Repurposing of Metformin in the Nervous System: Is metformin the ultimate solution for neurodegenerative diseases?

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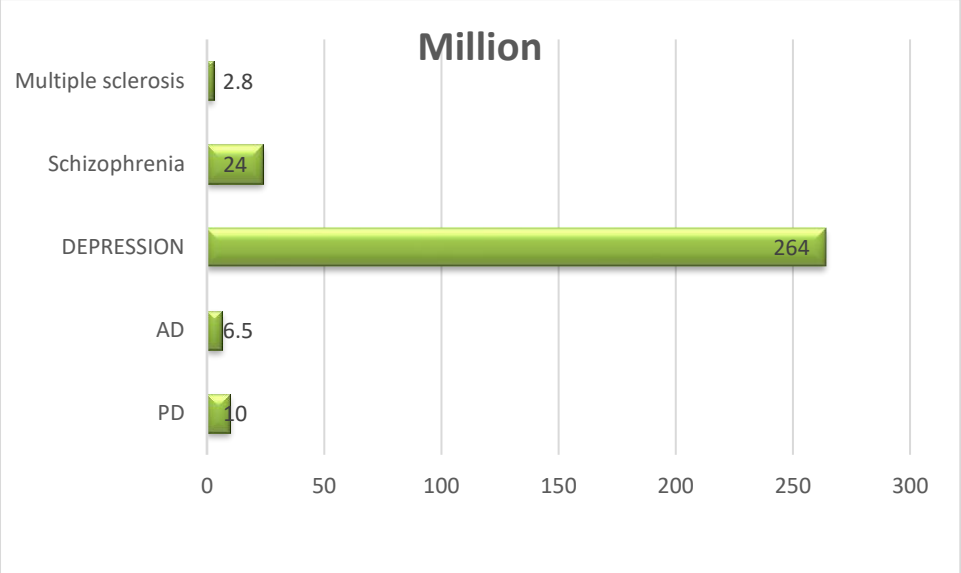
Abstract: -

Metformin belongs to the biguanide chemical family, which is largely used in the therapy of type 2 diabetes (T2D). Surprisingly, metformin's therapeutic potential goes beyond its prescribed anti-diabetic use. Nowadays Neurological diseases are very common for all age people. The medications and the treatments that we use to cure these diseases are also expensive and have side effects also. So It has been claimed that metformin medication has good effects on several neurological illnesses such as Parkinson's, Alzheimer's, schizophrenia, depression, and so on. Metformin can be a very good alternative medication for these diseases. This review examines how this medication can aid in neuroprotection for several neurological disorders. Furthermore, we investigate metformin's modes of action to better understand its neurological activity. There are pieces of information on metformin's neurological activity and its relationship with patients who is taking metformin for years. Here also explained how metformin delays neurological disorders in diabetic patients.

Keywords: - Metformin, Diabetes, AMPK, Neurodegenerative Disease, Repurposing, Diabetic agent

1. Introduction:

Aging is becoming a global concern, followed by a rise in aging-related neurodegenerative disorders (NDs). Dementia(mental illness), Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, depression, and moderate cognitive disorders are all examples of degenerative illnesses of the central nervous system (CNS)[1]. Regrettably, there is no known disease-specific treatment for these conditions, which are defined by the slow degeneration or demise of neurons, and they come at a high societal and financial cost[2].



The algorithm of different neurodegenerative diseases worldwide in 2023

New drugs for NDs are now in clinical testing, however, the failure-to-success ratio is dishearteningly 100:1.Worldwide, it is predicted that 5 crore individuals suffer from neurodegenerative disorders, and by 2050, this number will rise to 11.5 crores.[3]

Only a small number of medications have been authorized by the Food and Drug Administration (FDA) as first-line treatments for ischemic stroke and non-diabetic neuropathy (ND), with a mere 3% chance that CNS therapies will be introduced after entering phase-I clinical trials. Therefore, the creation of efficient treatments is essential, but this can only happen after the underlying causes of each illness are thoroughly understood. Additionally, the repurposing of medications that have shown notable outcomes in pre-clinical research might hasten the creation of efficient treatments.

Dopamine may mediate both cerebral and peripheral insulin sensitivity, pointing to a connection between ND and glucose metabolism. The function of metformin, a common oral biguanide that is the medicine of choice to treat type 2 diabetes (T2DM), in dementia and Parkinson's disease is extremely complicated, both in animal studies and clinical studies[4]. Considering how time-consuming ND is, there are currently very few randomized control trials (RCTs) of metformin in clinical studies of the degenerative neurological system. Assessing risk changes over such a short time is insufficient[5].

We conducted a meta-analytic review using a meta-analysis of the existing observational clinical trials investigating the influence of metformin on the emergence of ND to better

comprehend this query[6]. In several neurodegenerative disorders, metformin has recently been shown to offer neuroprotective qualities. In this work, we examine the neuroprotective potential of metformin based on collecting information from preclinical and clinical investigations blood-brain barrier is undoubtedly crossed by metformin, which has been associated with neuropathological changes in several preclinical studies that are suggestive of improved cognitive function[7].

2. Metformin in the Nervous System

2.1 Parkinson's Disease (PD)

Parkinson's disease (PD), a dreadful neurological illness, is characterized by Lewy pathology along with the slow demise of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [8].

PD, which is now a global health burden because of the aging population, is a worry. Despite the enormous gains that PD research has made recently, the gold standard medication only significantly slows the disease's progression by reducing symptoms[9] [10]. Therefore, there is an urgent need to research novel disease-modifying therapeutic strategies.

It has been demonstrated that metformin inhibits the phosphorylation and accumulation of -synuclein (SNCA), reduces oxidative stress, controls respiration predominantly by stimulating AMP-activated protein kinase (AMPK), and guards against neurodegeneration and aggravation disorders[11].

Overall, metformin's neuroprotective benefits in PD parthenogenesis present a novel prospective therapeutic method that has the potential to overcome the limitations of current PD treatment[12] [13].

Metformin(MT) is well-accepted and has no negative effects on weight or blood sugar levels[14].In addition to increasing insulin sensitivity, it decreases hepatic glucose synthesis and intestinal glucose absorption, all of which help treat hyperglycemia [15] [16]. AMP-activated protein kinase is activated to facilitate some of these activities (AMPK). In reaction to oxidative stress or hypoxia, AMPK regulates, among other things, cell survival.[17]

A recent study found that AGEs prevent the death of human neural stem cells (hNSCs) by blocking AMPK and its downstream pathways.[18] Human brain stem cells were protected by metformin's elevated AMPK activation. Given the critical role of -synuclein in the etiology of Parkinson's disease, there is fascinating evidence that metformin may mitigate some of the negative consequences of -synuclein in PD patients[19]. Furthermore, AMPK increases PGC1a, which increases mitochondrial activity. As expected, this increases mitochondrial function[20].

Metformin's antioxidant benefits were proven in a mouse study of catalepsy brought on by haloperidol[21]. Following haloperidol's induction of catalepsy, lower levels of glutathione, catalase, and superoxide dismutase (SOD) activity were found. These all have well-established antioxidant properties. However, metformin therapy markedly boosted SOD activity, glutathione, and catalase levels[22]. There was also a decrease in catalepsy, which the authors speculated was caused, at least in part, by the medication's ability to lower oxidative stress. It was examined in real time[23]. In this mouse model, decreased plasma oxidative stress following metformin therapy was linked to better mitochondrial dysfunction and defense

against mitochondrial swelling[24]. Oxidative stress in the brain was also eliminated. The mitochondrial permeability transition pore (mPTP), when it opens, can cause mitochondria to inflate[25]. ROS are known to trigger the mPTP. The authors proposed that the decrease in ROS during metformin therapy inhibits MPTP from opening, lowering mitochondrial swelling and providing a neuroprotective effect[26].

Additionally, it was demonstrated that following metformin therapy, learning and memory deficiencies brought on by a high-fat diet may be corrected[27]. The adverse effects and interactions of metformin may limit its use in the future[28].

Overall, the evidence suggests that metformin has neuroprotective effects that may help treat a range of neurodegenerative diseases[29]. Although there are numerous pathogenic pathways (some of which are listed above) that may be involved in the development of PD and are altered by metformin treatment, the exact reason why metformin medication reduces the risk of PD in diabetics is yet unknown[30]. Figure 1 shows the different pathways of the mechanism of action of metformin related to neuroprotection for NDD.

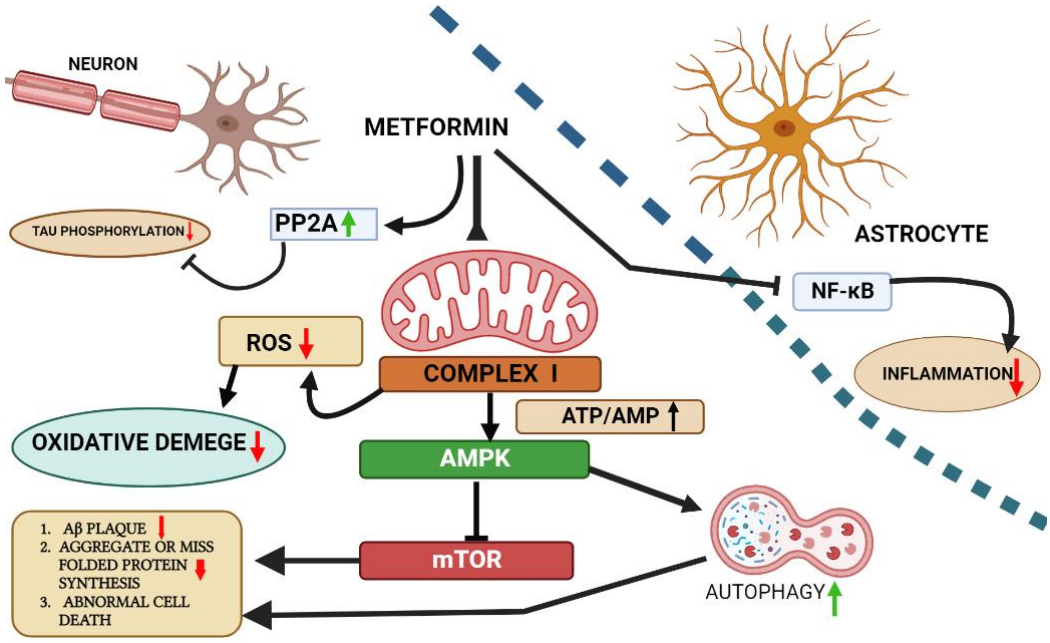


Figure 1 Mechanisms of metformin related to neuroprotection for NDD.[31]

2.2 Alzheimer's Disease (AD)

As far as dementia goes, Alzheimer's disease is the most prevalent. The condition is gradual, starting with minor memory loss and potentially progressing to the loss of communication and environmental awareness. The brain regions that are responsible for cognition, memory, and language are affected by Alzheimer's disease.

A disturbance in the electron transport chain (ETC) enzymes pyruvate dehydrogenase complex and cytochrome c, for example, causes a decrease in the number of mitochondria and a change in their function in AD brains[32]. Due to the role that mitochondria play in AD, it has been suggested that mitochondrial dysfunction happens before an accumulation of AD and may be

the cause of the damaging cascade in this illness[33]. Insufficient mitochondrial bioenergetics causes amyloid-protein precursor (APP) to be pushed towards amyloidogenic pathways, according to extensive in vivo and in vitro research[34].

This idea, however, was contested, and it was proposed that mitochondrial failure happens after amyloid aggregation and that A toxicity is predominantly mediated via the mitochondrial respiratory chain. It's interesting to note that there has been evidence of enhanced interaction between mitochondria and protein aggregates related to AD[35]. For instance, it has been discovered that APP and A fragments are trapped on the mitochondrial outer membrane, blocking the permeability transition pore (mPTP), steering to the build-up of dangerous oxidizing agents and cell death, and impairing cognitive function[36] [37].

The disruption of microtubules, which are in charge of the motion of mitochondria inside the cell, by tau protein has also been found to impair mitochondrial dynamics[38]. The significance of mitochondrial abnormalities in Alzheimer's disease is growing, and some have suggested that targeted drugs that specifically target these organelles could be a useful therapeutic approach for improving the cognitive, behavioral, and biochemical changes linked to the disease's progression [39] [38].

There's no cure for Alzheimer's, but there are treatments that may change disease progression, and drug and non-drug options that may help treat symptoms. Understanding available options can help individuals living with the disease and their caregivers cope with symptoms and improve quatheir lity of life.

From a molecular perspective, our findings suggest that metformin may be able to reverse the physio-pathological defects linked to AD[40].

A biguanide called metformin inhibits hepatic gluconeogenesis while promoting peripheral insulin sensitivity[41]. Although the exact mechanism of action is still unclear, it has been shown that metformin's antihyperglycemic effects are mostly caused by the inhibition of hepatic glucose production[42]. Other routes of action include increased glucose uptake from the blood into tissues, reduced glucose production in the liver, and reduced insulin demands for glucose disposal [43].

Scientists believe that metformin's neuroprotective benefits in Alzheimer's disease are generated by the activation of AMPK-dependent mechanisms in human brain stem cells, albeit the specific mechanism is unclear [44] [30]. Metformin has also been shown to significantly reduce beta-secretase 1 (BACE1) protein production and functionality in both in vivo and cell culture models. BACE1 is a protein that is required for the cleavage of amyloid precursor protein as well as the synthesis of -amyloid (A). Production is regulated by reducing BACE1 cleavage products [45].

Cheng et al. observed that individuals with T2D who took metformin or sulfonylureas for a lengthy period had a much lower risk of developing dementia.[46]

2.3 Depressive Disorders

Major depressive disorder (MDD) is defined by the American Psychiatric Association as either an irritable mood, a decrease in interest/pleasure, or both. Changes in the neurotransmitter system, as well as deregulation of the immunological and endocrine systems, have all been proposed as probable processes by which depression arises[47]. However, these views have been dismissed because traditional antidepressant therapies are only successful in 50% of

patients[48]. As a result, it is now widely understood that the etiology of depression is diverse, with genetic and environmental variables interacting to contribute to the pathophysiology of depressive illnesses[49]. Surprisingly, metabolic dysfunction appears to be a major initiator of depression[50].

Recent research has significantly broadened the area to regard metabolic disturbance as the primary mediator of depression. Clinical evidence has shown a tight relationship between emotions and metabolic disorders, particularly insulin sensitivity, resulting in depression being categorized as metabolic syndrome type II[51]. This notion has lately received a lot of attention, thanks to a flurry of research emphasizing the favorable implications of insulin in emotions and affection via the hypothalamic pituitary adrenal (HPA) axis, neurogenesis, synaptic plasticity, and neurotrophic properties [52]. Furthermore, in depressed brain regions, insulin receptors and their activity are reduced, indicating another hallmark of brain insulin resistance in such disorders. Other findings include the fact that intracerebral injections of STZ in mice resulted in depressive-like signs, which were reversed by insulin therapy, highlighting the function of insulin in the creation of depression[53]. Disparities in brain glucose metabolism have also been connected to the pathophysiology of depression, with a reduction in GLUT transporters in the hippocampus, PFC, and amygdala after the presence of depressive symptoms[54]. Another study has discovered that depressed rodents have altered glucose metabolism, which is accompanied by an increase in the glycolysis enzyme phosphofructokinase and a decrease in the Krebs cycle enzyme pyruvate dehydrogenase [55].

Apart from insulin resistance and altered glucose metabolism, the role of mitochondrial bioenergetics in the genesis of depression has received considerable attention [56]. In reality, mitochondria play an important part in cellular activities that, when disrupted, result in disrupted ATP generation, calcium build-up, ROS overproduction, and uncontrolled cell death[57]. Clinical investigations show a strong relationship between mitochondrial dysfunction and depression. In rodent investigations, depressive-like symptoms were connected to mitochondrial dysfunction, as demonstrated by lower stage 3 (ST3) oxygen utilization levels in the cortices, hippocampi, and hypothalamus regions of CMS-sensitive mice, as well as altered mitochondrial membrane potential[58].

Overall, these findings point to the relevance of resolving metabolic disturbances as a prospective therapeutic strategy for neurological illnesses like depression. In this regard, the use of specific anti-diabetic medications may be advantageous due to their efficacy in lowering metabolic changes comparable to those caused by diabetes[59]. The following part will go into the efficacy of metformin, commonly known as an insulin sensitizer, in addressing metabolic damage in depression [19].

Despite significant progress in the field, no effective therapies for depression are presently available. First-line treatments for depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine uptake inhibitors (SNRIs) [60]. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors are two further antidepressant groups (MAOIs). However, these antidepressant drugs have several disadvantages [61]. Monoaminergic medicines, for example, may take weeks or even months to be effective. Preclinical and clinical data indicate that glutamatergic drugs have a more rapid and long-lasting antidepressant impact; yet, these therapies are ineffective, with considerable resistance rates in almost 20- 30% of depression patients [60,62]. Long-term antidepressant treatment, on

the other hand, is known to cause metabolic abnormalities such as increased body weight, hyperglycemia, elevated fasting glucose, hyperinsulinemia, insulin resistance, and dyslipidemia [63]. As a result, there is an urgent need to develop new drugs or treatment methods for depression. Because brain diseases and diabetes mellitus have overlapping molecular targets, a new line of research was begun to evaluate the influence of glucose-lowering medications, which are routinely used in T2D therapy, on mental health outcomes[59,64].

Guo et al. discovered that giving depressed T2D patients metformin for 24 weeks progresses cognitive performance and glucose metabolism while decreasing the severity of depressive symptoms [64,65]. According to these findings, Chen et al. discovered that being overweight and having limited physical capacity were depression risk factors in elderly diabetes patients. Surprisingly, metformin was shown to have antidepressant properties in these people[66].

Metformin causes a molecular antidepressant chain reaction. Stress activation and a rise in glucocorticoids (GCs) govern the action of the HPA axis in physiological conditions via a negative-feedback loop involving the glucocorticoid receptor (GR) in the brain.[67]. Stress, on the other hand, causes a reduction in GR function, the loss of negative response, and a sequential shift in the HPA axis function [68]. Furthermore, activating the HPA axis rises glucocorticoid release, which decreases serotonin synthesis. Diabetes-related inflammation and oxidative damage in the brain can cause a comparable decrease in central serotonin availability[69].

2.4 Schizophrenia

Schizophrenia is a persistent, severe mental illness that has an impact on a person's relationships with others as well as their thinking, acting, and emotional expression. Despite not being as prevalent as other severe mental disorders, schizophrenia can be the most persistent and incapacitating.

Schizophrenia patients have an extraordinarily elevated percentage of metabolic comorbidities, such as obesity, dyslipidemia, as well as type 2 diabetes, all of which impart to the elevated mortality and morbidity rates seen in this patient population [70]. Type 2 diabetes is three to nine times more common in the schizophrenic community than in the overall population, and individuals with schizophrenia die from cardiovascular disease 15-20 years sooner on average[71]. This high comorbidity is caused by both endogenous (genetic) and external causes (i.e., lifestyle factors, a lack of opportunity for medical treatment, and drugs). Among these qualities are antipsychotic medicines, which constitute the cornerstone of schizophrenia therapy [72]. Young patients in the early phases of the disease are more susceptible to antipsychotic-influenced metabolic dysfunction, as demonstrated by rates of glucose intolerance (55%), or flawed fasting glucose (21%), discovered as early as the first year of therapy [73]. Relatively young age along with a deficit of prior antipsychotic medication exposure are also risk factors for antipsychotic-influenced metabolic adverse outcomes. Moreover, metabolic disruption, alongside glucose dysregulation, takes place immediately following antipsychotic administration[74]. These metabolic issues have far-reaching negative consequences for cognitive function, medication adherence, ego, and comfort in life[75].

There are relatively few weight reduction therapies for people with schizophrenia that have been authorized by the U.S. Food and Drug Administration (FDA). Given the possibility of

exacerbating psychosis, sympathomimetic drugs including diethylpropion, phentermine, and a recently authorized combination of phentermine and topiramate are generally contraindicated. Orlistat, a pancreatic lipase inhibitor, failed to significantly reduce weight in overweight people with schizophrenia throughout the course of a 16-week trial. Other weight reduction medications, such as the recently licenced 5-HT2c agonist lorcaserin and a naltrexone and bupropion combination that is presently in development, have not been studied for their safety and effectiveness in treating schizophrenia.

Metformin has already been shown to enhance insulin sensitivity (as studied by HOMA-IR) and weight loss in patients having schizophrenia. Metformin enhanced HOMA-IR in this experiment, although the weight loss effects were insignificant [76]. Individuals in this experiment demonstrated overt glucose dysregulation, which is a demographic that is frequently excluded from research investigating weight-loss therapy in schizophrenia [77]. Meta-analysis of metformin studies in schizophrenia indicated that it was more beneficial earlier in the disease; maybe the weight loss results are diminished after patients show symptoms of prediabetes/diabetes[78]. The disparity between metformin's effectiveness on insulin sensitivity measurements evaluated by fasting and post-glucose load is significant [79]. Metformin increased fasting blood glucose levels and HOMA-IR but not the insulin sensitivity index generated from the OGTT (i.e. Matsuda index)[76,80]. Small specimen size makes it difficult to draw firm conclusions, yet there are various aspects worth discussing. Matsuda is a whole-body measure of insulin sensitivity that is impacted by both hepatic and skeletal glucose distribution, whereas HOMA-IR is frequently used to assess hepatic insulin resistance[81]. Metformin's main impact is thought to be reduced hepatic glucose production, with comprehensive lowerings in insulin resistance owing mostly to hepatic effects [82].

According to research, Metformin shows a reduction of hepatic glucose synthesis by affecting AMPK (AMP-activated protein kinase), a critical regulator of energy balance in the liver and the duodenum. It is also capable of crossing the blood-brain barrier including affecting the hypothalamus[83]. Metformin was found in diabetic rats' cerebral fluid following oral dosage, and it lowered food intake by lowering the production of orexigenic peptides. It also enhanced liver function in obese agouti mice by restoring intrahypothalamic levels of leptin and insulin, along with AMPK activation[84]. Surprisingly, olanzapine caused total-body insulin resistance in rats, whereas metformin corrected hepatic but not peripheral insulin resistance [85]. This presents a fascinating hypothesis that, in the setting of antipsychotic-induced dysglycemia, metformin differentially works on hepatic and non-hepatic targets to lower hepatic tolerance but not enhance insulin sensitivity in other critical targets like skeletal muscle or adipose tissue[15].

2.5 Multiple sclerosis

Multiple sclerosis (MS) is a severe demyelinating sickness characterized by axon remyelination that is delayed, building the condition prone to permanent degeneration. This supports the notion of gradual neurologic degeneration in the latter stages of MS, which can last for decades[86]. Remyelination slows with age due to the delayed differentiation of oligodendrocyte progenitor cells (OPCs) into oligodendrocytes, the CNS's myelin-forming cells [87]. Indeed, research has shown that the regulatory mechanisms that govern OPC differentiation are non-functional in the aged brain [88,89]. An additional study found that

undifferentiated OPCs are present in chronically demyelinated MS lesions and that the quantity of OPCs in white matter lesions of old mice rises [90]. These OPCs failed to contribute to remyelination, indicating that remyelination requires OPC development into oligodendrocytes. It has also been shown that feeding the aged brain with pro-differentiating chemicals can enhance remyelination [91,92]. In contrast, aged OPCs progressively differentiate and become susceptible to pro-differentiation signals. Cellular aging indicators such as mitochondrial failure, unfolded protein response, autophagy, NF-kB, and p-38 MAPK signaling are associated with functional capacity decline.

How Metformin can be a help for Multiple sclerosis?

Metformin, when employed as a pharmaceutical method to target endogenous OPCs, enhanced myelin nation via an AMPK-dependent mechanism, resulting in improved mitochondrial activity, which is essential for OPC differentiation[93,94]. Metformin also lowered oxidative stress by activating antioxidative defenses in cytokine-exposed oligodendrocytes via AMPK activation[95]. Metformin may be able to ameliorate neurologic impairments in MS and other neurodegenerative diseases [96].

2.6 Neurogenesis

Neurogenesis is the process by which new neurons are formed in the brain. Neurogenesis is crucial when an embryo is developing but also continues in certain brain regions after birth and throughout our lifespan.

Following ischemic damage, there is a rise in neuron production and subsequent neuroblast migration to the injured region of the brain as part of the endogenous healing system [97]. As a result, drugs that promote post-ischemic neurogenesis might be a feasible treatment option for ischemic stroke. The study looked at metformin's long-term neuroprotective advantages after hypoxic-ischemic injury and reported that it reduced neuronal degeneration in the CA1 region of the hippocampus. [98]. The hippocampus's CA1 region is especially prone to HI injury. Similarly, metformin treatment reduced pro-apoptosis protein BAX expression while increasing anti-apoptosis protein cleaved caspase 3 expressions in the cortex and hippocampus[99,100]. Another study found that metformin boosted neuroblast proliferation and differentiation in the hippocampus [101].

Metformin has been shown to increase neurogenesis regulation and may help repair cerebral ischemia damage. An I/R event can also stimulate astrocytes, resulting in enhanced glial fibrillary acidic protein production (GFAP). As a result, glial scars form in the brain, limiting neuron regeneration and delaying recovery following an ischemic episode[102,103]. Furthermore, metformin treatment following I/R injury reduces GFAP+ cells, indicating neuron regeneration and hence functional recovery[104].

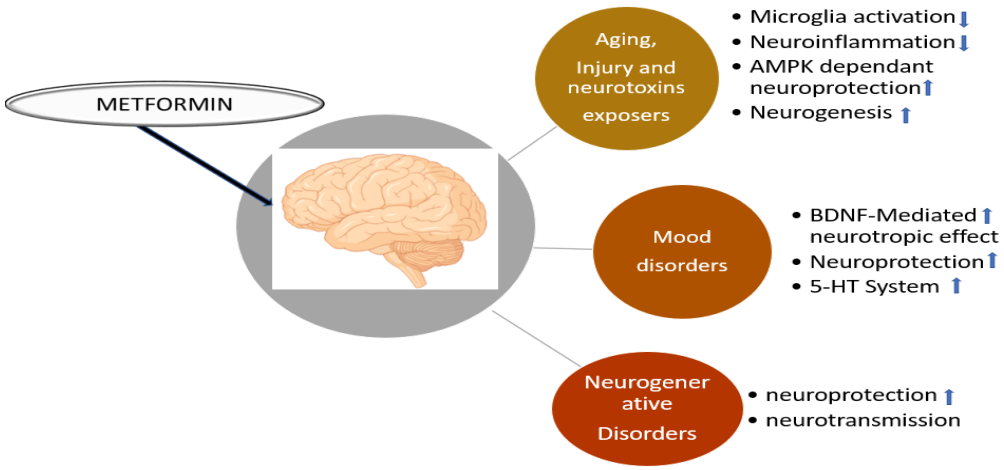


Fig2: Potential mechanisms of metformin regulation in CNS

3. Conclusion

As we can see metformin mainly help in treating neurodegenerative disease for those patients who are mainly taking metformin for treating diabetes for a long time. As we conclude that we can treat the disorders by using metformin. At least we can go for more research and combinations. Metformin is having well-known side effects and the formulation will be cost-friendly and no NDA and clinical- trial needed. Metformin can be a very good alternative for neurodegenerative disease.

4. Conflict of interest: -

Authors have zero conflict of interest.

5. Acknowledgement: -

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6. Reference: -

[1] Ageing as a risk factor for neurodegenerative disease - PubMed [Internet]. [cited 2022 Oct 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/31501588/.

[2] Przedborski S, Vila M, Jackson-Lewis V. Series Introduction: Neurodegeneration: What is it and where are we? J Clin Invest. 2003;111:3–10.

[3] Dementia [Internet]. [cited 2022 Nov 7]. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia.

[4] De Iuliis A, Montinaro E, Fatati G, et al. Diabetes mellitus and Parkinson's disease: dangerous liaisons between insulin and dopamine. Neural Regen Res. 2021;17:523–533.

[5] Ping F, Jiang N, Li Y. Association between metformin and neurodegenerative diseases of observational studies: systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2020;8:e001370.

[6] Dai J, Ports KD, Corrada MM, et al. Metformin and Dementia Risk: A Systematic Review with Respect to Time Related Biases. J Alzheimers Dis Rep. 2022;6:443–459.
[7] Lin Y, Wang K, Ma C, et al. Evaluation of Metformin on Cognitive Improvement in Patients With Non-dementia Vascular Cognitive Impairment and Abnormal Glucose Metabolism. Front Aging Neurosci. 2018;10:227.
[8] DeMaagd G, Philip A. Parkinson's Disease and Its Management. Pharm Ther. 2015;40:504–532.
[9] Ashraghi MR, Pagano G, Polychronis S, et al. Parkinson's Disease, Diabetes and Cognitive Impairment. Recent Pat Endocr Metab Immune Drug Discov. 2016;10:11–21.
[10] Alexander GE. Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder. Dialogues Clin Neurosci. 2004;6:259–280.
[11] (PDF) Neuronal AMP-activated protein kinase hyper-activation induces synaptic loss by an autophagy-mediated process [Internet]. [cited 2022 Nov 7]. Available from: https://www.researchgate.net/publication/331490069_Neuronal_AMP-activated_protein_kinase_hyper-activation_induces_synaptic_loss_by_an_autophagy-mediated_process.
[12] Sportelli C, Urso D, Jenner P, et al. Metformin as a Potential Neuroprotective Agent in Prodromal Parkinson's Disease—Viewpoint. Front Neurol. 2020;11:556.
[13] Lee TK, Yankee EL. A review on Parkinson's disease treatment. Neuroimmunol Neuroinflammation. 2021;8:222.
[14] Sami W, Ansari T, Butt NS, et al. Effect of diet on type 2 diabetes mellitus: A review. Int J Health Sci. 2017;11:65–71.
[15] Rines AK, Sharabi K, Tavares CDJ, et al. Targeting hepatic glucose output in the treatment of type 2 diabetes. Nat Rev Drug Discov. 2016;15:786–804.
[16] Hatting M, Tavares CDJ, Sharabi K, et al. Insulin regulation of gluconeogenesis. Ann N Y Acad Sci. 2018;1411:21–35.
[17] Hardie DG. AMP-activated protein kinase—an energy sensor that regulates all aspects of cell function. Genes Dev. 2011;25:1895–1908.
[18] Hasanvand A. The role of AMPK-dependent pathways in cellular and molecular mechanisms of metformin: a new perspective for treatment and prevention of diseases. Inflammopharmacology. 2022;30:775–788.
[19] Lv Z, Guo Y. Metformin and Its Benefits for Various Diseases. Front Endocrinol. 2020;11:191.
[20] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays Biochem. 2010;47:10.1042/bse0470069.
[21] The potential role of metformin in the treatment of Parkinso... : Journal of Bio-X Research [Internet]. [cited 2022 Nov 7]. Available from: https://journals.lww.com/jbioxresearch/Fulltext/2020/03000/The_potential_role_of_metformin_in_the_treatment.6.aspx.
[22] Adedeji HA, Ishola IO, Adeyemi OO. Novel action of metformin in the prevention of haloperidol-induced catalepsy in mice: Potential in the treatment of Parkinson's disease? Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:245–251.
[23] Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763.

[24] Belosludtsev KN, Belosludtseva NV, Dubinin MV. Diabetes Mellitus, Mitochondrial Dysfunction and Ca2+-Dependent Permeability Transition Pore. Int J Mol Sci. 2020;21:6559.
[25] Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia–reperfusion injury | Cardiovascular Research | Oxford Academic [Internet]. [cited 2022 Nov 7]. Available from: https://academic.oup.com/cardiovascres/article/60/3/617/335765.
[26] Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. Physiol Rev. 2014;94:909–950.
[27] Allard JS, Perez EJ, Fukui K, et al. Prolonged metformin treatment leads to reduced transcription of Nrf2 and neurotrophic factors without cognitive impairment in older C57BL/6J mice. Behav Brain Res. 2016;301:1–9.
[28] Drzewoski J, Hanefeld M. The Current and Potential Therapeutic Use of Metformin—The Good Old Drug. Pharmaceuticals. 2021;14:122.
[29] Ibrahim OHM, Hassan MA. The Use of Anti-Diabetic Drugs in Alzheimer's Disease, New Therapeutic Options and Future Perspective. Pharmacol Amp Pharm. 2018;9:157–174.
[30] Metformin – a Future Therapy for Neurodegenerative Diseases | SpringerLink [Internet]. [cited 2022 Nov 7]. Available from: https://link.springer.com/article/10.1007/s11095-017-2199-y.
[31] Frontiers | Exploring the Pharmacological Potential of Metformin for Neurodegenerative Diseases [Internet]. [cited 2022 Dec 23]. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2022.838173/full.
[32] Guo C, Sun L, Chen X, et al. Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen Res. 2013;8:2003–2014.
[33] Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances | Molecular Neurodegeneration | Full Text [Internet]. [cited 2022 Nov 7]. Available from: https://molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-020-00376-6.
[34] Wilkins HM, Swerdlow RH. Amyloid Precursor Protein Processing and Bioenergetics. Brain Res Bull. 2017;133:71–79.
[35] Nicoletti V, Palermo G, Del Prete E, et al. Understanding the Multiple Role of Mitochondria in Parkinson's Disease and Related Disorders: Lesson From Genetics and Protein–Interaction Network. Front Cell Dev Biol [Internet]. 2021 [cited 2022 Nov 7];9. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2021.636506.
[36] Rao VK, Carlson EA, Yan SS. Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. Biochim Biophys Acta. 2014;1842:1267–1272.
[37] Picca A, Calvani R, Coelho-Junior HJ, et al. Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation: Intertwined Roads to Neurodegeneration. Antioxidants. 2020;9:647.
[38] Blagov AV, Grechko AV, Nikiforov NG, et al. Role of Impaired Mitochondrial Dynamics Processes in the Pathogenesis of Alzheimer's Disease. Int J Mol Sci. 2022;23:6954.
[39] Ebneth A, Godemann R, Stamer K, et al. Overexpression of Tau Protein Inhibits Kinesin-dependent Trafficking of Vesicles, Mitochondria, and Endoplasmic Reticulum: Implications for Alzheimer's Disease. J Cell Biol. 1998;143:777–794.

[40] Rojas M, Chávez-Castillo M, Bautista J, et al. Alzheimer's disease and type 2 diabetes mellitus: Pathophysiologic and pharmacotherapeutics links. World J Diabetes. 2021;12:745–766.
[41] Madiraju AK, Qiu Y, Perry RJ, et al. Metformin Inhibits Gluconeogenesis by a Redox-Dependent Mechanism In Vivo. Nat Med. 2018;24:1384–1394.
[42] Cellular and Molecular Mechanisms of Metformin Action | Endocrine Reviews | Oxford Academic [Internet]. [cited 2022 Nov 7]. Available from: https://academic.oup.com/edrv/article/42/1/77/5902802.
[43] Wilcox G. Insulin and Insulin Resistance. Clin Biochem Rev. 2005;26:19–39.
[44] Chiang M-C, Cheng Y-C, Chen S-J, et al. Metformin activation of AMPK-dependent pathways is neuroprotective in human neural stem cells against Amyloid-beta-induced mitochondrial dysfunction. Exp Cell Res. 2016;347:322–331.
[45] Hettich MM, Matthes F, Ryan DP, et al. The Anti-Diabetic Drug Metformin Reduces BACE1 Protein Level by Interfering with the MID1 Complex. PLoS ONE. 2014;9:e102420.
[46] Zhang J-H, Zhang X-Y, Sun Y-Q, et al. Metformin use is associated with a reduced risk of cognitive impairment in adults with diabetes mellitus: A systematic review and meta-analysis. Front Neurosci. 2022;16:984559.
[47] Chand SP, Arif H. Depression. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Nov 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430847/.
[48] Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369–388.
[49] HASLER G. PATHOPHYSIOLOGY OF DEPRESSION: DO WE HAVE ANY SOLID EVIDENCE OF INTEREST TO CLINICIANS? World Psychiatry. 2010;9:155–161.
[50] Chan KL, Cathomas F, Russo SJ. Central and Peripheral Inflammation Link Metabolic Syndrome and Major Depressive Disorder. Physiology. 2019;34:123–133.
[51] Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr Dis Treat. 2017;13:1245–1262.
[52] Janssen JAMJL. New Insights into the Role of Insulin and Hypothalamic-Pituitary-Adrenal (HPA) Axis in the Metabolic Syndrome. Int J Mol Sci. 2022;23:8178.
[53] Kleinridders A, Cai W, Cappellucci L, et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. Proc Natl Acad Sci U S A. 2015;112:3463–3468.
[54] Pandya M, Altinay M, Malone DA, et al. Where in the Brain Is Depression? Curr Psychiatry Rep. 2012;14:634–642.
[55] Głombik K, Detka J, Góralska J, et al. Brain Metabolic Alterations in Rats Showing Depression-Like and Obesity Phenotypes. Neurotox Res. 2020;37:406–424.
[56] Sivitz WI, Yorek MA. Mitochondrial Dysfunction in Diabetes: From Molecular Mechanisms to Functional Significance and Therapeutic Opportunities. Antioxid Redox Signal. 2010;12:537–577.
[57] Bolisetty S, Jaimes EA. Mitochondria and Reactive Oxygen Species: Physiology and Pathophysiology. Int J Mol Sci. 2013;14:6306–6344.
[58] Allen J, Romay-Tallon R, Brymer KJ, et al. Mitochondria and Mood: Mitochondrial Dysfunction as a Key Player in the Manifestation of Depression. Front Neurosci. 2018;12:386.

[59] Markowitz S, Gonzalez JS, Wilkinson JL, et al. Treating Depression in Diabetes: Emerging findings. Psychosomatics. 2011;52:1–18.
[60] Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Exp Clin Psychopharmacol. 2015;23:1–21.
[61] Tricyclic antidepressants (TCAs) [Internet]. Mayo Clin. [cited 2022 Nov 8]. Available from: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20046983.
[62] Park M, Niciu MJ, Zarate CA. Novel Glutamatergic Treatments for Severe Mood Disorders. Curr Behav Neurosci Rep. 2015;2:198–208.
[63] Chokka P, Tancer M, Yeragani VK. Metabolic syndrome: relevance to antidepressant treatment. J Psychiatry Neurosci. 2006;31:414.
[64] Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care. 2009;32:193–203.
[65] Guo M, Mi J, Jiang Q-M, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin Exp Pharmacol Physiol. 2014;41:650–656.
[66] Chen F, Wei G, Wang Y, et al. Risk factors for depression in elderly diabetic patients and the effect of metformin on the condition. BMC Public Health. 2019;19:1063.
[67] Gjerstad JK, Lightman SL, Spiga F. Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. Stress Amst Neth. 2018;21:403–416.
[68] Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol. 2016;6:603–621.
[69] Xiong F, Zhang L. Role of the Hypothalamic-Pituitary-Adrenal Axis in Developmental Programming of Health and Disease. Front Neuroendocrinol. 2013;34:27–46.
[70] DE HERT M, SCHREURS V, VANCAMPFORT D, et al. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry. 2009;8:15–22.
[71] Annamalai A, Tek C. An Overview of Diabetes Management in Schizophrenia Patients: Office Based Strategies for Primary Care Practitioners and Endocrinologists. Int J Endocrinol. 2015;2015:969182.
[72] Patel KR, Cherian J, Gohil K, et al. Schizophrenia: Overview and Treatment Options. Pharm Ther. 2014;39:638–645.
[73] Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: a pilot double-blind randomized clinical trial | Translational Psychiatry [Internet]. [cited 2022 Nov 8]. Available from: https://www.nature.com/articles/s41398-021-01338-2.
[74] Libowitz MR, Nurmi EL. The Burden of Antipsychotic-Induced Weight Gain and Metabolic Syndrome in Children. Front Psychiatry. 2021;12:623681.
[75] Yang Y, Xie P, Long Y, et al. Previous exposure to antipsychotic drug treatment is an effective predictor of metabolic disturbances experienced with current antipsychotic drug treatments. BMC Psychiatry. 2022;22:210.
[76] Agarwal SM, Panda R, Costa-Dookhan KA, et al. Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: a pilot double-blind randomized clinical trial. Transl Psychiatry. 2021;11:219.

[77] Ringen PA, Engh JA, Birkenaes AB, et al. Increased Mortality in Schizophrenia Due to Cardiovascular Disease – A Non-Systematic Review of Epidemiology, Possible Causes, and Interventions. Front Psychiatry. 2014;5:137.
[78] Jarskog LF, Hamer RM, Catellier DJ, et al. Metformin for Weight Loss and Metabolic Control in Overweight Outpatients With Schizophrenia and Schizoaffective Disorder. Am J Psychiatry. 2013;170:10.1176/appi.ajp.2013.12010127.
[79] Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001;107:E55.
[80] Assessment of insulin sensitivity/resistance - PMC [Internet]. [cited 2022 Nov 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4287763/.
[81] Qureshi K, Clements RH, Saeed F, et al. Comparative Evaluation of Whole Body and Hepatic Insulin Resistance Using Indices from Oral Glucose Tolerance Test in Morbidly Obese Subjects with Nonalcoholic Fatty Liver Disease. J Obes. 2010;2010:741521.
[82] Wiernsperger NF, Bailey CJ. The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. Drugs. 1999;58 Suppl 1:31–39; discussion 75-82.
[83] Sun X, Zhu M-J. AMP-activated protein kinase: a therapeutic target in intestinal diseases. Open Biol. 2017;7:170104.
[84] He L. Metformin and Systemic Metabolism. Trends Pharmacol Sci. 2020;41:868–881.
[85] Remington GJ, Teo C, Wilson V, et al. Metformin attenuates olanzapine-induced hepatic, but not peripheral insulin resistance. J Endocrinol. 2015;227:71–81.
[86] Clinical and Biological Features - Multiple Sclerosis - NCBI Bookshelf [Internet]. [cited 2022 Nov 8]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222386/.
[87] Kuhn S, Gritti L, Crooks D, et al. Oligodendrocytes in Development, Myelin Generation and Beyond. Cells. 2019;8:1424.
[88] Egawa N, Shindo A, Hikawa R, et al. Differential roles of epigenetic regulators in the survival and differentiation of oligodendrocyte precursor cells. Glia. 2019;67:718–728.
[89] Fernandez-Castaneda A, Gaultier A. Adult oligodendrocyte progenitor cells - multifaceted regulators of the CNS in health and disease. Brain Behav Immun. 2016;57:1–7.
[90] Berghoff SA, Spieth L, Sun T, et al. Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. Nat Neurosci. 2021;24:47–60.
[91] Raffaele S, Boccazzi M, Fumagalli M. Oligodendrocyte Dysfunction in Amyotrophic Lateral Sclerosis: Mechanisms and Therapeutic Perspectives. Cells. 2021;10:565.
[92] Manousi A, Göttle P, Reiche L, et al. Identification of novel myelin repair drugs by modulation of oligodendroglial differentiation competence. EBioMedicine. 2021;65:103276.
[93] Muñoz-Carvajal F, Sanhueza M. The Mitochondrial Unfolded Protein Response: A Hinge Between Healthy and Pathological Aging. Front Aging Neurosci. 2020;12:581849.
[94] Sun N, Youle RJ, Finkel T. The Mitochondrial Basis of Aging. Mol Cell. 2016;61:654–666.
[95] AMP-activated protein kinase signaling protects oligodendrocytes that restore central nervous system functions in an experimental autoimmune encephalomyelitis model - PubMed [Internet]. [cited 2022 Nov 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/23759513/.
[96] Rotermund C, Machetanz G, Fitzgerald JC. The Therapeutic Potential of Metformin in Neurodegenerative Diseases. Front Endocrinol. 2018;9:400.

[97] Nemirovich-Danchenko NM, Khodanovich MYu. New Neurons in the Post-ischemic and Injured Brain: Migrating or Resident? Front Neurosci. 2019;13:588.
[98] Arbeláez-Quintero I, Palacios M. To Use or Not to Use Metformin in Cerebral Ischemia: A Review of the Application of Metformin in Stroke Rodents. Stroke Res Treat. 2017;2017:9756429.
[99] Mohsenpour H, Pesce M, Patruno A, et al. A Review of Plant Extracts and Plant-Derived Natural Compounds in the Prevention/Treatment of Neonatal Hypoxic-Ischemic Brain Injury. Int J Mol Sci [Internet]. 2021 [cited 2022 Nov 8];22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830094/.
[100] Albrakati A, Alsharif KF, Omairi NEA, et al. Neuroprotective Efficiency of Prodigiosins Conjugated with Selenium Nanoparticles in Rats Exposed to Chronic Unpredictable Mild Stress is Mediated Through Antioxidative, Anti-Inflammatory, Anti-Apoptotic, and Neuromodulatory Activities . Int J Nanomedicine. 2021;16:8447–8464.
[101] Reduced Cell Proliferation and Neuroblast Differentiation in the Dentate Gyrus of High Fat Diet-Fed Mice are Ameliorated by Metformin and Glimepiride Treatment | Request PDF [Internet]. [cited 2022 Nov 8]. Available from: https://www.researchgate.net/publication/51549205_Reduced_Cell_Proliferation_and_Neuroblast_Differentiation_in_the_Dentate_Gyrus_of_High_Fat_Diet-Fed_Mice_are_Ameliorated_by_Metformin_and_Glimepiride_Treatment.
[102] Sharma S, Nozohouri S, Vaidya B, et al. Repurposing metformin to treat age-related neurodegenerative disorders and ischemic stroke. Life Sci. 2021;274:119343.
[103] The Astrocytes in Brain Ischemia-Reperfusion Injury | Encyclopedia MDPI [Internet]. [cited 2022 Nov 8]. Available from: https://encyclopedia.pub/entry/23948.
[104] Liu L, Tian D, Liu C, et al. Metformin Enhances Functional Recovery of Peripheral Nerve in Rats with Sciatic Nerve Crush Injury. Med Sci Monit Int Med J Exp Clin Res. 2019;25:10067–10076.