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Review Paper

Exploring Neurotransmitter Dynamics: A Systematic Review of BDNF, IL-6, and TNF Biomarkers in Brain Health and Function

Chetana S Karadi[1], Babiker Bashir Haroun Baraka[2]*, Cherishma Raju P[3]

ABSTRACT

Biomarkers are very critical for the rational development of medical therapeutics but there is significant confusion that persists on the definition and concept involved in clinical practice and research, mainly in the field of nutrition and chronic diseases. Various autoimmune disorders like AHT (Autoimmune Hypothyroidism) is associated with occurrence and developing of depression. Depression is associated with changing levels of trophic factors and inflammatory factors-IL-6, TNF-alpha, bdnf, crp. Relationship between the coexistence of depression and aht indicates the etiology and pathomechanism of depression. Bidirectional relationship between cvd(cardiovascular disease) and depression suggests bdnf as reliable biomarker for prediction of cvd and depression, as it plays an important role in growth and survival. The aim of this systematic review is to understand the normal levels of BDNF, IL-6, TNF-alpha and to systematically study the elevated and decreased levels of each biomarkers. Also to examine the association of the changing levels of the biomarkers with underlying diseases-cvd, aht, depression. Methods: systematic study was carried out to obtain the relevant information. **Results:** abnormally low level of bdnf is associated with depression and simultaneously high levels of IL-6, TNF. Severity of depression is high in patients with elevated antithyroid antibodies and aht. This helps for better understanding of interrelationship between them and is very helpful in pharmacotherapy.

Keywords: *Brain derive neurotrophic factor, Interleukins-6, tumor necrosis factor alpha, biomarker, neurotransmitter*

Biomarker the term derived from word “Biological marker”. Biomarkers determines the medical condition observed from outside the patient and which is measured accurately and reproducibly. It not only helps in diagnosis of the disease but also helps in tracking the disease progression, regression, potential treatment identification. Hence in recent decades, biomarkers are progressively incorporated in clinical trials and

[1]Department of Pharmacology, KLE College of Pharmacy, 2nd Block Rajajinagar, Bangalore-560010, Karnataka, India
[2]Department of Pharmacology, KLE College of Pharmacy, 2nd Block Rajajinagar, Bangalore-560010, Karnataka, India
[3]Department of Pharmacology, KLE College of Pharmacy, 2nd Block Rajajinagar, Bangalore-560010, Karnataka, India
*Corresponding Author

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clinical routine in field of neurology.[1] Likewise BDNF, TNF, IL are few biomarkers which are used in diagnosis and treatment of many diseases. [2]

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor which helps in differentiation, maturation and survival of neurons in nervous system [3]. It shows neuroprotective nature under the extreme adverse condition like cerebral ischemia, neurotoxicity, hypoglycemia. BDNF aggravates neurogenesis (controls and stimulates growth of new neurons from neural stem cells) [4][5]. BDNF protein and mRNA are mostly identified in cortex, hippocampus, olfactory bulb, basal forebrain, spinal cord, hypothalamus, mesencephalon areas of brain. In diseases like Parkinson's disease, Huntington's disease, multiple sclerosis the levels of BDNF are found to be decreased. Not just neuroprotective effect BDNF also plays major role in homeostasis. [6][7][8].

Tumor necrosis factor alpha (TNF) is cytokine which has pleiotropic effect on various cell types. It is one of the major regulators of inflammatory responses and associated in pathogenesis of some inflammatory and autoimmune diseases. TNF is homotrimer protein which consists of 157 amino acids [9]. It exists in transmembrane and soluble form, binds to TNFR1 and TNFR2 and thus transmits molecular signals for biological functions like cell death and inflammation. [10][11][12].

Interleukins are clusters of cytokines which act as chemical signals between white blood cells. There are two distinguishing scenarios in function of IL, (1) the use of IL directly in antitumor treatment by blocking or increasing the interleukins with different immunological strategies, (2) the use of IL as biomarker in tumor remission or progression [13]. Family of interleukin consists of many division of interleukins namely Interleukin-1, Interleukin-2, Interleukin-3 and so on ranging till Interleukin-40, which have their own specific functions in the body. This article mainly focuses on understanding **Interleukin-6(IL-6)**. [14]IL-6 is another critical cytokine involved in several chronic inflammatory diseases like cancer pathogenesis. They are identified as cancer biomarkers by screening of inflammatory mediators in different fluids like saliva, serum, BALF. [15][16].
This article highlights on the role of BDNF, TNF, IL-6 as biomarkers in different diseases.

MATERIALS AND METHODS

Literature review: Initial step was literature search on the databases: Medline, Science direct. Reference list in the retrieved paper were examined. Key terms 'BDNF', 'brain derived neurotropic factor', 'depression', 'anxiety', 'TNF','IL-6'were used to obtain articles. Subsequently, each article was checked according to our inclusion criteria.

Inclusion and Exclusion criteria: Prospective studies that evaluated BDNF blood levels in patients with depression, hypothyroidism, CVD. Criteria like article written in English, studies that reported BDNF levels in the body-in serum and plasma, studies that reported tumour necrosis factor and IL-6 in relation to biomarkers. Articles with information in relation to activity of the biomarkers in development of brain were included. Series of cases and case reports were excluded and studies with incomplete data like reviews, statistical data, meta-analyses and abstracts were excluded.

RESULTS AND DISCUSSION

On doing the systematic review of the biomarkers, the activity of each of the biomarkers in brain development is as follows,

Activity of BDNF in brain development and as biomarker

Brain derived neurotrophic factor (BDNF) was initially isolated from a pig's brain in 1987. It belongs to neurotrophins family that is expressed throughout the brain, specifically in regions such as cerebral cortex, cerebellum, hippocampus, amygdala. BDNF plays very crucial role in various neurological processes like learning, memory, neuroprotection, regulation of neurons and glia. BDNF has ability to upregulate and downregulate signaling pathways because of its distinct synthesis pattern where biologically active isoforms interact with specific receptors. Thus, precursor of BDNF, pre-pro-BDNF is secreted from ER. The pre-region of precursor is cleaved in the Golgi apparatus which thus forms immature isoform, pro-BDNF [18]. This form is biologically active and bares N-terminal pro-domain, the pro-BDNF is further cleaved to form mature isoform(m-BDNF), which is also biologically active and possesses a C-terminal mature domain. Both the isoforms of BDNF are secreted into the extracellular space on depolarization of the membrane, and thus exhibit opposite biological action due to its binding receptors preferences. m-BDNF interacts with TrkB (tyrosine kinase B), triggers several cascade reactions that leads to prosurvival and neuronal antiapoptotic reactions. After m-BDNF-TrkB binding, activation of phosphorylated-TrkB receptors leads to activation of enzymes-PI3K (Phosphatidylinositol-3-kinase), GTPases (guanosine triphosphate hydrolases) that leads to certain specific cellular functions. Pro-BDNF interacts with p75NTR (P75 neurotrophin receptor) to form pro-BDNF/P75NTR/sortilin complex. On binding of pro-BDNF to its receptors initiates signalling pathways which influences and affects the fate of neurons in various regions of brain, like promoting cell death or cell survival. Increased in the levels of pro-BDNF leads to neuronal cell elimination instead of enhancing neuronal cell survival [17].

Effect on increased BDNF levels

BDNF-mRNA expression is modulated and regulated by neuronal activity as the epileptogenic activation of glutamatergic synapses elevates the expression of BDNF-mRNA in the regions of brain like hippocampus[19][20]. Increase in the synaptic activity of the receptor agonist induced by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is known to produce an elevation in the levels of mRNA enciphering BDNF and TrkB in cortex and hippocampus. BDNF-mRNA is found to be increased in visual cortex on light stimulation, BDNF-mRNA is found to be increased in hypothalamus on osmotic stimulation, BDNF-mRNA is found to be increased in somatosensory barrel cortex on whisker stimulation. [3][21][22]. A cellular model of memory and learning which is an electric stimuli that is known to induce long term potentiation(LTP) in hippocampus was found to enhance and increase BDNF and NGF expression. Physical exercise aids in increasing the NGF and BDNF levels in hippocampus, thus beneficial in improving memory and preventing Alzheimer's disease. [3][23].

Effect on decreased BDNF levels

Stimulation of GABAergic system or blockage of glutamate receptors is known to decrease BDNF-mRNA expression in hippocampus.[24][25][26]. Inducing monocular deprivation leads to decrease in BDNF-mRNA in the region of visual cortex commensuration to deprived eye. TrkB-IgG and AntiBDNF antiserum antagonizes the action of BDNF inflammatory hypersensitivity models and in neuropathic pain. . [27] They demonstrate the potency for antibody mediated TrkB agonism as potential therapeutic loom to enhance RGC (retinal ganglion cells) survival after optical nerve injury. Neurotrophin antagonist-Y1036 alters surface charge density and acts against BDNF and NGF by preventing the downstream signalling via p44/42 MAPK pathway and NT induced receptor activation [28]. Nitric oxide

which is produced endogenously downregulates BDNF secretion in hippocampus by activating cGMP dependent signal transduction pathway which leads to decrease in Ca2+ release from IP3 by PKG(protein kinase G). [29].

Plasma levels of BDNF

Normal plasma level of BDNF in healthy person ranges from 8.0-92.70pg/ml. It is higher in women and found to be decreased due to aging in both the genders. [30]. BDNF is distributed widely in various regions of the brain. It aids in survival, support and function of neurons. Sources of BDNF other than brain include lungs, heart, spleen, gastrointestinal tract and liver. It is also found in vascular smooth muscle cells thymic stroma, fibroblast and thymic stroma. [31]. It is to be noted that levels of BDNF in the lungs, urinary bladder, and colon is higher than in brain or skin. Women with low plasma BDNF levels have increased mortality risk [31][32][33] and significant reduction in plasma levels of BDNF in females corresponds to advancing age and body weight. [34][35].

Activity of Interleukin in development and as biomarker

Interleukins belongs to family of cytokines; these are small proteins which plays major role in immune system of our body. This article mainly focuses on interleukin-6(IL-6), it is identified as BSF-2(B-cell differentiation factor), known to induce the maturation of the B cells into antibody producing cells. It is also vital for the regulation of cardiovascular system, hepatocytes, skeletal system, hematopoietic progenitor cells, and endocrine system. Based on the type of receptors cytokines bind to, they are classified into class I-THE LARGEST FAMILY, cytokines receptor, class II-cytokine receptors, TNF receptors, tyrosine kinase receptors, chemokine receptors. The IL-6 family of cytokines utilises gp130 for signalling hence IL-6 family is also known as gp130 family of cytokines. IL-6 is synthesised in different brain cells like astrocytes, neurons. IL-6 thus binds to mIL-6R or to sIL-6R(membrane bound receptors and water soluble receptors respectively) and initiates signalling on interaction with sgp130 protein. [36] Under static conditions the normal levels of circulating IL-6 levels is as low as 1-5pg/ml, but during certain critical states like inflammatory states the circulating levels rise more than 1000 fold, under extreme conditions leading to sepsis IL-6 levels in µg/ml range [37][33]. Production of IL-6 is immensely amplified by feed forward loop of TNF-alpha,IL-6beta together with Toll-like receptor stimulation thus produces IL-6 by myeloid cells[37][38]. Hence IL-6 is major alarm signal in response to inflammation, infection, and cancer. [37][39]. IL-6 also plays very vital role in various types of cancer, this is because of the possibility that IL-6 via STAT-3 pathway stimulation is pre-eminent growth factors for many cancer cells[40].Thus selective blocking of the pathway by sgp130Fc protein blocks the invasion of pancreatic intraepithelial neoplasias to ductal adenocarcinomas[41] which indicates the role of IL-6 trans-signalling in the development of pancreatic cancer. Therapeutic targeting of IL-6 activity is known to be an efficient strategies to treat patients with conditions like IBD (inflammatory bowel disease), rheumatoid arthritis [42].

Activity of tumor necrosis factor in development and as biomarker

TNF belongs to family cytokine family that promotes inflammatory signaling. TNF signaling is known to have several functions within the CNS [43][44] which includes regulation of blood brain barrier permeability, injury-mediated microglial, astrocyte activation, glutamatergic transmission, febrile responses and synaptic plasticity and scaling[45][46][47][48][49][50]. TNF-dependent increases in AMPA receptors at the cell surface and decrease in $GABA_A$ receptor cell surface expression leads to control of synaptic strength

by TNF at the excitatory synapse by increasing the transmission at excitatory synapse and by reducing inhibitory transmission leading to excitatory synapse scaling. [49][51][50]. Pharmacologically, TNFR or anti-TNF antibody treatment prevents basal and thus the tetrodotoxin-induced increases in surface expression of AMPA receptors and also increases in mEPSC amplitude with decrease in mIPSC amplitude, hence plays an important role in synaptic scaling [49][51]TNF regulates neuronal development in hippocampus[53], on other hand, TNF potentiate excitotoxicity by two mechanisms, TNF potentiate glutamate excitotoxicity directly via activation of glutamate-NMDA receptors[49][54] and by localization of AMPA receptors to synapse [55][56][57], by inhibiting glial glutamate transporters on astrocytes [58].On understanding of the effects of the biomarker-BDNF,TNF,IL-6, are known to have a significant impact on many diseases like major depression, anxiety, thyroid, post stroke depression, cardiovascular disease. Depression is known to be accompanied by the changes in the levels of TNF-alpha, Interleukin-6,CRP, BDNF. The relationship between coexistence of autoimmune hypothyroidism and depression relates to change in the immune system. Treatment with levothyroxine and antidepressants leads to decrease in the levels of proinflammatory cytokines with simultaneous increase in the levels of BDNF, correlating to the improvement in the clinical parameters. Symptoms, assessment and diagnostic findings of AHT(Autoimmune hypothyroidism)is as follows.

Table1.Autoimmune hypothyroidism(AHT)-symptoms, assessment, and diagnostic findings.

Symptoms	Assessment findings	Diagnostic findings
Depression	Dry and coarse skin	Macrocytic anaemia
Weight gain	Bradycardia	Delayed bone age
Fatigue	Goitre	Hypercholesterolemia
Constipation	Galactorrhoea	Delayed bone age
Infertility	Ascites	Hyperprolactinemia
Sexual dysfunctioning	Hoarseness	Hyponatremia
Sleep disorders	Slow relaxation of tendon reflexes	-
Muscle cramps	Dull facial expression	-
Cold intolerance	Macroglossia	-
Menorrhagia	Reduced body and scalp hair	-

Etiological basis for mood disorder and AHT are seen in similar changes of growth, development and differentiation of neuronal system cells and hematopoietic and cytokine profiles[59] [60] .Various studies indicate that inflammatory system response is activated by depression leading to production of IL-6,TNF-alpha. [61][62].Through the study conducted by[59],it is to be noted that treatment with levothyroxine shows a significant decrease in the levels of interleukins and tumour necrosis factor[63][64].Incidence of mild and moderate depression among patience with hypothyroidism was 57% and it was found that after 6 months of treatment with levothyroxine, almost 42% of the group remitted the depressive symptoms[63].Selective serotonin reuptake inhibitors(SSRI) are most frequently used class of antidepressants which is known to reduce the promoting depression effects of proinflammatory cytokines. Fluoxetine is found to reduce the expression of IL-6, TNF-α.Tricyclic anti depressant-Desipramine is known to reduce the levels of TNF-α in hippocampus and brain stem.

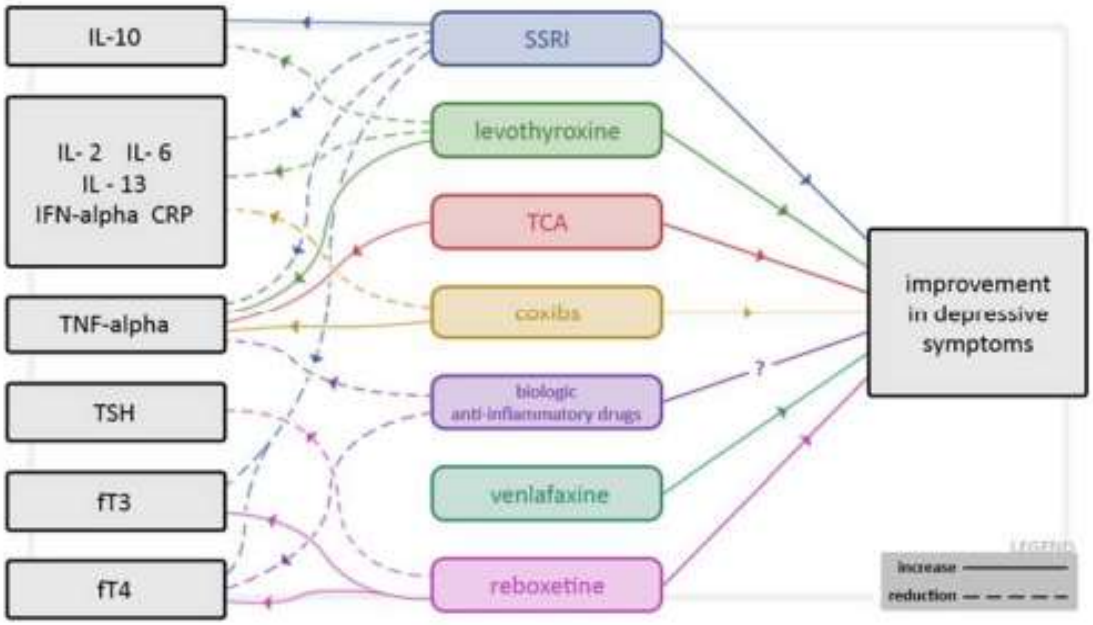

Figure 1. Relation between depressive symptoms and selected drugs with their influence on the selected hormonal and inflammatory parameters.

Anti-inflammatory drugs along with anti-TNF alpha antibodies like infliximab, adalimumab have a great potential use in treating depression. From the studies conducted by, high initial levels of pro inflammatory cytokines are more benefited with this treatment [65][66][67].IL-6 receptor blocker-Tocilizumab, has potential to decrease symptoms of depression in patients with rheumatoid arthritis [68][69].Patients with haematological problems the depressive symptoms were worsened with this drug[70]. Drugs like hallucinogens and bupropion are known to have the ability to block TNF-alpha or decrease its production [71]. We need to stress on the fact that depression with increased suicidal risk and thyroiditis a new onset or its exacerbation is most common side effects of TNF-alpha blockers. Euthyroid women have abnormal serum levels of hematopoietic and neural growth and differentiation factors important in the aetiology of depression-BDNF.BDNF belongs to the group of neurotrophins, proteins synthesized in the cells of the central and peripheral nervous system which is involved in the functioning, development, and protection of nerve cells. BDNF is involved in the regulation of neuronal plasticity which is related to learning and memory processes, influencing the process of synaptic long-term potentiation and long-term depression in the hippocampus and also influences the development of serotonergic, dopaminergic, noradrenergic, and cholinergic neurons. Dopaminergic neurons of the substantia nigra and striatum have been found to be the main source of BDNF secretion. BNDF easily crosses the blood-brain barrier [72]. Patients with extreme depressive symptoms tends to show lower levels of BDNF. The BDNF levels are also correlated with the markdown of the hippocampal volume[73].The BDNF concentration and its changes are not actually correlated with improvement in depression ,instead the levels of BDNF is increased during antidepressant treatment. Antidepressant-ketamine showed rapid antidepressant response after its administration, which is responsible for the increase in BDNF levels[74]. reduced BDNF values are more prominent in women with depression, and hence long-term use of antidepressant raises its concentration in women.

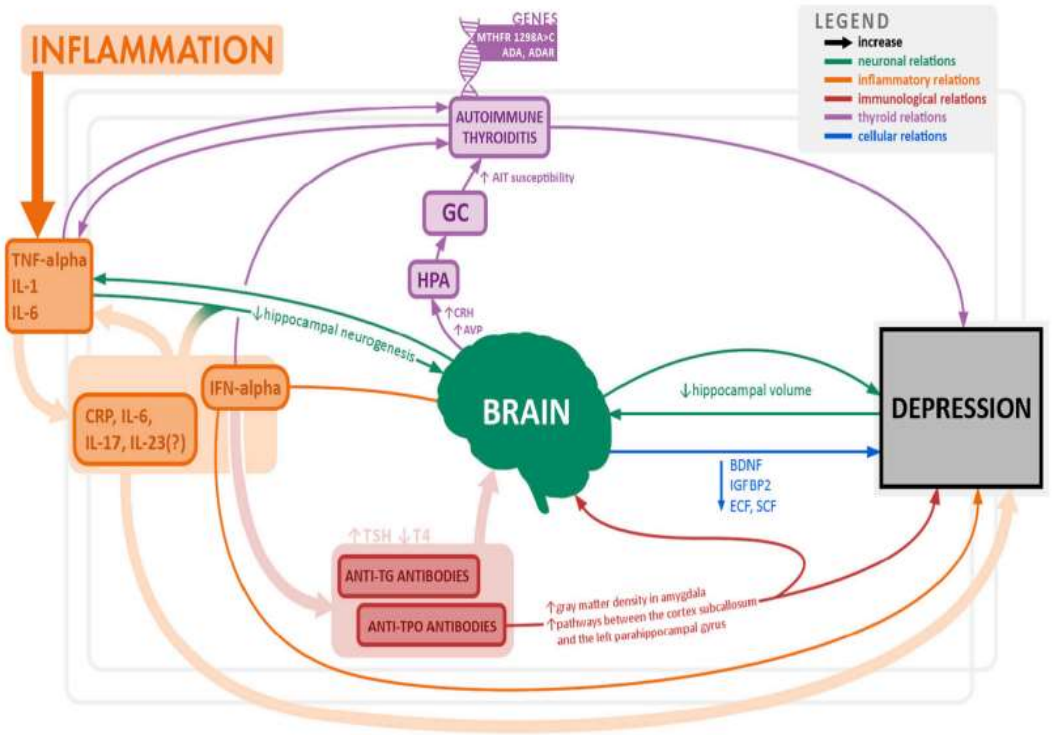

Figure 2. Overview of Patho mechanisms associated with depression and thyroid dysfunction

BDNF also plays a significant role in disease like cardiovascular disease and depression. There are many studies which are conducted that demonstrate the bidirectional relationship between depression and CVD on the grounds of epidemiological data, risk factors [75] [76] [77]. BDNF levels in serum are known to be a reliable biomarker for depression[78] [79]and one of the consistent parameter in prediction of cardiovascular risk[80] [81].Stress induced reduce in the BDNF levels are one of the major depressive symptoms[82], this is due to impairment of neuroplasticity, neurogenesis and promotion of cell atrophy[83].BDNF is known to be involved in inducing the oxidative stress by activating the enzyme oxidase in coronary artery smooth muscle cell that leads to atherosclerotic plaque instability[84]. High serum levels of BDNF protect against CVD and mortality by CVD and thus low serum levels are prone risks for coronary events [81][83][84]

LITERATURE REVIEW

Author	Title	Aim and Objective	Results and Outcome of the study	Journal name and Reference
Zofia *et al*,(2020)	Depression and Autoimmune Hypothyroidism—Their Relationship and the Effects of Treating Psychiatric and Thyroid Disorders on Changes in Clinical and Biochemical Parameters Including BDNF and Other Cytokines—A Systematic	Toestablish relationship between depression and AHT and the Effects of Treating Psychiatric and Thyroid Disorders on Changes in Clinical and Biochemical Parameters Including BDNF and Other Cytokines	Abnormal profiles of neuronal growth factors and haemopoietic factors including BDNF is observed in patients with high risk of AHT and mood disorder.	*Pharmaceuticals* [85]
Massimo *et al*,(2023)	The Role of Brain-Derived Neurotrophic Factor (BDNF) in Depression and Cardiovascular Disease: A Systematic Review	To examine the bidirectional relationship between CVD and depression, focusing on the potential role of low serum BDNFlevels in the development of either disease in the presence of the other	BDNF plays very vital role in explaining one side of the bidirectionalrelationship between CVD and depression.	*Life* [86]
Rachel *et al*,(2023)	Stress-induced alterations in hippocampal BDNF in the pathophysiology of major depressive disorder and the antidepressant effect of saffron	To review aimed to investigate the mechanistic link between stress-induced alterations in hippocampal BDNF and major depression disorder.	Saffron plausibly exert antidepressant effect by increasing BDNF levels but this is yet to be confirmed in clinical trials.	Journal of Affective Disorders Reports [87]
Andrea *et al*,(2023)	Implementation of effect biomarkers in human biomonitoring studies: A systematic approach synergizing toxicological and epidemiological knowledge	To determine the use of biomarker and their ability to detect early biological effects of chemical exposure	Establishes the grounds for achievingHuman biomonitoring research, which is to link exposure biomarkers.	International Journal of Hygiene and Environmental Health [88]

Title	Aim and Objective	Results and Outcome of the study	Journal name and Reference
Brain-derived neurotrophic factor and nerve growth factor expression in endometriosis: A systematic review and meta-analysis	To examine levels of expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)amongst patients with endometriosis.	Higher expression of BDNF in endometrial lesions and increased serum levels of BDNF in endometriosis patients.	Taiwanese Journal of Obstetrics & Gynecology [89]
The Effects of Treatment in Psychotic Disorders—Changes in BDNF Levels and Clinical Outcomes: Systematic Review	To outline emerging data regarding the influence of different antipsychotic drugs and non-pharmacological treatment methods on BDNF and discuss their role as predictors of treatment outcome.	Findings for both pharmacological and non-pharmacological treatments show that an increase in BDNF levels does not correlate with clinical response to treatment.	International Journal of Environmental Research and Public Health [90]
The Neurobiological Basis of Cognitive Side Effects of Electroconvulsive Therapy: A Systematic Review	To comprehensively summarize current evidence assessing potential biomarkers of ECT-related cognitive side effects	Emphasized that ECT does not induce neuronal damage but also pointed out biochemical, genetic, and neuroimaging measures as potential predictive biomarkers of ECT-induced cognitive impact.	*Brain Sciences* [91]
Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies	To analyse the association between BDNF levels and the severity of affective symptoms in BD as well as the effects of acute drug treatment of mood episodes on BDNF levels	peripheral BDNF level, better documented in plasma than in serum, is a potential biomarker of disease activity in BD.	BMC medicine [92]

Aim and Objective	Results and Outcome of the study	Journal name and Reference	Author
To demonstrate the higher frequency of the ancestral (wild) GG (Val/Val) genotype, although associations of the polymorphic A (Met) allele, changes in BDNF protein serum levels, or both were also found in MDD.	Associations of the polymorphic A (Met) allele, changes in BDNF protein serum levels, or both were found in MDD	**Behavioural Neurology | Hindawi** [93]	**Danqiu *et al*,(2023)**
To determine association between this BDNF polymorphism and hippocampal volumes	No association between BDNF polymorphism and hippocampal volumes.Hippocampal volumes were significantly lower in neuropsychiatric patients than in healthy controls.	Neuroscience and Biobehavioral Reviews [94]	**Anna *et al*,(2023)**
To evaluate whether BDNF levels are correlated with improvement of depression	Antidepressant treatments are associated with an increase in BDNF suggest that this neuropeptide might be a ' final common pathway' in MDD.	International Journal of Neuropsychopharmacology [95]	**Adriana *et al*,(2021)**
To determine CRP or IL-6 levels and subsequent depressive symptoms	Raised inflammatory markers have a small but significant association with the subsequent development of depressive symptoms.	Journal of Affective Disorders [96]	**Brisa *et al*,(2015)**

Results and Outcome of the study	Journal name and Reference	Author	Title
No definitive results were drawn regarding the association between TNF-α and vitamin D and COVID-19 severity and mortality.	*Pathogens* [97]	**Caroline *et al*,(2021)**	BDNF Genetic Variant and Its Genotypic Fluctuation in Major Depressive Disorder
Each inflammatory marker was positively associated with depression. Depression was related to CRP and IL-6 among patients with cardiac disease or cancer.	psychosomatic medicine [98]	**Harrisberger*et al*, (2015)**	BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: A systematic review and meta-analysis
The higher level of IL-6 in AF patients is related to long-term thromboembolic events including stroke	Portuguese Journal of Cardiology [99]	**Andre´ Russowsky *et al*, (2008)**	A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression
Association of IL-6 and JAK2 genetic variants with the increased risk of CRC while STAT3 genetic variants in our study failed to prove the correlation in the whole population	[100]	**Vyara *et al*, (2013)**	CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies

Journal name and Reference	Author	Title	Aim and Objective
Alimentary Pharmacology and Therapeutics [101]	**Ceria *et al*, (2022)**	To determine he Association between TNF-α, IL-6, and Vitamin D Levels and COVID-19 Severity and Mortality: A Systematic Review and Meta-Analysis	aims to determine the relationship, if any, between TNF-α, IL-6, vitamin D, and COVID-19 severity and mortality
Cytokine [102]	**Bryant *et al*, (2015)**	To determine Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis	To assess the magnitude and direction of associations of depression with C-reactive protein (CRP), interleukin (IL)-1, and IL-6 in community and clinical samples.
International Journal of Hygiene and Environmental Health [103]	**Peng *et al*, (2020)**	To evaluate the increased serum interleukin-6 level as a predictive biomarker for atrial fibrillation: A systematic review and meta-analysis	to investigate the association between IL-6 and thromboembolic events, as well as bleeding events, acute coronary syndrome (ACS) events and all-cause mortality in AF.
Drug Discovery Today [104]	**Shuwei *et al*, (2015)**	To study genetic variants in IL-6/JAK/STAT3 pathway and the risk of CRC	To determine he relationship between polymorphisms in IL-6/JAK/STAT3 pathway genes and CRC risk

Author	Title	Aim and Objective	Results and Outcome of the study
S. Bek*et al*, (2017)	Systematic review: genetic biomarkers associated with anti-TNF treatment response in inflammatory bowel diseases	To identify polymorphisms and candidate genes from the literature that are associated with anti-tumour necrosis factor treatment response in patients with inflammatory bowel diseases,Crohn's disease and ulcerative colitis.	Status of pharmacogenomics of anti-TNF treatment is evaluated and it is found that biomarkers for clinical treatment selection are not yet available
Mohammad *et al*, (2020)	Interleukin-6 in irritable bowel syndrome: A systematic review and metaanalysis of IL-6 (-G174C) and circulating IL-6 level	To determine the level of IL-6 concentrations in patients with complicated Covid-19 compared with patients with noncomplicated disease	Higher IL-6 levels in IBS and IBS-D suggests a pro-inflammatory phenotype in these patients.Increased IL-6 in IBS might be an acquired phenomenon or mediated by other genotypes.
Claudia *et al*, (2021)	Lead (Pb) and neurodevelopment: A review on exposure and biomarkers of effect (BDNF, HDL) and susceptibility	To determine Pb exposure and biomarkers of effect and susceptibility, neurodevelopmental toxicity, epigenetic modifications, and transcriptomics	Serum BDNF and plasma HDL are potential candidates to be further validated as effect markers for routine use in HBM studies of Pb, complemented by markers of Fe and Ca status.
Saumya *et al*, (2022)	Brain-derived neurotrophic factor (BDNF) in perinatal depression: Side show or pivotal factor?	To establish the emerging role of BDNF in reproductive biology and discuss evidence suggesting its deficiency as a risk factor for perinatal depression.	With the strengthening link of BDNF deficiency and depression in pregnant women highlights the use of changes in neurotrophin as a surrogate endpoint for clinical and preclinical studies

CONCLUSION

the previous systematic review has conducted by clinical study in meta-analysis suggest that major depressive disorder is associated with neuroplasticity and the ethnic group with greater risk of developing depressive disorder are more likely to develop the auto immune thyroid disorder and vice versa. Abnormal levels of BDNF are observed in such patients and with those who are prone to develop AHT. Cytokine profile, similarly, in those patients having both disease-it is seen that there is increase in proinflammatory interleukin concentration-IL-6 and TNF. Anti-depressant drugs are known to be associated with the

increase in BDNF levels and the effects of SSRI's imply that inflammatory factors contribute to the pathogenesis of depression. Hence in conclusion, it is seen that patients with elevated antithyroid antibodies and AHT the severity of depression and occurrence is high. In contrast, levothyroxine and other antidepressant drugs decrease the pro-inflammatory cytokine levels which enable to explore and conduct studies on the role of BDNF in neurogenesis and neuroplasticity and explore the role of TNF and IL-6 as biomarkers in developments of brain and human body. However, not much information is available to fill the gap between the biomarkers and the associated diseases hence it is necessary to conduct in depth studies and research to determine the link and relationship between depression, cytokine levels and auto-antibodies in the body, that would help to facilitate the use of pharmacotherapy and it is also possible for congruity of those groups which are at higher risk of developing depression, also to predict the treatment to be given.

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Conflict of Interest
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