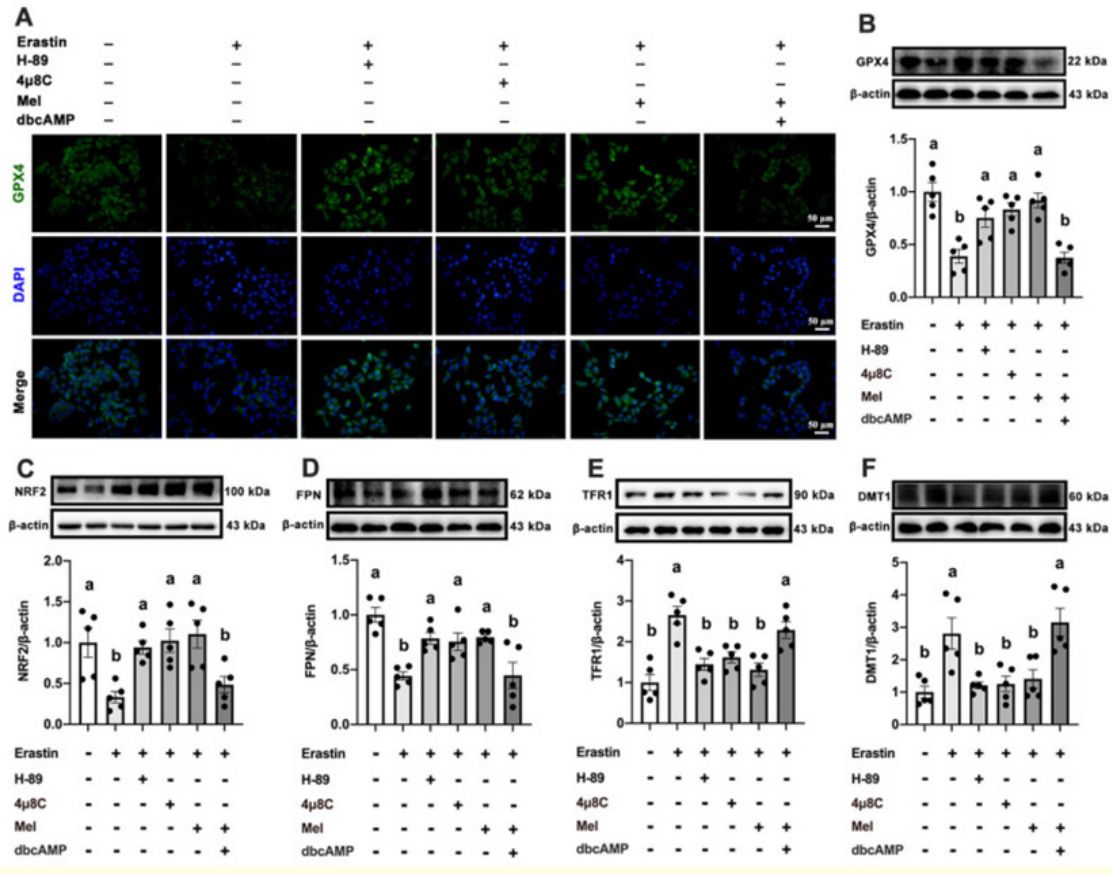

Figure 6: Courtesy reference no-31Mel ameliorated hepatic ferroptosis by inhibiting ER stress through the MT2/cAMP/PKA/IRE1 signaling pathway. (A) Immunofluorescence analysis of GPX4 in HepG2 cells treated with Erastin, H-89, 4μ8C, Mel, or dbcAMP (scale: 50 μm). (B-F) Relative protein levels of *GPX4, NRF2, FPN, TFR1, and DMT1 in HepG2* cells (n = 5). The results are presented as the mean ± SEM. Differences were assessed by one-way ANOVA. Values without the same superscript letter were significantly different ($p < 0.05$); those with the same letter do not differ significantly ($p \geq 0.05$).

Discussion and Conclusions

ER stress is believed to be a sequel of ferroptosis, whose activation might further aid in ferroptosis. ER stress stimulates unique cell demise designs via the three main transmembrane receptors on the ER membrane [IRE1α, PERK, as well as activating transcription factor 6 (ATF6)]. Subsequently , Guan., *et al.* [16], further evaluated the part of Mel in the association amongst hepatic ferroptosis in addition to ER stress. Mel recuperated the hepatic expression quantities of GRP78 Bip, p-PKA, p-IRE1, Xbp1, Xbp1s, as well as paradigmatic binding protein1 (XBP1) based - UPR target genes escalated by HFD. *In vitro*, Mel/MT2 significantly inhibited Erastin-activated p-PKA along with p-IRE1 (Ser724). When ER occurs, IRE1 undergoes oligomerization in addition to trans autophosphorylation on segregating from GRP78 Bip in the ER lumen, leading to the activation of endoribonuclease along with cleavage of its target gene, Xbinding protein1 (XBP1) mRNA, as well as following unfolded UPR. Studies already present on ER stress in addition to ferroptosis basically have concentrated on the PERK pathway. Here Guan., *et al.* [30], illustrated that Mel/MT2 signals possess the capacity of influencing the IRE1 pathway in the liver. Mel treatment hampers IRE1, which is believed to improve acute pancreatitis. , kidney injury, as well as osteoarthritis. Thereby, Mel's hampering of IRE1 might further aid in the attenuation of hepatic ferroptosis. MT2 is a G protein-coupled receptor, along with its downstream

signaling molecules, for instance cAMP/PKA, portray one of the substantially studied receptor families. Guan., *et al.* [30], observed that p-PKA in addition to p-IRE1 were co-expressed in the liver cytoplasm, which was escalated by 4P-PDOT. Earlier studies illustrated that activating IRE1α phosphorylation via the PKA led to hepatic ER stress. Thereby, Guan., *et al.* [30], further evaluated the part of PKA/IRE1-modulated ER stress in ferroptosis. Hampering of PKA in addition to IRE1 significantly ameliorated Erastin- stimulated hepatocyte ferroptosis, whereas the cAMP/PKA agonist blocked the improvement action of Mel. Taken together, such observations pointed that the ER stress-mediated by the MT2/cAMP/PKA/IRE1 signaling pathway is crucial for hepatic ferroptosis, which is also the main pathway for Mel to play an improving role.

Bibliography

1. Kulvinder Kochar Kaur., *et al.* "A Mini Review on Development of Newer Therapies for Non Alcoholic Fatty Acid Liver Disease with Emphasis on Vitamin D and its Receptor and Allyl Isothiocyanate (AITC)". *Acta Scientific Nutritional Health* 3.12 (2019): 1-5.

2. Kulvinder Kochar Kaur., *et al.* "An Update on Further Progression of NAFLD, NASH with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin as Alternatives". *The International Journal of Clinical and Medical Cases* 3.3 (2020): 138.

3. Kulvinder Kochar Kaur., *et al.* "Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review". *Advances in Obesity, Weight Management and Control* 9.1 (2019): 21-28.

4. Kulvinder Kochar Kaur., *et al.* "Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? - A Systematic Review". *Journal of Physiology and Biochemistry* 9 (2020): 257.

5. Kulvinder Kochar Kaur., *et al.* "Rosmarinic Acid-A New Hope for Liver Diseases Like Cirrhosis, Hepatocellular Carcinoma-NeedsTranslation to Humans". *EC Endocrinology and Metabolic Research* 4.6 (2019): 289-301.

6. Kulvinder Kochar Kaur., *et al*. "How do we apply advances in knowledge of Hepatic Macrophages in treating Liver Diseases especially non alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepapititis(NASH), with the increasing incidence of Diabesity-A Systematic Review". *EC Endocrinology and Metabolic Research* (2020).

7. Kulvinder Kochar Kaur., *et al.* "Mechanisms that associate extension of Nonalcoholic fatty liver diseases(NAFLD) to NASH (Non-alcoholic steatohepatitis) and further progressing to cirrhosis and Hepatocellular carcinoma(HCC) in addition to few proposed biomarkers for poor prognosis". *Journal of Gynecology* 1.16 (2021): 1-18.

8. Kulvinder Kochar Kaur., *et al.* "How can we optimize therapy of Non-Alcoholic Fatty Acid Liver Disease-A Short Communication on role of Astragaloside IV and other prospective agents". *Clinical Research and Clinical Case Reports* 1.3 (2021): 1-4.

9. Kulvinder Kochar Kaur., *et al.* "Paradoxical Additional Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection-A Mini-review". *Acta Scientific Gastrointestinal Disorders* 4.7 (2021): 15-26.

10. Kulvinder Kochar Kaur M., *et al.* "An update on management of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepapititis-Is the time ripe for achieving resolution of NAFLD and NASH soon". *Journal of Endocrinology Research* 3.2 (2021): 44-60.

11. Kulvinder Kochar Kaur., *et al.* "The Association of Non-Viral Liver Diseases from NAFLD to NASH to HCC with the Pandemic of Obesity ,Type 2 Diabetes, or Diabesity and Metabolic Syndrome -Etiopathogenetic Correlation along with Utilization for Diagnostic and Therapeutic Purposes-A Systematic review''. *Journal of Endocrinology Research* 3.2 (2021): 10-34.

12. Kulvinder Kochar Kaur, ., *et al.* "An update on the etiopathogenesis of NAFLD including Organokines for early diagnosis and improvement of management and preventing early HCC development: A narrative review". *Liver Research - Open Journal* 4.1 (2023): 18-41.

13. Kulvinder Kochar Kaur., *et al.* "An update on Targeting Gut Microbiota (GM) for Avoidance of Metabolic dysfunction associated steatohepatitis propagation to Hepatocellular Carcinoma-A Narrative Review". *MAR Clinical Case Reports* 5 (2023): 9.

14. Kulvinder Kochar Kaur., *et al.* "Combined use of Cell Death Mechanisms as plausible therapeutic targets with canonical therapies for Breast Cancer: potentially decreasing dose, toxicity, expenditure and improved survival -A narrative review". under review (2023).

15. Younossi Z., *et al.* "Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention". *Nature Reviews Gastroenterology and Hepatology* 15 (2018): 11-20.

16. Yip T., *et al.* "Asian perspectives on NAFLD associated HCC". *Journal of Hepatology* 76 (2022): 72-34.

17. Ji J., *et al.* "Gut microbiome and ferroptosis in MAFLD". *Clinical and Translational Gastroenterology* 11 (2023): 174-187.

18. Zhou J., *et al.* "Epidemiological features of NAFLD from 1999 to2018 in China". *Hepatology* 71 (2020): 1851-1864.

19. Tang D., *et al.* "Ferroptosis: mechanisms, and health implications". *Cell Research* 31 (2021): 107-125.

20. Chen X., *et al.* "Characteristics and biomarkers of ferroptosis". *Frontiers in Cell and Developmental Biology* 9 (2021): 637162.

21. Zheng J and Conrad M. "The metabolic underpinnings of ferroptosis". *Cell Metabolism* 39 (2020): 920-937.

22. Wu S., *et al.* "Macrophage extracellular traps aggravate iron load related liver ischaemia reperfusion injury". *British Journal of Pharmacology* 169 (2013): 92232.

23. Qi J., *et al.* "Ferroptosis affects the progression of non alcoholic steatohepapititis viathe modulation of lipid peroxidation- mediated cell death in mice". *The American Journal of Pathology* 190 (2020): 68-91.

24. Zhang X., *et al.* "Resveratrol protected acrolein induced ferroptosis and insulin secretion dysfunction via ER stress related PERKpathway inMIN6cells". *Toxicology* 465 (2022): 153048.

25. Jiang D., *et al.* "Targeting the IRE1/XBP1 branches of the unfolded protein response in human diseases". *Seminars in Cancer Biology* 33 (2015): 45-56.

26. Wei R., *et al.* "Taginin C induces ferroptosis through PERK-Nrf2-HO signaling pathway in colorectal cancer cells". *International Journal of Biological Sciences* 17 (2021): 2703-2717.

27. Liu J., *et al.* "MT1 and MT2 membrane receptors:a therapeutic perspective". *Annual Review of Pharmacology and Toxicology* 56 (2016): 361-383.

28. Wang X., *et al.* "Melatonin alleviates acute ,sleep deprivation induced memory loss in mice by supressing hippocampal ferroptosis". *Frontiers in Pharmacology* 12 (2021): 708645.

29. Guohua F., *et al.* "Melatonin protects s against PM 2.5 induced lungs injury by inhibiting ferroptosis of lung epithelial cells in a Nrf2 dependent manner". *Ecotoxicology and Environmental Safety* 223 (2021): 112588.

30. Guan Q., *et al.* "Melatoninameliorates hepatic ferroptosis in NAFLD by inhibiting ERstress viathe MT2/cAMP/PKA)/IRE1 signaling pathway". *International Journal of Biological Sciences* 19 (2023): 3937-3950.