Identification of target genes and pathways regulated by miRNA-132, miRNA-182, and miRNA-124 in depression: a bioinformatics analysis

Shamaila Wadud[1,2✉], Sadia Fatima [1], Roshan Ali [1], Rubina Nazli [1], Zahid Khan [3], Muhammad Irfan [4]

ABSTRACT

OBJECTIVE: To investigate the associations of miRNA-132, miRNA-182, and miRNA-124 with long-term depression and elucidate their target genes and translational implications utilizing miRabel, a bioinformatics tool.

METHODS: This study is a part of a randomized controlled trial conducted in Psychiatry OPD of a teaching hospital, Peshawar, Pakistan from February-2021 till December-2021. It's a computational study using miRabel which is a miRNA target prediction instrument. This software improves bioinformatic analysis by anticipation of microRNAs targets by grading and grouping.

RESULTS: By utilizing the miRabel software, our research reveals that miRNA-132, miRNA-182, and miRNA-124 target a total of 123 genes involved in long-term depression. Out of these genes, twelve (PRKCB, PLA2G4A, PRKCG, GNAZ, GNAO1, GUCY1B3, GNAI2, PLCB3, PPP2R1A, PLCB2, GNA11, and GUCY1A2) display significant potential impact, with scores close to 1.0 (0.9). These particular genes exhibit a stronger influence compared to other target genes of miRNA-132, miRNA-182, and miRNA-124 concerning long-term depression. Our investigation also revealed that these genes target several pathways, including beta-catenin independent WNT signaling, corticotropin-releasing hormone relating pathway, ErbB communicating path, G protein signaling, glutamic acid attachment, triggering of AMPA receptors, GnRH communication, Ras signaling, Serotonin and anxiety-related events, communication by WNT, signaling by GPCR, MAPK pathway, NO/cGMP/PKG neural-preservation, phosphodiesterases neuronal tasks, neuroinflammation and glutamatergic signing, along with several other pathways.

CONCLUSION: miRNAs such as miRNA-132, miRNA-182, and miRNA-124, identified via comprehensive bioinformatic analysis, show potential as depression biomarkers and treatment targets. Insight into their roles and target genes within depression pathways could inspire innovative treatment strategies.

KEYWORDS: Depression (MeSH); miR-132 (Non-MeSH); miR-182 (Non-MeSH); miR-124 (Non-MeSH); miRabel software (Non-MeSH); Target genes (Non-MeSH); Genes (MeSH).

1: Department of Biochemistry, Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan

2: Department of Biochemistry, Peshawar Medical College, Peshawar, Pakistan

3: Department of Chemistry, University of Peshawar, Peshawar, Pakistan

4: Department of Mental Health, Psychiatry & Behavioral Sciences, Peshawar Medical College, Peshawar Pakistan and Director Research, Prime Foundation, Pakistan

Cell #:   +92-301-8905683
Email✉ :   drshumailaasim@gmail.com

highlights the need for biomarkers to improve diagnosis and treatment outcomes in psychiatry. MicroRNAs (miRNAs) have emerged as promising biomarker candidates for depression. These small non-coding RNA molecules, composed of 17 to 25 nucleotides, regulate post-transcriptional gene expression, influencing various cellular processes.[6] They achieve this by binding to partially complementary sequences in the 3' untranslated region of target messenger RNAs (mRNAs), leading to mRNA degradation or translational suppression.[7]

Despite advancements, accurately predicting miRNA targets remains challenging with current bioinformatics tools. miRabel stands out as a superior resource, offering enhanced predictive capabilities compared to other algorithms like MBSTAR, miRWalk, ExprTarget, and miRMap.[8,9] Bioinformatics has evolved over two decades, revolutionizing biological research and facilitating the effective management and analysis of extensive data.[8] It bridges biological details with knowledge storage and exploration, supporting various domains, including clinical medicine.[9] Despite challenges, miRabel addresses limitations by providing superior predictions, crucial

INTRODUCTION

Depression presents a significant global health burden, impacting millions worldwide.[1] Major Depressive Disorder (MDD) is characterized by emotional instability, reduced activity, anhedonia, and disturbances like sleep and appetite changes, affecting approximately 4.7% of the population.[2,3] By 2030, the World Health Organization projects it to become the leading cause of disability.[2]

Diagnosing depression relies heavily on subjective symptom assessment due to the lack of reliable biological markers.[4] Although antidepressants are effective for many, about one-third of patients do not respond satisfactorily.[5] This

for exploring miRNA functions in biological contexts. Our study leverages this to analyze targeted genes and pathways associated with specific miRNAs, aiming to illuminate molecular pathways underlying MDD and identify potential biomarkers for further investigation and therapeutic intervention.

METHODS

This research is a component of a project (the role of ascorbic acid in the expression of miRNA and improvement of mood in patients with depression: a randomized control trial) conducted in a teaching hospital's psychiatry outpatient department (OPD) in Peshawar, Pakistan, spanning from February 2021 to December 2021. Within this study, bioinformatic analysis was performed using the software miRabel. This software encompasses a comprehensive repository of miRNAs, genes, and signaling pathways, akin to an exploration toolkit.

The miRabel dataset encompasses comprehensive human outcomes derived from four prominent miRNA target prediction algorithms: miRanda, PITA, SVmicrO, and TargetScan.[10,11] This software can freely accessed via the following website: http://bioinfo.univ-rouen.fr/mirabel/. Upon visiting this website, there will be three options: miRNAs, genes, and signaling pathways. Then, choose the miRNAs exploration option, and a separate page will be presented. This page contains information about the potential targets of miRNAs and their associated pathways. To proceed, enter the specific miRNAs you're interested in, such as hsa-miR-132, hsa-miR-182, and hsa-miR-124, and select the relevant pathway, such as "long-term depression," from the drop-down menu. Afterward, click the "compute" button. Another page will open, displaying a table containing information about the genes impacted by the selected miRNAs and their corresponding target scores in the context of long-term depression. The complete entries will be copied and subsequently sorted in descending order. Genes were ranked according to their scores like those with scores, so

approaching 1, such as 0.99, were ranked higher than those with scores like 0.98, and so forth. Each gene is accompanied by three icons: one for NCBI, another for Ensembl, and a third for Gene Cards. Clicking on any of these icons will provide comprehensive information about the selected genes, including their name, gene ID, and associated pathways. Since this is a computational study, all the relevant details are obtained from this software and then correlated with existing literature on depression.

RESULTS

In long-term depression, the target genes of miRNA-132 are given in Table I.

In this research, we centered on miR-132 and its involvement in long-term depression. We identified a total of 38 target genes of miR-132 associated with this condition. Among these target genes, seven showed a particularly high potential impact with a score of 0.9, indicating their close relevance to miR-132-mediated long-term depression. These high-impact genes include PLA2G4A, PRKCB, PRKCG, GNAZ, GNAO1, GUCY1B3, and GNAI2

1. PRKCB Gene: PRKCB encrypts a protein kinase that performs diverse roles in biological activities, namely B cell triggering, apoptosis introduction, endothelial cell expansion, and intestinal sugar consumption. Experiments on mice proposed that this kinase may also adjust neuronal activities and be associated with fear-induced disputed behavior after pressure and strain exposure. PRKCB shows higher expression in the brain.[12]

2. PLA2G4A Gene: The present gene encrypts a component of the cytoplasmic phospholipase A2 category IV group, which catalyzes the decomposition of membrane phospholipids, liberating icosanoic acid. This icosanoic acid is then chemically processed to produce eicosanoids, essential lipid-based essential hormones that modulates hemodynamics and inflammatory feedbacks PLA2G4A is expressed in the brain, urinary bladder, and adrenals.[13]

3. PRKCG Gene: PRKCG is associated with Protein kinase C (PKC) family and

is exclusively exhibited in the brain and spinal cord, particularly in neurons. Corresponding protein kinase performs a crucial function in nerve cells activities, including long-term potentiation (LTP) and long-term depression (LTD). Defects in PRKCG have been linked to neurodegenerative disorder spinocerebellar ataxia-14 (SCA14). The gene shows increased expression in the brain and testis.[14]

4. GNAZ Gene: The product of GNAZ belongs to a G protein subdivision specially participates in sign transduction in pertussis toxin-insensitive systems. It plays significant participation in keeping up the ionic harmony of cochlear liquid, which is necessary for auditory function. GNAZ exhibits wide expression across various tissues, including the brain.[15]

5. GNAO1 Gene: GNAO1 encrypts the alpha subdivision of the Go heterotrimeric G-protein signal-processing network. Mutations inside gene are linked to initial-onset epileptic encephalopathy. GNAO1 is expressed prominently in the brain and testis.[16]

6. GNAI2 Gene: GNAI2 encrypts an alpha subdivision of guanine nucleotide-binding proteins (G proteins). It takes part a vital character in the hormone-based modulation of adenylyl cyclase by binding guanine nucleotides. The gene exhibits widespread expression in various tissues, including spleen, bone marrow, and brain.[17]

7. GUCY1B3 Gene: GUCY1B3 encrypts the beta subdivision of solvable guanylate cyclase (sGC), an enzyme responsible for converting GTP into cGMP. The encrypted protein holds an HNOX domain, acting just as receptor for molecules like nitric monoxide, oxygen, and nitrovasodilator drugs. GUCY1B3 is expressed in various tissues, including the brain and placenta.[18]

miR-132 regulates a network of target genes involved in long-term depression. The identified high-impact genes provide valuable insights into the molecular mechanisms underlying this mental health condition. Further investigation of these genes and their associated pathways may contribute to the recognition of probable biomarkers

Table I: Target genes of miR-132 and its potential impact on the target genes

Target genes of miR-132	Potential impact of miR-132 on the target genes
PRKCB, PLA2G4A, PRKCG, GNAZ, GNAO1, GNAI2 and CY1B3	0.99
GUCY1A2, PRKG2, PRKG1, GNAS, GRID2, HRAS, CACNA1A, PLCB1,C7orf16, NRAS and ITPR3	0.98----0.91
GRM1, GRIA1, GNAI3, IGF1R, PPP2R1B, PPP2CA,GUCY1A3,ITPR2, GRIA2, GNA13, PLCB4, GNA12,1, KRAS, APK3 and PPP2CB	0.89----0.0007

and curative goals for managing long-term depression

In long term depression the objective genes of miRNA-182 are given in Table II.

We investigated miR-182 and its involvement in long-term depression, identifying a total of 37 target genes associated with this condition. Among these target genes, four displayed the highest potential impact with a score of 0.99, indicating their close relevance to miR-182-mediated long-term depression. These high-impact genes include PLCB3, PPP2R1A, PLCB2, and GNAZ.

1. PLCB2 Gene: PLCB2 encodes a phosphodiesterase responsible for hydrolyzing phosphatidylinositol 4,5-bisphosphate, causes production of intracellular mediators, inositol 1,4,5-trisphosphate (IP3), and diacylglycerol. Its activation is facilitated by G proteins, and it is engaged in the wave's conversion tracks of the type 2 taste receptor. The transcription of corresponding gene can be regulated by nuclear factor kappa B, and its protein product serves as an essential regulator of platelet responses. PLCB2 exhibits broad expression in various tissues, including spleen, bone marrow, and several others.[19]

2. GNAZ Gene: The protein expressed by this gene linked to a G protein subdivision associated in signaling pathways within pertussis toxin-insensitive systems. Widely expressed in brain tissue.[15]

3. PLCB3 Gene: Corresponding gene is linked to the phosphoinositide phospholipase C beta enzyme group, playing a crucial role in catalyzing the producing of intracellular mediators, diacylglycerol, and inositol 1,4,5-trisphosphate from phosphatidylinositol during G-protein-linked receptor-mediated signal transportation. Substitute splicing generates numerous transcript versions, resulting in functional diversity. PLCB3 is extensively demonstrated in several tissues, including duodenum, small intestine, brain, and others.[20]

4. PPP2R1A Gene: PPP2R1A encrypts a fixed regulative subdivision of protein phosphatase 2, among four major Ser/Thr phosphatases that negatively control cell development and fractions. Protein phosphatase 2 comprises a heteromeric core enzyme, consisting of a catalytic subdivision and a persistent supervisory subdivision, which associates with several governing subdivision. The continuous principle subdivision A, encoded by PPP2R1A, acts as a supporting molecule, facilitating the group of the catalytic subdivision along with an inconsistent regulative B subdivision. The genetic code expresses an alpha isotype of the fixed regulative subdivision A, and alternative joined transcript forms have

Table II: Target genes of miR-182 and its potential impact on the target genes

Target genes of miR-182	Potential impact of miR-182 on the target genes
PLCB2, GNAZ, PLCB3 and PPP2R1A.	0.99
GNA12, GUCY1A2, GRID2, ARAF, GNA11, PLCB1, C7orf16, GUCY1B3, GNAI2 and MAP2K1	0.98----0.93
PLA2G4D, GNAS, ITPR2, GRIA2, GNA11, KRAS, GUCY1A3, NRAS,PRKCB, PRKCA, GRIA3, MAPK1 IGF1, GNAI3, GRIA1, PPP2R1B, PLCB4, GNAO1, ITPR1, GNAQ, IGF1R, GNA13 and GRM1	0.89----0.003

Table III: Target genes of miR-124 and its potential impact on the target genes

Target genes of miR-124	Potential impact of miR-124 on the target genes
GNA11, PPP2R1A and GUCY1A2	0.99
RKCB, C7orf16, PLCB2, MAP2K1, GNAQ, PPP2CA, ITPR2, GRID2, PLA2G4F, PPP2CB, PRKCG, CRHR1 and PLA2G4C.P	0.98----0.91
ITPR1, LYN, GUCY1B3, IGF1, HRAS, PLA2G4D, GNAS, GNAO1, IGF1R, PRKG2, PPP2R1B, GNAZ, GRIA1, RAF1, GRIA3, KRAS, PRKCA, MAPK1, PLCB4, GNA12, ARAF, GNAI3, PRKG1, GNAI1, GNAI3, RM1, GNAI2, NRAS, ITPR3, GRIA2, PLCB1 and RYR1	0.88----0.0007

Table IV: Comparison of the target genes of miR-132, miR-182 and miR-124 having high potential impact

miR-132	miR-182	miR-124
PLA2G4A	PPP2R1A	PPP2R1A
PRKCB	PLCB3	GNA11
PRKCG	PLCB2	GUCY1A2
GNAZ	GNAZ	
GNAO1		
GUCY1B3		
GNAI2		

been described. PPP2R1A exhibits widespread presence in various tissues, including heart, adrenal, brain, and others.[21]

miR-182 targets a network of genes involved in long-term depression, and the four identified high-impact genes provide valuable insights into the molecular mechanisms underlying this mental health condition. Further exploration of these genes and their associated pathways may lead to the discovery of prospective biomarkers and curative objectives for managing long-term depression.

In long term depression, the target genes of miR-124 are given in Table III.

In our investigation of miR-124 and its role in long-term depression, we identified a total of 48 target genes associated with this condition. Among these target genes, only three demonstrated the highest potential impact with a score of 0.99, signifying their close relevance to miR-124-mediated long-term depression. These high-impact genes include GNA11, PPP2R1A, and GUCY1A2.

1. GNA11Gene: Corresponding protein encrypted by GNA11 is a representative of the guanine nucleotide-binding proteins (G proteins) family, that play vital roles as restrainers or sensors in numerous transmembrane signaling network. G proteins consist of three units: alpha, beta, and gamma. GNA11 encrypts particular alpha subunits, specifically subunit alpha-11. Transformation in this gene have been connected with two conditions: hypocalciuric hypercalcemia type II (HHC2) and hypocalcemia dominant 2 (HYPOC2). Individuals with HHC2 and HYPOC2 reveals reduced or enhanced responsiveness correspondingly, to alterations in extracellular calcium levels. GNA11 exhibits broad expression in various tissues, including small intestine, duodenum, brain, and others.[22]

2. PPP2R1A Gene: Discussed previously with miRNA-182.[21]

3. GUCY1A2 Gene: Soluble guanylate cyclases are protein complexes composed of heterodimers that facilitate the turning of GTP to 3',5'-

Table V: Target genes and pathways related to depression

Target Genes	Pathways
PRKCB	Beta-catenin independent WNT signaling, Corticotropin-releasing hormone signing tract, ErbB signaling pathway, G protein signing tract, Glutamic acid banding, triggering of AMPA receptors and synaptic flexibility, GnRH Signaling Pathway, Ras signaling,5-hydroxytryptamine (5-HT) and apprehension, 5-hydroxytryptamine (5-HT) and worries-linked incidents, Signing by WNT, Wnt signalizing.[12]
PLA2G4A	Signal amplification, Metabolism of lipids, Signaling Pathways, MAPK signaling pathwayRas signaling, Signaling by GPCR, GPCR downstream signalling.[14]
PRKCG	Beta-catenin independent WNT signaling, ErbB signaling pathway, G protein signaling pathways, Glutamic acid banding, triggering of AMPA receptors and synaptic flexibility, MAPK signaling pathway, Ras signaling, Signaling by WNT, Signaling by WNT and Wnt ignaling.[15]
GNAZ	G protein signaling pathways, GPCR downstream signalling and Signaling by GPCR.[16]
GNAO1	Corticotropin-releasing hormone communicating track and G protein signalizing routes.[17]
GNA12	G protein signalizing routes, GPCR downstream signalling, MAPK signing tracks, Signalizing by GPCR.[18]
GUCY1B3	NO/cGMP/PKG moderated neuronal shielding and Phosphodiesterases in neural activities.[19]
PLCB2	WNT signaling, Alzheimer's disease, Sensory Perception, Neuroinflammation and glutamatergic signaling.[20]
PPP2R1A	ErbB1 downstream signaling, Focal point adherance: PI3K-Akt-mTOR-signing track and Wnt signing track and multipotent[22]
GNA11	Corticotropin-releasing hormone communicating track, G protein signalizing routes and Prostaglandin and leukotriene metabolism in senescence.[23]

cyclic GMP and pyrophosphate. GUCY1A2 encodes the alpha subdivision of this compound, which links along a beta subdivision to set up the guanylate cyclase enzyme, specifically triggered by nitrogen monoxide. Two transcription different forms have been identified for the already stated gene, producing different isoforms. GUCY1A2 exhibits broad expression in various tissues, including endometrium, placenta, brain, and others.[23]

miR-124 targets a network of genes involved in long-term depression, and the three identified high-impact genes provide valuable insights into the molecular mechanisms underlying this mental health condition. Further exploration of these genes and their associated pathways may give rise to the detection of possible biomarkers and curative designs for managing long-term depression.

In long term depression, the target genes of miRNA-132, miRNA-182 and miRNA-124 with the highest potential impact of 0.99 are given in table IV.

It shows that miRNA-132, miRNA-182 and miRNA-124 have two common genes GNAZ gene and PPP2R1A gene, with a potential impact of 0.99.

Table V shows the target genes and pathways related to depression.

DISCUSSION

Utilizing the miRabel software, our findings indicate that miR-132, miR-182, and miR-124 collectively target 123 genes involved in long-term depression. Among these genes, twelve (PRKCB, PLA2G4A, PRKCG, GNAZ, GNAO1, GUCY1B3, GNAI2, PLCB3, PPP2R1A, PLCB2, GNA11, and GUCY1A2) demonstrate the highest potential impact, with a score of 0.9, indicating a strong influence on long-term depression.

MicroRNAs (miRNAs) are endogenous small RNA particles that perform a critical function in post-transcriptional gene modulation by causing controlled mRNA degradation or inhibiting transcription.[24] In 2015, a study conducted by Guo X and colleagues involved a cohort of Han Chinese individuals diagnosed with depression. The findings revealed a down-regulation of PRCKB1 gene impression in circulating white blood cells among the depressed persons.[25] Our bioinformatic analysis has additionally demonstrated that the PRKCB gene ranks among the top target genes for these three miRNAs. Specifically, miR-132 exhibits a notable potential impact of 0.99, while miRNA-182 shows a potential impact of 0.23, and miRNA-124 demonstrates a substantial potential impact of 0.98. The subsequent target gene on our list is PLA2G4A, and it is tasked with encoding a member of the cytosolic phospholipase A2 class IV family-line. Our bioinformatic analysis has revealed that miRNA-132 exerts a significant potential impact of 0.99 on this particular gene.

In earlier studies, Su KP and his research team investigated a group of individuals with chronic hepatitis C viral disease to explore the potential consequences of seven single nucleotide polymorphisms in the COX2 and PLA2 genes on the progress of depression during interferon management. Their results indicated that hereditary deviations within the COX2 and PLA2 genes extend the vulnerability to IFN-α-influenced depression, probably by influencing the levels of EPA and DHA. Furthermore, the PLA2 genotype was correlated with somatic manifestations in individuals with depression, as per their findings.[26]

Our study has shown that miR-132 exerts a substantial potential impact of 0.99, while miRNA-124 demonstrates a significant potential impact of 0.95 on the PRKCG gene. The protein encrypted by this gene is associated to the PKC community and is exclusively expressed in the brain and spinal cord, with its distribution limited to neurons. Panday GN and colleagues conducted a study to assess the mRNA impression levels of different PKC isoforms in the prefrontal cortical section among normal control individuals, persons with depression who passed away by suicide, and those with depression who did not die by suicide. They observed a notable reduction in mRNA impression of PKC and a decrease in protein impression in each of the membrane or cytosol fraction of PKC isoforms. Their findings led to the conclusion that particular deregulation of particular PKC isoforms occurs in the autopsy brains of both individuals with depression who died by suicide and those who did not.[27] Our investigation revealed that the GNA12 gene is also targeted by miRNA-132, miRNA-182, and miRNA-124, with respective potential impacts of 0.99, 0.98, and 0.07, as indicated by miRabel. According to existing literature, Tsolakidou A and colleagues conducted an animal-based investigation aimed at identifying genes that respond, either leading or misleading, to distress. Their study unveiled that Guanine nucleotide attaching protein, alpha inhibiting 2 (GNAi2), and amyloid β (A4) precursor protein (APP) were identified as stress-modulated genes in the paraventricular nucleus regarding hypothalamus (PVN).[28]

Our investigation also revealed particular selected genes are associated in several pathways, including Beta-catenin independent WNT signaling, corticotropin-releasing hormone signing track, ErbB signing pathway, G protein signalizing routes, glutamic acid banding, triggering of AMPA receptors and synaptic flexibility, GnRH signalizing pathway, Ras signaling, 5-hydroxytryptamine (5-HT) pathway, signaling by WNT, GPCR downstream trafficking, signaling by GPCR, MAPK signaling route, NO/cGMP/PKG moderated neuronal preservation, phosphodiesterases in neural activities neuroinflammation and glutamatergic signing, Alzheimer and other disorders, and other routes. Literature shows that β-Catenin independent WNT signaling pathway has been associated with altered social interactions and repetitive behaviors observed in autism.[29] Dysfunction in the glutamatergic neurotransmission and AMPAR-mediated synaptic transmission has been linked to depression, and NMDA receptor antagonists,[30] like ketamine show promising effects as antidepressants.[31] The central Renin-Angiotensin System (RAS) has a notable aspect in the pressure effect[32] and can accept an influential aspect in the pathological process of depression, given along dysfunction of the HPA axis

observed in depression. The MAPK pathway,[33] as well as the PI3K-Akt-mTOR signaling pathway,[34] are implicated within depression, and dysregulation regarding these pathways may add to the beginning and advancement of the disorder. Neuroinflammation and glutamatergic signaling are implicated in depression. Increased inflammation markers in major depressive disorder are linked to higher basal ganglia glutamic acid, causing anhedonia and neuro-behavioral slowing. Research suggests that elevated inflammatory cytokines impact the reaction to glutamic acid antagonists like ketamine, indicating that inflammation may contribute to depressive symptoms through disrupted glutamate metabolism.[35]

These findings indicate that the potential target genes and linked pathways of miRNA-132, miRNA-182, and miRNA-124 are associated with related pathological processes involved in depression.

CONCLUSION

In conclusion, miRNAs, particularly miRNA-132, miRNA-182, and miRNA-124, show relevance in the pathophysiology of depression and offer potential as innovative biomarkers and therapeutic targets for depression treatment. Understanding the purpose of these miRNAs and their target genes in depression-related signaling pathways may pave the way for novel and effective therapeutic approaches in the future.

REFERENCES

1. Ferrúa CP, Giorgi R, da Rosa LC, do Amaral CC, Ghisleni GC, Pinheiro RT, et al. MicroRNAs expressed in depression and their associated pathways: A systematic review and a bioinformatics analysis. J Chem Neuroanat 2019;100:101650. https://doi.org/10.1016/j.jchemne u.2019.101650

2. Alvarez-Mon MA, Ortega MA, García-Montero C, Fraile-Martinez O, Monserrat J, Lahera G, et al. Exploring the role of nutraceuticals in major depressive disorder (MDD): Rationale, state of the art and future prospects. Pharmaceuticals 2021;14(8):821. https://doi.org/10.3390/ph140808 21

3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018;392(10159):1789-858. https://doi.org/10.1016/S0140 -6736(18)32279-7

4. Wan Y, Liu Y, Wang X, Wu J, Liu K, Zhou J, et al. Identification of differential microRNAs in cerebrospinal fluid and serum of patients with major depressive disorder. PLoS One 2015;10(3):e0121975. https://doi.org/10.1371/journal.po ne.0121975

5. Lopez JP, Kos A, Turecki G. Major depression and its treatment: microRNAs as peripheral biomarkers of diagnosis and treatment response. Curr Opin Psychiatry 2018;31(1):7-16. https://doi.org/10.1097/YCO.0000 000000000384

6. Hassan M, Amir A, Shahzadi S, Kloczkowski A. Therapeutic implications of microRNAs in depressive disorders: a review. Int J Mol Sci 2022;23(21):13530. https://doi.org/10.3390/ijms23211 3530

7. Xu YY, Xia QH, Xia QR, Zhang XL, Liang J. MicroRNA-based biomarkers in the diagnosis and monitoring of therapeutic response in patients with depression. Neuropsychiatr Dis Treat 2019;15:3583-97. https://doi.org/10.2147/NDT.S235 186

8. Wani MY, Ganie NA, Rani S, Mehraj S, Mir MR, Baqual MF, et al. Advances and applications of Bioinformatics in various fields of life. Int J Fauna Biol Stud 2018;5(2):03-10.

9. Quillet A, Saad C, Ferry G, Anouar Y, Vergne N, Lecroq T, et al. Improving bioinformatics prediction of microRNA targets by ranks aggregation. Front Genet 2020;10:1330. https://doi.org/10.3389/fgene.201 9.01330

10. LITIS lab, University of Rouen Normandy, France. Accessed on: June 20, 2023. Available from URL: http://bioinfo.univ-rouen.fr/

11. Lesk, Arthur M. "bioinformatics". Encyclopedia Britannica. 2023. Accessed on: June 20, 2023. Available from URL: https://www.britannica.com/scien ce/bioinformatics

11. Lesk, Arthur M. "bioinformatics". Encyclopedia Britannica. 2023. Accessed on: June 20, 2023. Available from URL: https://www.britannica.com/scien ce/bioinformatics

12. National library of Medicine. PRKCB protein kinase C beta [Homo sapiens (human)] Gene ID: 5579. 2022. Accessed on: June 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gen e/5579

13. National library of Medicine. PLA2G4A phospholipase A2 group IVA [Homo sapiens (human)] Gene ID: 5321, updated on 21-Jun-2023. Accessed on: July 15, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gen e/5321

14. National library of Medicine. PRKCG protein kinase C gamma [Homo sapiens (human)] Gene ID: 5582. 2023. Accessed on: July 25, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gen e/5582

15. National library of Medicine. GNAZ G protein subunit alpha z [Homo sapiens (human)] Gene ID: 2781. 2023. Accessed on: July 21, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gen e/2781

16. National library of Medicine.

GNAO1 G protein subunit alpha o1 [Homo sapiens (human)] Gene ID: 2775. 2023. Accessed on: July 21, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/2775

17. National library of Medicine. GNAI2 G protein subunit alpha i2 [Homo sapiens (human)] Gene ID: 2771.2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/2771

18. National library of Medicine. GUCY1B1 guanylate cyclase 1 soluble subunit beta 1 [Homo sapiens (human)] Gene ID: 2983. 2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/2983

19. National library of Medicine. PLCB2 phospholipase C beta 2 [Homo sapiens (human)] Gene ID: 5330. 2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/5330

20. National library of Medicine. PLCB3 phospholipase C beta 3 [Homo sapiens (human)] Gene ID: 5331. 2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/5331

21. National library of Medicine. PPP2R1A protein phosphatase 2 scaffold subunit Alpha [Homo sapiens (human)] Gene ID: 5518. 2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/5518

22. National library of Medicine. GNA11 G protein subunit alpha 11 [Homo sapiens (human)] Gene ID: 2767. 2023. Accessed on: July 20, 2023. Available from URL: https://www.ncbi.nlm.nih.gov/gene/2767

23. National library of Medicine. GUCY1A2 guanylate cyclase 1 soluble subunit alpha 2 [Homo sapiens (human)] Gene ID: 2977. 2023. Accessed on: July 20, 2023.

Available from URL: https://www.ncbi.nlm.nih.gov/gene/2977

24. Qian Y, Song J, Ouyang Y, Han Q, Chen W, Zhao X, et al. Advances in roles of miR-132 in the nervous system. Front Pharmacol 2017;8:770. https://doi.org/10.3389/fphar.2017.00770

25. Guo X, Li Z, Zhang C, Yi Z, Li H, Cao L, et al. Down-regulation of PRKCB1 expression in Han Chinese patients with subsyndromal symptomatic depression. J Psychiatr Res 2015;69:1-6. https://doi.org/10.1016/j.jpsychires.2015.07.011

26. Su KP, Huang SY, Peng CY, Lai HC, Huang CL, Chen YC, et al. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. Biol Psychiatry 2010;67(6):550-7. https://doi.org/10.1016/j.biopsych.2009.11.005

27. Pandey GN, Sharma A, Rizavi HS, Ren X. Dysregulation of Protein Kinase C in Adult Depression and Suicide: Evidence from Postmortem Brain Studies. Int J Neuropsychopharmacol 2021;24(5):400-408. https://doi.org/10.1093/ijnp/pyab003

28. Tsolakidou A, Czibere L, Pütz B, Trümbach D, Panhuysen M, Deussing JM et al. Gene expression profiling in the stress control brain region hypothalamic paraventricular nucleus reveals a novel gene network including amyloid beta precursor protein. BMC Genomics 2010;11:546. https://doi.org/10.1186/1471-2164-11-546

29. Alexander JM, Pirone A, Jacob MH. Excessive β-catenin in excitatory neurons results in reduced social and increased repetitive behaviors and altered expression of multiple genes linked to human autism.

Front. Synap Neurosci 2020;12:14. https://doi.org/10.3389/fnsyn.2020.00014

30. He JG, Zhou HY, Wang F, Chen JG. Dysfunction of Glutamatergic Synaptic Transmission in Depression: Focus on AMPA Receptor Trafficking. BP GOS 2023;3(2):187-96. https://doi.org/10.1016/j.bpsgos.2022.02.007

31. Dwivedi Y. MicroRNAs in depression and suicide: recent insights and future perspectives. J Affect Disord 2018;240:146-54. https://doi.org/10.1016/j.jad.2018.07.075

32. Zhao C, Cai H, Wang H, Ge Z. Correlation between serum renin-angiotensin system (RAS) level and depression and anxiety symptoms in patients with Parkinson's disease. Saudi J Biol Sci 2021;28(4):2146-54. https://doi.org/10.1016/j.sjbs.2021.02.029

33. Philips GT, Ye X, Kopec AM, Carew TJ. MAPK establishes a molecular context that defines effective training patterns for long-term memory formation. J Neurosci 2013;33(17):7565-73. https://doi.org/10.1523/JNEUROSCI.5561-12.2013

34. Jernigan CS, Goswami DB, Austin MC, Iyo AH, Chandran A, Stockmeier CA, et al. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Progress in Prog Neuro-Psychopharmacol Biol Psychiatry 2011;35(7):1774-9. https://doi.org/10.1016/j.pnpbp.2011.05.010

35. Haroon E, Miller AH, Sanacora G. Inflammation, Glutamate, and Glia: A Trio of Trouble in Mood Disorders. Neuropsychopharmacol 2017;42(1):193-215. https://doi.org/10.1038/npp.2016.199

AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SW: Concept and study design, acquisition of data, drafting the manuscript, approval of the final version to be published

SF, RA, RN, ZK & MI: Analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST
Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

GRANT SUPPORT AND FINANCIAL DISCLOSURE
Authors declared no specific grant for this research from any funding agency in the public, commercial or non-profit sectors

DATA SHARING STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request

KMUJ web address: www.kmuj.kmu.edu.pk
Email address: kmuj@kmu.edu.pk