Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 4
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Application of Enzyme Inhibition Therapy in the Management/Treatment of Neurological Conditions, Diseases, and Disorders

Kirubanandan Shanmugam[1]*

[1]Independent Research Professional, Chennai, India

Corresponding author: Kirubanandan Shanmugam, ksh1005@yahoo.com

Abstract: Enzyme inhibition therapy uses specific molecules to inhibit enzyme activity, targeting disease-related enzymes in medical treatments like cancer treatment and infectious disease management. Different types of inhibitors, competitive and non-competitive, bind to different sites and alter enzyme function. The success of this therapy depends on the inhibitor's specificity and delivery to the target site. Further research could lead to more effective treatments. Nowadays, the majority of medications are enzyme inhibitors and are in the clinical or pre-clinical stages of drug development. Enzyme inhibitors are often prescribed medications for a variety of illnesses, including neurological problems. There is only symptomatic therapy available for many neurological conditions, particularly neuro-degenerative disorders, as opposed to therapy based on knowledge of the underlying mechanisms of these diseases. Enzyme inhibitors are useful as they block the function of certain enzymes whose aberrant activity could be contributing to the illness. They also alleviate the symptoms and stop the disease's progression. This review discusses the mechanism of action of several enzyme inhibitors that have been prescribed as medications for neurological illnesses as well as some that are still in research stages.

Keywords: Enzyme inhibitors; Neurology; Mechanism of action; Enzymes

Online publication: April 30, 2024

1. Introduction

Protein molecules, known as enzymes, catalyze a variety of biological reactions. Enzyme inhibitors are substances that prevent an enzyme from catalyzing a reaction. Enzyme inhibitors, which are low molecular weight chemicals, can decrease an enzyme's activity either irreversibly or reversibly [1]. The basis of chemotherapy medications is to lower the activity of hyperactive enzymes, which slow the spread of the illness and relieve symptoms [2]. The mechanism by which enzyme inhibitors are employed as pharmaceutical agents is known as competitive enzyme inhibition. Inhibitors that share structural similarities with typical biochemical substrates are used to compete with the natural substrate for the enzyme's active site, preventing the formation of unwanted metabolic products [2]. Therefore, a sizable portion of oral therapeutic medications used in clinical practice are enzyme inhibitors.

Enzymes are currently popular targets for drug discovery, and efforts are being undertaken in drug development to identify and optimize drug candidates that specifically inhibit enzyme targets [3].

Enzyme inhibition therapy involves using specific molecules to inhibit the activity of certain enzymes in the body. This approach can be used in various medical treatments to target enzymes that are involved in disease processes. By blocking the activity of specific enzymes, this therapy aims to regulate or stop the biochemical pathways that contribute to the disease. There are different types of enzyme inhibitors, such as competitive inhibitors that bind to the active site of the enzyme and prevent substrate binding, or non-competitive inhibitors that bind to a different site and alter the enzyme's shape or function. Enzyme inhibition therapy can be used in various fields, such as cancer treatment, infectious disease management, and metabolic disorders. However, it is essential to consider the potential side effects and interactions of enzyme inhibition therapy, as disrupting enzyme activity can cause unintended consequences. Additionally, the specificity of the inhibitor and its delivery to the target site are crucial factors to consider for the success of this therapeutic approach. Further research and development in this area can lead to more effective and targeted enzyme inhibition therapies for a wide range of medical conditions. One key area is the treatment of Alzheimer's disease, where the inhibition of acetylcholinesterase (AChE) enzymes can help maintain higher levels of acetylcholine (ACh) in the brain, improving cognitive function. In Parkinson's disease, targeting enzymes involved in dopamine metabolism can help regulate neurotransmitter levels and alleviate symptoms. Enzyme inhibition therapy has also been explored in the treatment of epilepsy, where inhibiting specific enzymes involved in the metabolism of neurotransmitters like gamma-aminobutyric acid (GABA) can help control seizures. Additionally, enzyme inhibition therapy has shown potential in managing neurodegenerative disorders such as Huntington's disease, where targeting enzymes involved in protein aggregation can help slow the disease progression. In cases of stroke, inhibiting enzymes that contribute to neuroinflammation and oxidative stress can aid in reducing neuronal damage and improving recovery. Overall, enzyme inhibition therapy holds great promise in the field of neurology by providing targeted approaches to modulate enzymatic activity, regulate neurotransmitter levels, and mitigate neuronal damage.

Neural disorders are diseases affecting the spine, brain, and nerves. Humans suffer from around 600 common nervous system disorders, including Parkinson's, Alzheimer's, and stroke. As aging is coupled with inflammation, apoptosis, and excitotoxicity, age is a major risk factor for neurodegenerative illnesses, and these conditions are very common nowadays [4]. The Food and Drug Administration (FDA) has approved the majority of enzyme inhibitor medications for neurological illnesses, although some are under development. This review provides a summary of certain enzyme inhibitors that have been prescribed to treat neurological conditions/disorders/diseases, as well as their mechanism of action.

2. Types of neurodegenerative diseases

Neurodegenerative diseases are a group of conditions characterized by the progressive degeneration of the structure and function of the nervous system. These diseases are often chronic and debilitating, causing memory loss, impaired movement, and cognitive decline. Common examples include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). The exact causes of neurodegenerative diseases are not yet fully understood, but they are believed to result from a combination of genetic, environmental, and lifestyle factors. In many cases, these diseases are associated with the accumulation of abnormal proteins in the brain, leading to the death of nerve cells and the disruption of neural pathways. Treatment options for neurodegenerative diseases are currently limited, focusing on managing symptoms and slowing down disease progression. Early diagnosis and interventions, such as lifestyle modifications and medication, are important in improving the quality of life for individuals with neurodegenerative diseases.

2.1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects the brain, leading to memory loss and cognitive decline. It is the most common form of dementia and is characterized by the buildup of abnormal protein deposits in the brain, including amyloid plaques and tau tangles. These deposits interfere with communication between brain cells, ultimately leading to their death. The exact cause of the disease is not clear, but it is believed to be influenced by a combination of genetic, environmental, and lifestyle factors. Age is the biggest risk factor, with the majority of cases occurring in people over the age of 65. Symptoms typically start with mild memory problems and confusion, which worsen over time and can eventually interfere with daily activities and independent living. While there is no cure, treatments are available to help manage symptoms and improve the patient's quality of life. Research into AD is ongoing, with efforts focused on understanding its underlying mechanisms, developing new treatments, and finding ways to prevent or slow its progression. Early detection and intervention are key in managing the disease and improving outcomes for those affected.

The therapy of choice for AD is symptomatic. The most common clinical indication of dementia is poor learning and memory, but as the disease worsens, other symptoms like irritability, disorientation, and behavioral abnormalities appear. The pathological features of AD are peptides such as neurofibrillary tangles and β-amyloid (Aβ) plaques, which accumulate in the brain. β-secretase, an enzyme that cleaves amyloid precursor protein (APP), increases proteolysis as a result of mutations in APP, which in turn causes γ-secretases to generate more Aβ plaques. The buildup of Aβ plaques causes an increase in free radicals, which leads to neuronal loss. As a result, aggregation made of Aβ plaques closely correlates with the neurotoxicity caused by AD in the brain [4]. Cholinergic medication, anti-glutamatergic treatment, nonsteroidal anti-inflammatory medicines (NSAIDs), vitamins and antioxidants, and pharmacological control of neuropsychiatric symptoms are the five main drug classes used to treat AD. AChE inhibitors are frequently used to treat AD [5].

2.1.1. Inhibition of cholinesterases

ACh is a neurotransmitter responsible for the conduction of electrical impulses among neurons. When AChE hydrolyses Ach, its level decreases [6]. ACh is generated in neurons by the action of choline acetyltransferase concentrated in vesicles, and released from the presynaptic cell. On post- and presynaptic cells, nicotinic and muscarinic cholinergic receptors release ACh. After being released, it interacts with postsynaptic cells' muscarinic receptors. Ach hydrolyzes when it interacts with the muscarinic receptor, catalyzed by AChE. Neurotransmission can be sustained while ACh molecules are unhydrolyzed and able to engage with muscarinic receptors when AChE is suppressed. AChE inhibitors preserve neurotransmission by reducing ACh breakdown. The production of ACh should not be hampered by clinical AChE inhibitors [5]. Tacrine was the first AChE-inhibiting medication approved by the FDA and was initially given for AD, despite individuals exhibiting hepatotoxicity during clinical trials. Currently, clinical trials have shown donepezil, galantamine, and rivastigmine to be safer and more effective [5]. However, these medications may cause nausea, vomiting, diarrhea, cramping in the muscles, fatigue, headaches, weight loss, and bruises.

Cholinesterase inhibitors are commonly used in the treatment of AD to improve cognitive function and manage disease symptoms. These medications work by blocking the action of cholinesterase enzymes, which break down ACh in the brain. ACh is a neurotransmitter that is important for memory, learning, and other cognitive functions. By inhibiting cholinesterases, more Ach is available in the brain, which can help improve communication between nerve cells and alleviate the symptoms of AD. Common cholinesterase inhibitors used in the treatment of AD include donepezil, rivastigmine, and galantamine. These can help to slow the progression of cognitive decline and may also help to improve quality of life. However, it is important to note that cholinesterase inhibitors do not cure AD or stop the underlying progression of the disease. Overall,

cholinesterase inhibitors are an important part of the treatment plan for AD as they can help to improve cognitive function and quality of life in some patients.

2.2. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects movement. It is characterized by tremors, slowness of movement, muscle stiffness, and impaired balance. PD is caused by the loss of dopamine (DA)--producing neurons in the brain, which leads to a disruption in the brain's ability to control movement. There is currently no cure, but treatment options are available to help manage symptoms. Medications such as levodopa, dopamine agonists, and monoamine oxidase B (MAO-B) inhibitors are commonly used to alleviate motor symptoms. Physical therapy, occupational therapy, and speech therapy can also be beneficial in managing symptoms and improving motor function. Deep brain stimulation (DBS) is a surgical procedure that can help alleviate symptoms in some patients with advanced PD. Research into new treatments, such as gene therapy and stem cell therapy, is ongoing to discover a potential cure. Overall, early diagnosis and a multidisciplinary approach to treatment are crucial in managing PD and improving the quality of life for those affected.

PD is the second most prevalent neurodegenerative illness after AD. PD patients exhibit tremors, rigidity, hypokinesia, difficulty moving, and poor balance due to the loss of dopaminergic and striatal neurons in the substantia nigra, which are responsible for coordinating motor movements. Lewy bodies are aberrant protein aggregates that are present in PD-affected brains and are therefore thought to be the pathological hallmark of PD's progression [4]. Symptomatic therapy is the foundation for both PD and AD. PD can present with notable symptoms at an early stage, such as diminished olfactory sensitivity, autonomic dysfunction, and affective disturbance. However, the most noticeable symptoms are caused by DA depletion in the nigrostriatal pathway [7]. Levodopa, DA agonists, amantadine, antimuscarinics, catechol-o-methyl-transferase (COMT) inhibitors, and MAO-B enzyme inhibitors are commonly used to treat PD [8].

2.2.1. Inhibition of MAO

In neural tissues, the mitochondrial enzyme MAO is extensively expressed. **Figure 1** illustrates the oxidative deamination of amines facilitated by MAO. It also has a significant impact on the detoxification of amines and the metabolism of neurotransmitters such as noradrenaline, serotonin (5-HT), and DA. PD is currently being treated clinically with drugs that suppress MAO [7,9].

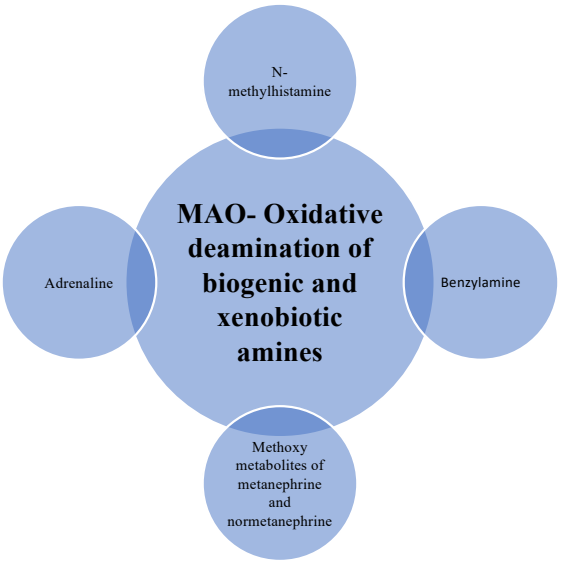

Figure 1. Oxidative deamination of amines catalyzed by MAO

Since MAO inhibitors prevent the breakdown of 5-HT and noradrenaline and lower the amount of amine present in their receptors, they were initially employed to treat depression disorders. Because DA levels in PD patients' brains are lower than normal, inhibiting DA oxidative metabolism effectively restores normal neurotransmitter levels [7]. The following equation represents the overall enzyme reaction of MAO-B [9]:

$$R - CH_2 - NH_2 + O_2 + H_2O \rightarrow R - CHO + NH_3 + H_2O_2$$

Inhibition of MAO is one of the treatment strategies for PD. MAO is an enzyme that breaks down neurotransmitters such as dopamine, norepinephrine, and serotonin. In PD, there is a decrease in dopamine levels due to degeneration of dopaminergic neurons in the brain, leading to motor symptoms. MAO inhibitors block the activity of MAO, increasing the levels of dopamine in the brain and helping to alleviate the motor symptoms of PD. These medications can improve motor function, reduce tremors, and enhance overall quality of life for individuals with PD. However, MAO inhibitors can have side effects such as interactions with certain foods or other medications, which can lead to a potentially dangerous increase in blood pressure known as the "cheese effect." It is important for patients taking MAO inhibitors to follow a specific diet and to be cautious when taking other medications to avoid adverse reactions.

2.3. Drugs

There are several types of drugs used in the treatment of PD. Levodopa is a precursor to DA, the primary neurotransmitter affected in PD. Levodopa is usually combined with carbidopa to prevent its breakdown before it reaches the brain. Dopamine agonists mimic the effects of DA in the brain to help alleviate PD symptoms. MAO-B helps prevent the breakdown of DA in the brain, thereby increasing DA levels. 4. COMT inhibitors help prolong the effects of levodopa by blocking an enzyme that breaks it down. Anticholinergics help reduce tremors and muscle stiffness in some PD patients. Amantadine helps reduce symptoms such as tremors and dyskinesias. It is important to note that the choice of medication and the treatment plan should be individualized based on the specific symptoms and needs of each patient. Rasagiline binds covalently to the N5 nitrogen of the flavin residue of MAO to inactivate the enzyme, making it a specific inhibitor of MAO-B [7]. Another MAO-B inhibitor that stops enzyme activity is selegiline. It works through an irreversible noncompetitive inhibition mechanism. As a result, it lowers DA levels and produces free radicals. Proteins and lipids are harmed by free radical generation in the pathophysiology of PD [10]. Dizziness, joint pain, headaches, depression, nausea, fever, muscular soreness, vomiting, impotence, and other common adverse effects are associated with rasagline. It is important to note that the choice of medication and the treatment plan should be individualized based on the specific symptoms and needs of each patient.

3. Heart attack

Both heart attacks and strokes are cardiovascular events that can be linked through common risk factors and underlying causes. A heart attack, also known as a myocardial infarction, occurs when blood flow to the heart muscle is blocked, leading to tissue damage. On the other hand, a stroke happens when blood flow to the brain is interrupted, either by a blockage (ischemic stroke) or bleeding (hemorrhagic stroke), resulting in brain cell damage. The interlink between heart attack and stroke is primarily due to the shared risk factors such as hypertension, diabetes, high cholesterol, obesity, and smoking. These risk factors contribute to the development of atherosclerosis, a condition where plaque buildup narrows and hardens the arteries, increasing the risk of both heart attacks and strokes. Additionally, certain underlying conditions like atrial fibrillation (an irregular heartbeat) can also raise the risk of both heart attacks and strokes. Moreover, individuals who have had a heart

attack are at higher risk of experiencing a stroke, and vice versa, due to the systemic nature of cardiovascular disease. Proper management of risk factors and lifestyle modifications like healthy diet, regular exercise, and medication adherence can help reduce the incidence of both heart attacks and strokes.

Stroke is ranked second among the neurological conditions of AD and is the leading cause of death for all diseases. **Figure 2** lists the many types of strokes. Known risk factors for stroke include heart disease, diabetes, atherosclerosis, and hypertension. Both heart attacks and strokes are cardiovascular events that can be linked through common risk factors and underlying causes. A heart attack, also known as a myocardial infarction, occurs when blood flow to the heart muscle is blocked, leading to tissue damage. On the other hand, a stroke happens when blood flow to the brain is interrupted, either by a blockage (ischemic stroke) or bleeding (hemorrhagic stroke), resulting in brain cell damage. The interlink between heart attack and stroke is primarily due to the shared risk factors such as hypertension, diabetes, high cholesterol, obesity, and smoking. These risk factors contribute to the development of atherosclerosis, a condition where plaque buildup narrows and hardens the arteries. Additionally, certain underlying conditions like atrial fibrillation (an irregular heartbeat) can also increase the risk of both heart attacks and strokes. Moreover, individuals who have had a heart attack are at higher risk of experiencing a stroke, and vice versa, due to the systemic nature of cardiovascular disease. Proper management of risk factors and lifestyle modifications like healthy diet, regular exercise, and medication adherence can help reduce the incidence of both heart attacks and strokes.

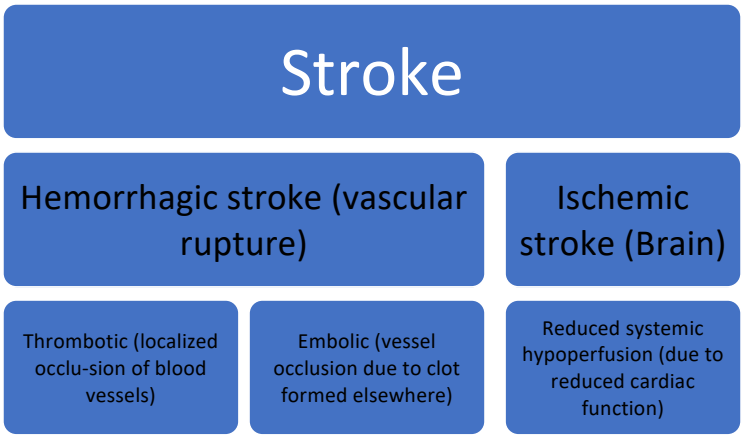

Figure 2. Types of strokes

Figure 3 illustrates the mechanism of stroke. Vascular blockage in the brain is the primary cause of stroke damage. As the blood arteries are damaged, the brain receives less blood, which reduces the amount of oxygen and glucose received. The brain's tissues are dependent on aerobic metabolism. In contrast to the surrounding areas, the brain parenchyma dies instantly from a lack of oxygen supply and insufficient respiratory reserve [4]. The most popular pharmaceutical intervention for preventing stroke is the use of antiplatelet medicines. Antithrombotic medications such as aspirin, ticlopidine, dipyridamole, clopidogrel, and extended-release warfarin are also used to prevent ischemic stroke. Since aspirin is inexpensive and does not require constant monitoring, it is typically recommended as the first-line medication for stroke [11].

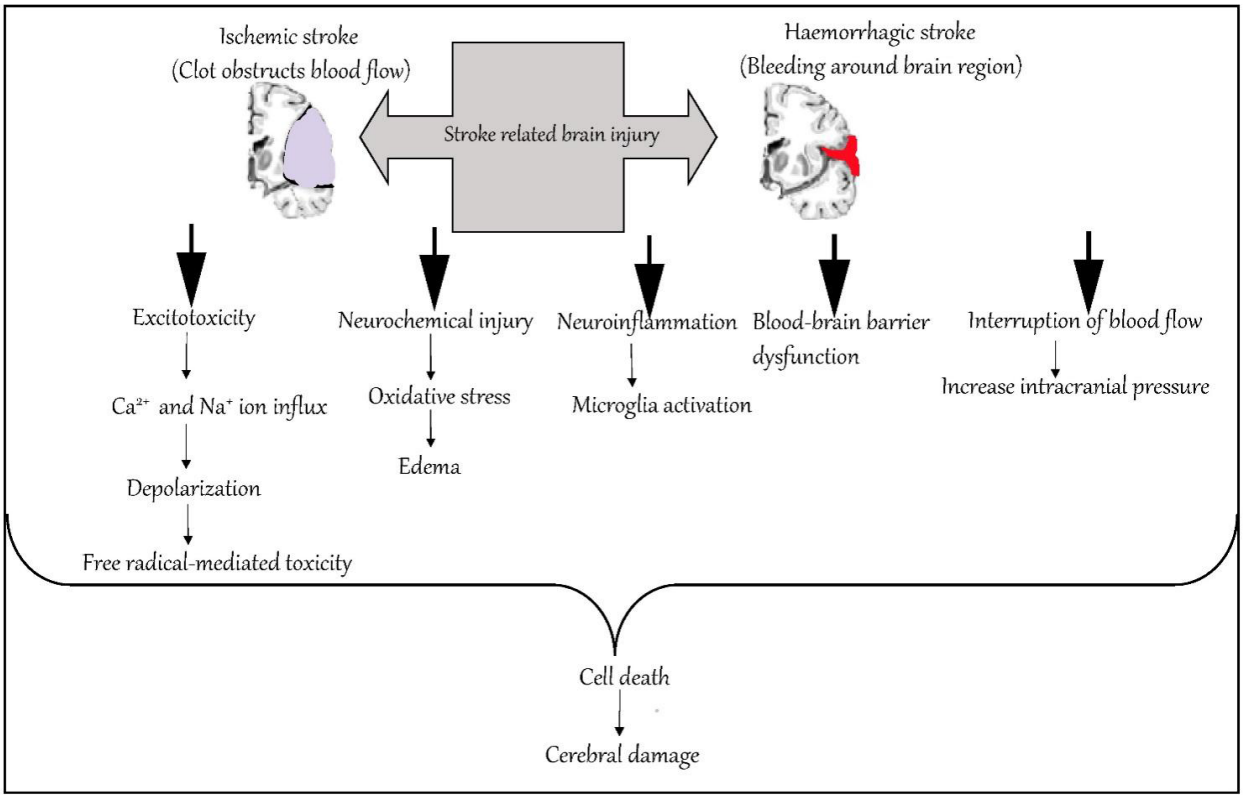

Figure 3. Mechanism of stroke

4. Brain Tumor

Tumors and cancer are generally defined as diseases or states in which cells divide erratically and kill healthy cells. A brain tumor is an amorphous mass of aberrant cells inside the skull. Primary and secondary brain tumors are the two varieties that exist. Since they start in the brain itself, primary brain tumors are benign, while secondary brain tumors are metastatic as they spread to the brain from other organs [12]. Brain tumors are abnormal growths of cells in the brain that can be either benign (non-cancerous) or malignant (cancerous). Symptoms of brain tumors can vary depending on their location and size but may include headaches, seizures, vision changes, difficulty with speech or memory, and personality changes. Diagnosis typically involves imaging tests such as computed tomography (CT) scans or magnetic resonance imaging (MRI), followed by a biopsy to determine the tumor type. Treatment options include surgery, radiation therapy, chemotherapy, targeted drug therapy, or a combination of these. The choice of treatment depends on factors such as the type of tumor, its location, and the patient's overall health. The prognosis for brain tumors varies widely depending on the type and stage of the tumor, but advancements in treatment have improved outcomes for many patients. It is important for individuals experiencing symptoms to seek medical attention promptly for proper evaluation and treatment. Support from healthcare professionals, family, and friends is also vital in coping with the challenges associated with brain tumors.

5. Therapeutic strategies

5.1. Inhibition of cyclooxygenase

The inhibition of cyclooxygenase (COX) is a pharmacological approach used to reduce inflammation, pain,

and fever by blocking the production of pro-inflammatory prostaglandins. There are two isoforms of COX: COX-1 and COX-2. COX-1 is constitutively expressed in various tissues and is involved in maintaining normal physiological functions, such as gastric mucosal protection and platelet aggregation. In contrast, COX-2 is induced in response to inflammatory stimuli and is mainly responsible for generating prostaglandins that mediate pain and inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, and naproxen work by inhibiting both COX-1 and COX-2 enzymes, leading to the reduction of prostaglandin synthesis. Selective COX-2 inhibitors, such as celecoxib, target only the COX-2 enzyme to achieve anti-inflammatory effects while minimizing gastrointestinal side effects associated with COX-1 inhibition. However, the use of COX-2 inhibitors has been linked to an increased risk of cardiovascular events. Overall, the inhibition of COX enzymes is a common therapeutic strategy for managing pain and inflammation, but it is essential to weigh the benefits against potential risks when selecting specific medications for individual patients.

5.1.1. Aspirin

By blocking the effects of platelets, aspirin helps to avoid vascular problems. Antiplatelet effects occur within 30 minutes of consumption and last the entire platelet life. Because thromboxane A2 (TXA2) causes platelet aggregation and vasoconstriction by deactivating COX enzymes, aspirin prevents the prostanoid TXA2 from being produced. Aspirin also has an impact on thrombogenesis and hemostasis. Because it inhibits platelets, stimulates fibrinolysis, and decreases plasma coagulation factors, aspirin is an effective anti-thrombogenic drug. Above all, it is crucial for preventing arterial thrombosis because of its capacity to inactivate COX-1 [11]. However, aspirin frequently causes rash, stomach ulcers, heartburn, abdominal pain, sleepiness, headaches, and cramps.

5.2. Inhibition of matrix metalloproteinases

Inhibition of matrix metalloproteinases (MMPs) is a therapeutic strategy used in various diseases such as cancer, cardiovascular diseases, and inflammatory conditions. MMPs are a family of enzymes that play a crucial role in tissue remodeling by degrading extracellular matrix proteins. Overexpression or dysregulation of MMPs can lead to tissue damage and disease progression. Several approaches can be used to inhibit MMP activity, including small molecule inhibitors, natural compounds, antibodies, and gene therapy. Small molecule inhibitors target the active site of MMPs and prevent their enzymatic activity. Natural compounds, such as polyphenols and flavonoids, have also shown promise in inhibiting MMP activity through various mechanisms. Antibodies can be used to target specific MMP isoforms, while gene therapy approaches aim to modulate MMP expression levels. Inhibition of MMPs can help prevent excessive tissue degradation, reduce inflammation, and inhibit tumor metastasis. However, the challenge lies in developing selective inhibitors that target specific MMP isoforms without interfering with normal physiological processes. Further research is needed to optimize the efficacy and safety of MMP inhibitors for clinical use.

MMPs, which include monocytes, fibroblasts, macrophages, endothelial cells, and metastatic tumor cells, are implicated in the breakdown of connective tissues. Matrilysin, collagenases, gelatinases, and stromelysins are some examples [13]. These enzymes have a 40%–50% identical amino acid sequence and are entirely dependent on calcium and zinc. Collagen, proteoglycan, fibronectin, and laminin are among the protein constituents that MMPs break down. Therefore, dysregulation of MMP results in an uncontrollable degradation of the extracellular matrix in pathological circumstances such as tumor metastasis. Since MMP inhibitors slow down the rate at which connective tissues degrade, they can be utilized as therapeutic medications for tumors. Marimastat, metastat, and prinomastat are medications used to suppress MMPs.

5.3. Inhibition of phosphoinositide 3-kinase

Lipid kinases known as phosphoinositide 3-kinase **(**PI3Ks) catalyze the phosphorylation of phosphorylate phosphatidylinositol 4, 5-bisphosphate to phosphatidylinositol 3, 4, 5-trisphosphate. This triggers the activation of protein kinase B (Akt), a key player in the development of cancer. As a result, PI3K is a key target for anticancer drugs and the route in cancer metabolism that is most frequently activated [14]. By blocking PI3K activity, downstream signaling through the Akt/mammalian target of the rapamycin (mTOR) pathway is disrupted, leading to the inhibition of cell growth and induction of apoptosis in cancer cells. Several small molecule inhibitors targeting PI3K isoforms have been developed and are being investigated in preclinical and clinical studies. However, the clinical efficacy of PI3K inhibitors has been limited by toxicity and acquired resistance mechanisms. Combination therapies with other targeted agents or immunotherapies are being explored to overcome resistance and enhance therapeutic outcomes. Additionally, patient selection based on molecular profiling to identify those most likely to benefit from PI3K inhibition is crucial. Further understanding of the complex signaling networks involving PI3K and its interactions with other pathways is essential for developing more effective and targeted cancer therapies.

5.3.1. Idelalisib

The first-class PI3K inhibitor approved for use in cancer therapy in the USA and Europe is called idelalisib. BKM120 and ZSTK474 are two more PI3K inhibitors that are presently undergoing clinical testing. Idelalisib is a medication used in the treatment of certain types of blood cancers, specifically chronic lymphocytic leukemia (CLL), follicular lymphoma, and small lymphocytic lymphoma. It works by blocking the action of the PI3K enzyme, which is involved in the growth and survival of cancer cells. Common side effects may include diarrhea, fever, fatigue, cough, nausea, and elevated liver enzymes. More serious side effects can occur, such as infections, severe diarrhea, lung problems, and liver toxicity. It is important for patients taking idelalisib to be closely monitored by their healthcare provider to manage and mitigate these potential side effects. Idelalisib is usually prescribed after other treatments have been tried without success or if the cancer has relapsed. It is typically taken orally, and the dosage and duration of treatment will be determined by a healthcare provider based on the patient's condition and response to the medication.

5.4. Inhibition of Ras: farnesyl transferase

A low molecular weight GDP/GTP-binding guanine triphosphatase called Ras (rat sarcoma) is essential for the malignant transformation, invasion, and dissemination of gliomas [15]. A mutation in Ras causes a sequence of posttranslational changes that activate gliomas. Farnesylation is one of the post-translational changes. Farnesyl transferase (FTase) is a lipid modification catalyzed by farnesylation. This procedure is dependent on FTase's identification of a particular amino acid sequence with a carboxyl terminus known as CAAX (C – Cystine, AA - Aliphatic amino acids, X - Amino acid, preferably methionine or serine). Ras must be able to attach to the cell membrane to initiate cancer, and farnesylation makes this possible.

Inhibition of Ras FTase is a potential therapeutic strategy for targeting Ras-driven cancers. FTase is an enzyme responsible for adding a farnesyl group to Ras proteins, a modification crucial for their proper functioning in cell signaling pathways. By inhibiting FTase, the farnesylation of Ras proteins can be prevented, leading to impaired Ras signaling and potentially inhibiting cancer cell growth. Several small molecule inhibitors have been developed to target FTase, with some showing promising results in preclinical studies. These inhibitors work by binding to the active site of FTase, preventing it from farnesylating Ras proteins effectively. By disrupting Ras signaling, these inhibitors have the potential to selectively target cancer cells harboring Ras mutations while sparing normal cells. However, challenges such as drug resistance and off-target

effects need to be addressed in the development of FTase inhibitors. Combination therapies targeting multiple points in the Ras signaling pathway may also be necessary to overcome resistance mechanisms and improve the efficacy of FTase inhibition as a therapeutic approach for Ras-driven cancers.

5.4.1. Lonafarnib, Sarasar, Tipifarnib

Lonafarnib/Sarasar is an oral FTase non-inhibitor that works well against tumors that include Ras proteins. Among the G proteins that are susceptible to farnesylation are the proteins Rho, Rheb, and CENP-F. Because these proteins may serve as substrates for farnesylation, they are targeted by FTase inhibitors. These inhibitors are also capable of inhibiting P-glycoprotein, a byproduct of a multidrug-resistant gene that is crucial in cancer cell development of chemotherapy resistance. Tipifarnib is a methyl-quinolone that is non-peptidomimetic and was first created to treat fungal infections. It also inhibits FTase selectively and non-peptidomimetically. As a radiosensitizer, it causes radioresistant tumor cell lines to undergo postmitotic necrotic cell death.

5.5. Inhibition of proteasome

Proteasomes are responsible for the degradation of proteins involved in the cell cycle, DNA transcription and repair, apoptosis, angiogenesis, and cell proliferation, hence they are possible targets for cancer medications [15]. Proteasomes are cellular complexes responsible for degrading unwanted or damaged proteins. Inhibition of proteasome activity can have significant effects on cell function and viability. Proteasome inhibitors are used in cancer therapy as cancer cells are more sensitive to proteasome inhibition compared to normal cells. These inhibitors disrupt the proteasome's ability to break down proteins, leading to an accumulation of misfolded or damaged proteins within the cell. This buildup can trigger cell death pathways, ultimately resulting in the death of cancer cells. However, proteasome inhibition can also have adverse effects on normal cells, as they rely on the proteasome for degrading regulatory proteins. This can lead to toxicity and side effects such as peripheral neuropathy, gastrointestinal issues, and hematological abnormalities. Understanding the molecular mechanisms of proteasome inhibition is crucial for developing more targeted and effective therapies while minimizing off-target effects.

5.5.1. Velcade

Velcade induces apoptosis in the G2-M phase of cells to combat cancerous transformations.

5.6. Inhibition of COX-2

Both healthy and malignant astrocytes actively participate in the cyclooxygenase pathways [15]. The COX-2 enzyme has a significant role in carcinogenesis and is highly expressed in cancer cells. It is reported to be elevated in human high-grade gliomas. Human glioblastoma cell lines can be made to proliferate and migrate less by blocking the COX-2 enzyme, which also causes growth suppression and apoptosis. Inhibition of cyclooxygenase-2 (COX-2) is a pharmacological strategy often used to reduce inflammation, pain, and fever. COX-2 is an enzyme that plays a key role in the synthesis of prostaglandins, which are lipid compounds involved in inflammation and pain signaling. By inhibiting COX-2, the production of prostaglandins is reduced, leading to decreased inflammation and pain. Selective COX-2 inhibitors, such as celecoxib, have been developed to target COX-2 specifically while sparing COX-1, another isoform of the enzyme that plays a role in maintaining the stomach lining and platelet function. This selectivity helps to minimize the gastrointestinal side effects associated with non-selective COX inhibitors like aspirin and ibuprofen. Inhibition of COX-2 is commonly used in the treatment of conditions such as rheumatoid arthritis, osteoarthritis, and acute pain. However, it is important to note that long-term use of COX-2 inhibitors has been associated with an increased risk of cardiovascular events, so these medications should be used with caution and under the supervision of a

healthcare provider.

5.6.1. Celecoxib

One NSAID that prevents prostaglandin formation is celecoxib, which works by selectively blocking the COX-2 enzyme.

6. Glioblastoma

Malignant brain tumors and glioblastomas are similar. It differs from typical brain tumors in that it is the result of star-shaped glial cells, like oligodendrocytes and astrocytes, which maintain the health of nerve cells. They function in the brain as immune cells [16]. Abnormal gliomas grow because of the blood supply, just like regular brain tumors do. Although aberrant astrocytic cells make up the majority of the tumor, it also contains other cell types, such as blood vessels and patches with dead cells. Through the corpus callosum, which serves as a bridge between two fibers, glioblastomas can readily spread from one hemisphere of the brain to the other (intrahemispheric metastasis). Seldom do glioblastomas spread to non-cognitive organs [17]. Glioblastoma is a type of aggressive brain tumor that typically arises in the cells of the brain known as astrocytes and is the most common and deadliest form of primary brain tumor in adults. Glioblastomas are highly invasive and grow rapidly, making treatment difficult. Common symptoms may include headaches, seizures, cognitive impairment, and changes in personality or behavior. Treatment for glioblastoma usually involves a combination of surgery, radiation therapy, and chemotherapy. However, due to the tumor's aggressive nature and tendency to recur, the prognosis for patients with glioblastoma is often poor, with a low overall survival rate. Research into new treatment options, such as immunotherapy and targeted therapies, is ongoing to improve outcomes for patients with glioblastoma. Early detection and a comprehensive treatment approach involving a multidisciplinary team of healthcare professionals are crucial in managing glioblastoma. Supportive care and palliative measures are also important to help patients manage symptoms and improve their quality of life.

6.1. Inhibition of protein kinase C

Cytoplasmic threonine/serine kinases, or PKC, control tumor cell proliferation, apoptosis, and survival [18]. PKC phosphorylates key proteins involved in several cellular signaling pathways. Additionally, it is crucial for controlling angiogenesis through vascular endothelial growth factor (VEGF). PKC is therefore a target receptor for the identification and creation of therapeutics for neurological disorders.

PKC is a family of enzymes involved in various cellular processes, including cell proliferation, differentiation, and survival. Inhibition of PKC has been a target for therapeutic interventions in conditions such as cancer, diabetes, and cardiovascular diseases. The development of PKC inhibitors has shown promise in preclinical studies and clinical trials. Several classes of PKC inhibitors have been identified, including ATP-competitive inhibitors, non-competitive inhibitors, and allosteric inhibitors. These inhibitors target different domains of PKC to disrupt its activity and downstream signaling pathways. PKC inhibitors have demonstrated anti-tumor effects by promoting apoptosis, inhibiting cell proliferation, and reducing angiogenesis. In diabetes, PKC inhibitors have been shown to improve insulin sensitivity and reduce complications associated with hyperglycemia. In cardiovascular diseases, PKC inhibitors have been investigated for their potential to reduce inflammation, oxidative stress, and vascular remodeling. While PKC inhibition shows therapeutic potential, challenges remain in developing selective inhibitors that target specific isoforms of PKC without causing off-target effects. Further research is needed to optimize the design of PKC inhibitors and evaluate their efficacy and safety in clinical settings.

6.1.1. Tamoxifen and Ezastaurin

Tamoxifen is a blood-brain barrier permeable medication that is fat soluble, non-steroidal, and used to treat breast cancer. Through inhibition, it causes cancer cells to undergo more apoptosis. It can overcome chemoresistance at large doses. Similar to tamoxifen, ezastaurin is a tiny lipid-soluble chemical that inhibits the PKCb receptor and has good blood-brain barrier permeability.

6.2. Inhibition of histone acetylation

Gene regulation and epigenetic modification are intrinsically impacted by histone acetylation [18]. Histone acetylases and deacetylases are enzymes that alter the lysine residues on histone core proteins, which causes, positive-charged proteins to become negative. Chromatin relaxation and transcription are examples of histone acetylation. Additionally, histone deacetylases and acetylases play a role in the death, differentiation, survival, and proliferation of cells. Inhibition of histone acetylation refers to the process of blocking the addition of acetyl groups to histone proteins, which are crucial components of chromatin structure in cells. Histone acetylation typically leads to a more open chromatin conformation, allowing for increased gene expression. By inhibiting this process, gene expression is downregulated, leading to potential changes in cell function and phenotype. Various compounds can inhibit histone acetylation, including histone deacetylase (HDAC) inhibitors. HDAC inhibitors work by blocking the activity of histone deacetylases, enzymes that remove acetyl groups from histone proteins. This results in increased histone acetylation, leading to altered gene expression patterns. Research has shown that targeting histone acetylation through HDAC inhibitors can have therapeutic potential in various diseases, including cancer, neurodegenerative disorders, and inflammatory conditions. By modulating gene expression through histone acetylation inhibition, it is possible to potentially regulate cellular processes and offer new treatment avenues for these conditions.

6.2.1. Vorinostat

Vorinostat is a linear suberoylanilide hydroxamic acid that tightly coils the chromatin and operates on histone deacetylases to silence gene expression.

7. Multiple sclerosis

The most prevalent inflammatory disorder of the brain, spinal cord, and nerves is multiple sclerosis (MS). It is an immune system-related neurodegenerative disease in which the white matter that covers the nerves is destroyed. Hence, it is also an autoimmune disease [19]. MS occurs when the body's immune system mistakenly attacks the protective covering of nerve fibers, known as myelin, leading to inflammation and damage. This disrupts the normal flow of electrical impulses along the nerves, causing symptoms like fatigue, muscle weakness, numbness or tingling, difficulties with coordination and balance, problems with vision, and cognitive impairment. The severity and progression of MS vary widely among individuals. Diagnosis of MS typically involves a combination of medical history, neurological exams, imaging tests such as MRI, and analysis of cerebrospinal fluid. While there is currently no cure for MS, various treatments are available to manage symptoms, slow disease progression, and improve quality of life. These may include medications, physical therapy, lifestyle modifications, and psychological support.

7.1. Inhibition of histone deacetylases

In MS, there is interest in studying the potential therapeutic effects of inhibiting histone deacetylases (HDACs). HDACs are enzymes that regulate gene expression by removing acetyl groups from histone proteins, affecting

chromatin structure and gene transcription. In MS, aberrant gene expression and immune system dysfunction contribute to disease progression. Preclinical studies have shown that HDAC inhibitors can modulate immune responses, promote remyelination, and protect against neurodegeneration in MS models. By altering gene expression patterns, HDAC inhibitors may regulate immune cell function, reduce inflammation, and promote repair mechanisms in the central nervous system. However, more research is needed to fully understand the specific mechanisms involved and to optimize dosing and treatment regimens. Overall, targeting HDACs in MS holds potential as a therapeutic strategy to modulate immune responses, promote repair processes, and potentially slow down disease progression.

Enzymes facilitate the access of transcription factors to gene sequences that code for vital proteins, including neurotransmitters and enzymes, during gene expression. HDAC is one such enzyme [20]. Nucleosomes are formed inside the nucleus by the assembly of histone proteins and DNA. Histone proteins include acetylated lysine residues, which are essential for transcriptional activation. The addition of acetyl groups is mediated by the enzyme histone acetyltransferases, while HDACs are responsible for their removal. Therefore, for particular gene sets to be expressed, the balance between these two enzymes is essential. Their imbalance disrupts acetylation and deacetylation, which gives rise to inflammatory diseases like MS. It can be resisted by blocking HDAC, since these inhibitors are therapeutically beneficial in the treatment of mood disorders, MS, epilepsy, and other immunological illnesses. HDAC targets transcription factors, cytoskeletal components, and nuclear hormone receptors in addition to core histone proteins.

7.1.1. HDAC inhibitors

The hydroxamate chemicals trichostatin A, suberoylanilide hydroxamic acid, aliphatic acids, sodium butyrate, and valproic acid are the most often prescribed HDAC inhibitors. **Table 1** lists the various neurological conditions along with the enzymes and medications that are used to treat them.

8. Plant-based enzyme inhibitors

Since the beginning of medicine, chemicals produced from plants have been utilized to treat neurological disorders. The majority of chemotherapy medications created in the last 20 years come from natural sources. Technological developments and advancements have reignited interest in natural products such as pharmaceuticals. The effectiveness of certain natural inhibitors can only be demonstrated by conventional procedures. Hence, scientific study is required to validate their potential [21].

Plant-based enzyme inhibitors have a variety of functions and are known for their potential health benefits. Some common plant-based enzyme inhibitors include polyphenols, flavonoids, tannins, and lectins. These inhibitors can help regulate enzyme activity in the body by blocking specific enzymes from catalyzing reactions. For example, polyphenols found in green tea and red wine are known to inhibit enzymes involved in inflammation and oxidative stress. Flavonoids, found in fruits and vegetables, can inhibit enzymes involved in cell proliferation and migration, potentially helping to prevent cancer. Tannins, found in tea, coffee, and berries, can inhibit digestive enzymes and affect nutrient absorption. Lectins, found in foods like legumes and grains, can interfere with carbohydrate digestion and absorption. While plant-based enzyme inhibitors can have beneficial effects on health, it is important to note that excessive consumption may also have negative consequences. It is always recommended to consume a balanced diet and consult with a healthcare professional before making significant changes to your diet or supplement regimen. **Table 2** lists a large number of plant chemicals that are employed as enzyme inhibitors in clinical and pre-clinical drug discovery trials.

Table 1. Disease, inhibited enzyme, and prevalent drugs

Disease	Inhibited enzyme	Drugs
AD	AChE	Tacrine
		Donepezil
		Rivastigmine
		Galantamine
PD	MAO	Rasagiline
		Selegiline
Stroke	COX-1	Aspirin
Brain tumor	MMP	Marimastat
		Metastatic
		Prinomastat
	PI3k	Idelalisib
	Ftase	Lonafarnib/Sarasar
		Tipifarnib
	Proteasome	Velcade
	COX-2	Celecoxib
Glioblastoma	PKC	Tamoxifen
		Enzastaurin
	Histone Acetylase	Vorinostat
MS	HDAC	Trichostatin A
		Suberoylanilide hydroxamic acid
		Valproic acid
		Sodium butyrate

Table 2. Plant compounds, inhibited enzymes, and their disease targets

Compound	Enzyme inhibition	Disease target	Origin
Huperzine A	AChe	AD	*Huperzia serrata*
Zt-1	AChe	AD	*Huperzia serrata*
Physostigmine	AChe	AD and Myasthania Gravis	*Physostigma venenosum* L
Curcumin	MAO-B	PD and other Neurological Disorders	*Curcuma longa*
Ellagic Acid	MAO-B	PD and other Neurological Disorders	Wide range of plant species
Genistein	Tyrosine Kinases	Amyotropic Lateral Sclerosis (ALS)	Wide range of plant species
Apocynin	NADPH-Oxidase (NOX)	Ischemic Stroke	Canadian hemp (*Apocynum cannabinum*), *Picrorhiza kurroa*
Honokiol	NADPH-Oxidase (NOX)	Ischemic Stroke	*Magnolia officinalis*
Plumbagin	NOX	Ischemic Stroke	*Plumbago zeylanica*
Hypericin	MAO	MS	*Hypericum perforatum* L
Arecaidine, Arecoline, Guvacine	MAO-A	Depression	Areca palm
Galanthamine	AChe	AD	*Galanthus nivalis*
Gastrodin, Vanillin	GABA Transaminase	PD	*Gastrodia elata*

In addition, several plant chemicals have natural inhibitory effects on cholinesterase and MAO-B [29–35]. It has been discovered that more plant extracts exhibit enzyme-inhibiting qualities. Moreover, extracts of curcumin, *Centella asiatica*, and ginkgo include phospholipase 2 (PLA2) inhibitors, which have been researched for the treatment of neurological illnesses [36]. Natural COX-2 inhibitors found in rosemary (Satapatrika) include apigenin, thymol, carvacrol, oleanolic acid, eugenol, and ursolic acid [30].

9. Other enzymes

9.1. Beta-site amyloid precursor protein cleaving enzyme-1

The Beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1) breaks down amyloid precursor protein (APP) to produce the protein-soluble APPβ and the N-terminus of Aβ peptides [37]. BACE-1 triggers the production and accumulation of Aβ plaques, leading to the development of neurodegenerative illnesses, particularly AD. As an alternative to addressing the symptoms of AD, inhibition of BACE-1 stops Aβ from being produced and accumulated.

9.2. γ-secretase

Aβ is formed by γ-secretase, according to the amyloid hypothesis [38]. Therefore, substances that obstruct γ-secretase hold promise as AD treatments.

9.3. Sirtuin 2 deacetylase

Huntington's disease (HD) and PD cell and invertebrate models are protected when Sirtuin 2 (SIRT2) deacetylase is inhibited. Though its exact function is yet unknown, SIRT2 is a highly prevalent protein in the adult brain that is expressed in both neurons and oligodendrocytes [39]. It has been possible to create thiazole-containing SIRT2 deacetylase inhibitors with neuroprotective properties [40].

9.4. Phospholipases A2

Membrane phospholipids are hydrolyzed by PLA2 to produce lysophospholipids and arachidonic acid [36]. Arachidonic acid undergoes further metabolism to produce prostaglandins, thromboxanes, leukotrienes, and lysophospholipids, which are then transformed into platelet-activating factors, following hydrolysis. These substances are important contributors to neuroinflammation and oxidative stress. Inhibitors of PLA2 should also be considered as options for treating neurological illnesses, as these conditions are marked by oxidative stress, inflammatory responses, and elevated brain PLA2 activity. **Figure 4** displays the PLA2 inhibitors for the treatment of neurological diseases.

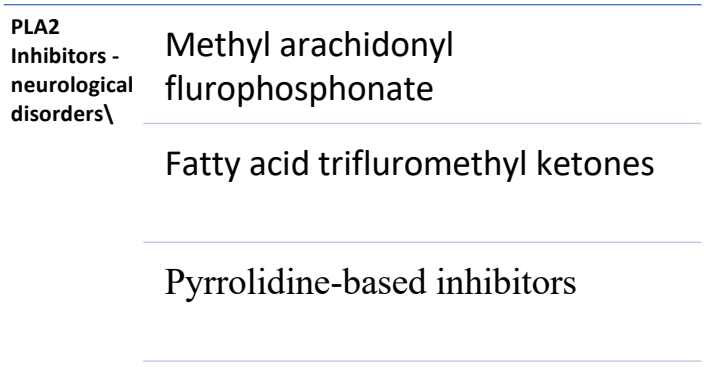

Figure 4. Old and new synthetic inhibitors of PLA2 for the treatment of neurological disorders in cell culture and animal models

9.5. Glutathione S transferases

The main role of glutathione S transferases (GST) is to protect cells against oxidative stress and toxicity, and are involved in the creation and modification of leukotrienes and prostaglandins [41]. GSTs can conjugate glutathione with oxidative metabolic products, medicinal medications, and carcinogens. They become less hazardous and prepared for cell release as a result. Oxidants that are overproduced as a result of dysregulated GST may result in oxidative stress. Drugs that inhibit GST should be researched for their potential therapeutic role in treating diseases, as neurons are particularly susceptible to oxidative stress and play a role in the development of neurological illnesses.

9.6. Dipeptidyl peptidase IV

Inhibition of dipeptidyl peptidase IV **(**DPP-IV) can effectively treat diabetes [42]. Nonetheless, further studies are required to determine whether DPP-IV can be used therapeutically to treat neurological diseases.

9.7. Carbonic anhydrase

Widely distributed zinc enzymes known as carbonic anhydrase (Cas) are effective catalysts for the reversible hydration of carbon dioxide to bicarbonate. To create pharmacological drugs, unsubstituted sulphonamides limit the activity of CAs [44]. Methazolamide, a CA inhibitor, has also been found to reduce Aβ (plaques) neurovascular mitochondrial toxicity [43]. This is because AD is primarily caused by mitochondrial dysfunction.

10. CRISPR/CAS9 for treatment of neurological disorders

Clustered regulatory interspaced short palindromic repeat-associated 9 (CRISPR/Cas9) technology holds promise for treating neurological disorders by enabling precise gene editing to correct genetic mutations associated with these conditions. Researchers are exploring its potential to target specific genes linked to disorders such as HD, PD, and AD. By editing these genes, CRISPR/Cas9 could potentially slow down or even reverse disease progression. Despite its potential, challenges remain in using CRISPR/Cas9. Delivery of the CRISPR/Cas9 components to the brain and ensuring accurate gene editing without off-target effects are key areas of focus. Additionally, the ethical implications of editing the human genome must be considered. Clinical trials are underway to evaluate the safety and efficacy of CRISPR/Cas9 in treating neurological disorders. These trials will provide valuable insights into the feasibility of this technology in a clinical setting. Overall, CRISPR/Cas9 presents an exciting avenue for developing novel therapies for neurological disorders, but further research is needed to fully understand its potential benefits and limitations in the complex landscape of the brain.

The process of precisely and permanently altering a living organism's genome is known as genome editing. It is used to insert or knock out certain genes and has evolved into a repair mechanism [45]. With the use of gene editing technologies, neuroscientists may now successfully access and modify the genome in neurodegenerative illnesses such as AD and PD. This opens up new avenues for studying the links between the brain and behavior [46]. Among the many gene editing instruments, CRISPR/CAS9 is a sophisticated method for precise, accurate, and targeted genetic modification of DNA. It can be used to eliminate viruses that cause infections and neurological problems as well as single- and double-stranded DNA viruses. Therefore, the method can be used to eliminate DNA viruses that result in illnesses of the nervous system. This simple gene editing technique uses guide RNA (gRNA) to target a particular sequence that may be easily modified to fit a variety of target nucleotide sequences. To combat viruses, CRISPR/Cas nucleases activate the adaptive immune system in almost all Archaea and the majority of bacteria. Target DNA is guided and degraded in a sequence-specific manner by the gRNA in CRISPR/Cas9 [47]. By inducing mutations in the gene causing neurological illnesses, CRISPR

technology may be utilized to investigate disease-associated epigenetic modifications in cell models [48].

The CRISPR/Cas9 system is tunable to either gain-of-function (activating transcription) or lose-of-function (silencing genes) [49]. Both gene knockout (inhibition of enzymes) and mutant knockin (over-expression of enzymes) are possible with CRISPR/Cas9. With this method, a gene that encodes the enzymes whose overactivity causes neurological diseases can be selectively inhibited. Additionally, the CRISPR/Cas9 system can target numerous genes at once by generating additional sgRNA sequences that are directed against distinct gene targets. This technology has made it possible to explore how removing proteins that are encoded by several genes affects behavior [46]. Animal models of neurological conditions can be created using CRISPR/CAS9, which could lead to advances in neurodegenerative disease research and medication development [50]. The potential therapeutic benefits of fixing or integrating genes have thus drawn interest in the use of this type of gene editing technology in neurology [45].

Unless a cellular DNA target is necessary for the viruses' life cycle of growth—CRISPR/Cas9 can be used to treat neurological problems and infections. For instance, the RNA strand retroviruses that include the varicella-zoster virus (CMV) contain a DNA intermediary in their life cycle. Another illustration is the neurological pathological illness known as myelopathy/tropical spastic paraparesis, which is brought on by the human T-lymphotropic virus-1 (HTLV-1). Therefore, the CRISPR/Cas9 method represents a promising therapeutic strategy for HTLV-1-caused CNS illnesses [47]. Treatment techniques based on CRISPR/Cas9 may be utilized both therapeutically and preventively. By introducing Cas9 and HIV-1-specific gRNAs to uninfected cells, the CRISPR/Cas9 system in neuro-AIDS not only eliminates provirus that is already present in cells (i.e., inactivating gene expression and replication of retrovirus HIV-1 in a variety of promonocytic, microglial, and T-cells of infected cells) but also stops the infection [47].

A serious neurological condition known as progressive multifocal leukoencephalopathy (PML) results in immune system dysfunction. It is typified by an opportunistic JCV infection of the central nervous system. Since CRISPR/Cas9 can completely remove JCV infection from the human central nervous system, it may be utilized as a therapeutic agent for PML [47]. HD is typified by choreatic motions, dementia, and behavioral abnormalities. It has been demonstrated that the CRISPR/Cas9-based gene-editing technique may inactivate the HD-associated mutant Huntington allele, and it has been used to remove genes unique to the brain in a mouse model of schizophrenia [51]. Considering that this technology modifies the Alzheimer's amyloid pathway, it may also provide a novel therapeutic approach for AD. It modifies endogenous APP, which attenuates β cleavage by blocking the interaction between BACE-1 and APP while upregulating neuroprotective α-cleavage [52]. ALS results in the death of the neurons that regulate voluntary muscular movements. It is thought that the aberrant protein buildup causes neuron toxicity. Recently, researchers have discovered over 200 genes that may either sensitize or protect cells against harmful proteins using genome-wide CRISPR sgRNA libraries. It demonstrates that a few of these genes are strong ALS protein protectors and may be promising therapeutic targets for the disease. A novel and interesting method for comprehending the origins of diseases that we were previously unable to identify is the application of genome-wide CRISPR screens in research [53]. Nevertheless, the efficient delivery of gRNA and Cas9 nuclease to the brain is restricting the application of this technology [51].

11. Conclusion

Currently, there is no proven treatment for patients with neurological illnesses and our understanding of their mechanism of action is limited. It is not required to limit treatment to inhibitors or antagonists to prevent the hyperactive enzyme from functioning normally in the central nervous system. With the aid of gene editing

tools, it can be rendered silent or rendered unconscious. Given this, enzyme inhibition therapy plays a crucial role in managing neurological conditions, diseases, and disorders by targeting specific enzymes involved in disease processes. In AD, enzyme inhibitors can target enzymes like Ache to increase neurotransmitter levels and improve cognitive function. In PD, inhibitors of MAO-B can help increase DA levels in the brain and alleviate symptoms. Enzyme inhibition therapy is also used in treating epilepsy by targeting enzymes involved in neurotransmitter regulation to reduce seizure activity. In migraine treatment, inhibitors of calcitonin gene-related peptide enzymes can help prevent vasodilation and decrease pain sensation. Furthermore, enzyme inhibition therapy is being explored for neurodegenerative diseases like HD and ALS by targeting specific enzymes associated with protein aggregation and neuronal damage. Overall, enzyme inhibition therapy offers a promising approach to the management of various neurological conditions by modulating enzyme activity to restore normal physiological processes, alleviate symptoms, and potentially slow down disease progression. Ongoing research and drug development in this field holds great promise for improving treatment outcomes in neurological disorders.

Disclosure statement

The author declares no conflict of interest.

References

[1] Sharma R, 2012, Enzyme Inhibition: Mechanisms and Scope. Enzyme Inhibition and Bioapplications, InTech, 10.5772/39273.

[2] Mohan C Long KD Mutneja M, 2013, An Introduction to Inhibitors and Their Biological Applications. EMD Millipore Corp, 2013: 3–13.

[3] Copeland RA, Harpel MR, Tummino PJ, 2007, Targeting Enzyme Inhibitors in Drug Discovery. Expert Opinion on Therapeutic Targets, 11(7): 967–978.

[4] Kanwar JR, Sriramoju B, Kanwar RK, 2012, Neurological Disorders and Therapeutics Targeted to Surmount the Blood–Brain Barrier. International Journal of Nanomedicine. 7: 3259–3278.

[5] Lleo A, Greenberg SM, Growdon JH, 2006, Current Pharmacotherapy for Alzheimer's Disease. Annu Rev Med, 57: 513–533.

[6] Gonçalves S, Romano A, 2017, Inhibitory Properties of Phenolic Compounds Against Enzymes Linked with Human Diseases. Phenolic Compounds-Biological Activity, InTech.

[7] Finberg JP, 2010, Pharmacology of Rasagiline, A New MAO-B Inhibitor Drug for The Treatment of Parkinson's Disease with Neuroprotective Potential. Rambam Maimonides Medical Journal, 1(1): e0003.

[8] Perez-Lloret S, Rascol O, 2011, Safety of Rasagiline for The Treatment of Parkinson's Disease. Expert Opinion on Drug Safety, 10(4): 633–643.

[9] Finberg JPM, Rabey JM, 2016, Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. Frontiers in Pharmacology, 7: 340.

[10] Aronson JK, (ed) 2016, Meyler's Side Effects of Drugs, The International Encyclopedia of Adverse Drug Reactions and Interactions, Elsevier, Netherlands, 338–339.

[11] Ansara AJ, Nisly SA, Arif SA, et al., 2010, Aspirin Dosing for The Prevention and Treatment of Ischemic Stroke: An Indication-Specific Review of The Literature. Annals of Pharmacotherapy, 44(5): 851–862.

[12] Lights V, 2022, Understanding Brain Tumors, Healthline, viewed 7 December, 2018, https://www.healthline.com/health/brain-tumor

[13] New Drug Approvals, n.d., Prinomastat, viewed 7 December, 2018, https://newdrugapprovals.org/2014/03/25/prinomastat/

[14] Zhao W, Qiu Y, Kong D, 2017, Class I Phosphatidylinositol 3-Kinase Inhibitors for Cancer Therapy. Acta Pharmaceutica Sinica B, 7(1): 27–37.

[15] Tremont-Lukats IW, Gilbert MR, 2003, Advances in Molecular Therapies in Patients with Brain Tumors. Cancer Control, 10(2): 125–137.

[16] American Brain Tumor Association, n.d., Glioblastoma (GBM), viewed 7 December, 2018, https://www.abta.org/tumor_types/glioblastoma-gbm/

[17] American Association of Neurological Symptoms, n.d., Glioblastoma Multiforme, viewed 7 December, 2018, https://www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme

[18] Lau D, Magill ST, Aghi MK, 2014, Molecularly Targeted Therapies for Recurrent Glioblastoma: Current and Future Targets. Neurosurgical Focus, 37(6): E15.

[19] Faraco G, Cavone L, Chiarugi A, 2011, The Therapeutic Potential of HDAC Inhibitors in The Treatment of Multiple Sclerosis. Molecular Medicine, 17(5–6): 442–447.

[20] Dietz KC, Casaccia P, 2010, HDAC Inhibitors and Neurodegeneration: At the Edge Between Protection and Damage. Pharmacological Research, 62(1): 11–17.

[21] Rajput MS, 2010, Natural Monoamine Oxidase Inhibitors: A Review. J Pharmacy Res, 3: 482–485.

[22] Babitha KV, Shanmuga Sundaram R, Annapandian VM, et al., 2014, Natural Products and Its Derived Drugs for The Treatment of Neurodegenerative Disorders: Alzheimer's Disease–A Review. British Biomedical Bulletin, 2: 359–370.

[23] Suganthy N, Karutha P, Pandima D, 2009, Cholinesterase Inhibitors from Plants: Possible Treatment Strategy for Neurological Disorders-A Review. International Journal of Biomedicine and Pharmaceutical Sciences, 3: 87–103.

[24] Khatri DK, Juvekar AR, 2016, Kinetics of Inhibition of Monoamine Oxidase Using Curcumin and Ellagic Acid. Pharmacognosy Magazine, 12(Suppl 2): 116–120.

[25] F Nabavi S, Daglia M, D'Antona G, et al., 2015, Natural Compounds Used as Therapies Targeting Amyotrophic Lateral Sclerosis. Current Pharmaceutical Biotechnology, 16(3): 211–218.

[26] Kim JY, Park J, Lee JE, et al., 2017, NOX Inhibitors- α Promising Avenue for Ischemic Stroke. Experimental Neurobiology, 26(4): 195–205.

[27] Mojaverrostami S, Bojnordi MN, Ghasemi-Kasman M, et al., A Review of Herbal Therapy in Multiple Sclerosis, Adv Pharm Bull, 8(4): 575–590.

[28] Kumar GP, Anilakumar KR, Naveen S, 2015, Phytochemicals Having Neuroprotective Properties from Dietary Sources and Medicinal Herbs. Pharmacognosy Journal. 7(1): 1–17.

[29] Zarmouh NO, Messeha SS, Elshami FM, et al., 2016, Natural Products Screening for The Identification of Selective Monoamine Oxidase-B Inhibitors. European Journal of Medicinal Plants, 15(1): 14802.

[30] Singhal AK, Naithani V, Bangar OP, 2012, Medicinal Plants with A Potential to Treat Alzheimer's and Associated Symptoms. International Journal of Nutrition, Pharmacology, Neurological Diseases, 2(2): 84.

[31] Murray AP, Faraoni MB, Castro MJ, et al., 2013, Natural AChE Inhibitors from Plants and Their Contribution to Alzheimer's Disease Therapy. Current Neuropharmacology, 11(4): 388–413.

[32] Mazzio E, Deiab S, Park K, et al., 2013, High Throughput Screening to Identify Natural Human Monoamine Oxidase B Inhibitors. Phytotherapy Research, 27(6): 818–828.

[33] Erdogan Orhan I, 2016, Potential of Natural Products of Herbal Origin as Monoamine Oxidase Inhibitors. Current Pharmaceutical Design, 22(3): 268–276.

[34] Viña D, Serra S, Lamela M, et al., 2012, Herbal Natural Products as A Source of Monoamine Oxidase Inhibitors: A Review. Current Topics in Medicinal Chemistry, 12(20): 2131–2144.

[35] Passos CD, Simoes-Pires C, Henriques A, et al., 2014, Alkaloids as Inhibitors of Monoamine Oxidases and Their Role in The Central Nervous System. Studies in Natural Products Chemistry, Elsevier, 43: 123–144.

[36] Ong WY, Farooqui T, Kokotos G, et al., 2015, Synthetic and Natural Inhibitors of Phospholipases A2: Their Importance for Understanding and Treatment of Neurological Disorders. ACS Chemical Neuroscience, 6(6): 814–831.

[37] Neumann U, Ufer M, Jacobson LH, et al., 2018, The BACE-1 Inhibitor CNP520 for Prevention Trials in Alzheimer's Disease. EMBO Molecular Medicine, 10(11): e9316.

[38] Barten DM, Meredith JE, Zaczek R, et al., 2006, γ-Secretase Inhibitors for Alzheimer's Disease. Drugs in R&D, 7(2): 87–97.

[39] Chopra V, Quinti L, Kim J, et al., 2012, The Sirtuin 2 Inhibitor AK-7 is Neuroprotective in Huntington's Disease Mouse Models. Cell reports, 2(6): 1492–1497.

[40] Quinti L, Casale M, Moniot S, et al., 2016, SIRT2-and NRF2-Targeting Thiazole-Containing Compound with Therapeutic Activity in Huntington's Disease Models. Cell Chemical Biology, 23(7): 849–861.

[41] Allocati N, Masulli M, Di Ilio C, et al., 2018, Glutathione Transferases: Substrates, Inhibitors, and Pro-Drugs in Cancer and Neurodegenerative Diseases. Oncogenesis, 7(1): 8.

[42] Al-Badri G, Leggio GM, Musumeci G, et al., 2018, Tackling dipeptidyl Peptidase IV in Neurological Disorders. Neural Regeneration Research, 13(1): 26.

[43] Solesio ME, Peixoto PM, Debure L, et al., 2018, Carbonic Anhydrase Inhibition Selectively Prevents Amyloid B Neurovascular Mitochondrial Toxicity. Aging Cell, 17(4): e12787.

[44] Supuran CT, Scozzafava A, 2000, Carbonic Anhydrase Inhibitors and Their Therapeutic Potential. Expert Opinion on Therapeutic Patents, 10(5): 575–600.

[45] Madigan NN, Staff NP, Windebank AJ, et al., 2017, Genome Editing Technologies and Their Potential to Treat Neurologic Disease. Neurology, 89(16): 1739–1748.

[46] Walters BJ, Azam AB, Gillon CJ, et al., 2016, Advanced *in vivo* use of CRISPR/Cas9 and anti-sense DNA Inhibition for Gene Manipulation in The Brain. Frontiers in Genetics, 6: 362.

[47] White MK, Kaminski R, Wollebo H, et al., 2016, Gene Editing for Treatment of Neurological Infections. Neurotherapeutics, 13(3): 547–554.

[48] Ostick J, 2017, CRISPR for Gene Editing in Neuroscience and Neurological Disease. ACNR, 18: 9–10.

[49] Raikwar SP, Thangavel R, Dubova I, et al., 2018, Neuro-Immuno-Gene-and Genome-Editing-Therapy for Alzheimer's Disease: Are We There Yet? Journal of Alzheimer's Disease, 65(2): 321–344.

[50] Vesikansa A, 2018, Unraveling of Central Nervous System Disease Mechanisms Using CRISPR Genome Manipulation. Journal of Central Nervous System Disease, 10: 1179573518787469

[51] Khan S, Mahmood MS, ur Rahman S, et al., 2018, CRISPR/Cas9: the Jedi Against the Dark Empire of Diseases. Journal of Biomedical Science, 25(29).

[52] Sun J, Carlson-Stevermer J, Das U, et al., 2018, A CRISPR/Cas9 Based Strategy to Manipulate The Alzheimer's Amyloid Pathway. bioRxiv, 1: 310193.

[53] Kramer NJ, Haney MS, Morgens DW, et al., 2018, CRISPR–Cas9 Screens in Human Cells and Primary Neurons Identify Modifiers of C9ORF72 Dipeptide-Repeat-Protein Toxicity. Nature Genetics, 50(4): 603.