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REVIEW ARTICLE

From the Molecular Mechanism to Pre-clinical Results: Anti-epileptic Effects of Fingolimod

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Abstract: Epilepsy is a devastating neurological condition characterized by long-term tendency to generate unprovoked seizures, affecting around 1-2 % of the population worldwide. Epilepsy is a serious health concern which often associates with other neurobehavioral comorbidities that further worsen disease conditions. Despite tremendous research, the mainstream anti-epileptic drugs (AEDs) exert only symptomatic relief leading to 30% of untreatable patients. This reflects the complexity of the disease pathogenesis and urges the precise understanding of underlying mechanisms in order to explore novel therapeutic strategies that might alter the disease progression as well as minimize the epilepsy-associated comorbidities. Unfortunately, the development of novel AEDs might be a difficult process engaging huge funds, tremendous scientific efforts and stringent regulatory compliance with a possible chance of end-stage drug failure. Hence, an alternate strategy is drug repurposing, where anti-epileptic effects are elicited from drugs that are already used to treat non-epileptic disorders.

Herein, we provide evidence of the anti-epileptic effects of Fingolimod (FTY720), a modulator of sphingosine-1-phosphate (S1P) receptor, USFDA approved already for Relapsing-Remitting Multiple Sclerosis (RRMS). Emerging experimental findings suggest that Fingolimod treatment exerts disease-modifying anti-epileptic effects based on its anti-neuroinflammatory properties, potent neuroprotection, anti-gliotic effects, myelin protection, reduction of mTOR signaling pathway and activation of microglia and astrocytes. We further discuss the underlying molecular crosstalk associated with the anti-epileptic effects of Fingolimod and provide evidence for repurposing Fingolimod to overcome the limitations of current AEDs.

Keywords: Epilepsy, fingolimod, drug repurposing, S1P receptor, neuroinflammation.

1. INTRODUCTION

Epilepsy is a disorder of the central nervous system (CNS) characterized by an enduring tendency to generate seizures due to abnormal brain activity. It presents a serious health concern distressing around 70 million of the global population [1]. Moreover, epilepsy rarely exist alone and is often associated with several neurobehavioral conditions such as cognitive decline, anxiety disorder, depression, autism spectrum disorder and psychiatric diseases with severe impact on patients' quality of life [2]. Epilepsy is among the very few diseases, where people at risk can be identified easily, but unfortunately, with limited options to prevent or modulate its progression [3].

Epileptogenesis refers to the process of developing epilepsy, and it is described as a combination of structural and functional changes occurring after an epileptogenic insult that leads to the generation of spontaneous epileptic seizures [4]. Although the etiopathogenesis of epilepsy has not been completely understood yet, several causative factors are speculated to play a role. They include brain injuries (neurotrauma, stroke, brain tumors or status epilepticus), mutations of specific genes, infection of CNS, metabolic disorders and autoimmune disorders [5]. A precise understanding of the pathogenesis of epileptogenesis and seizure recurrence remains the topic of tremendous pre-clinical and clinical investigation and would pave the way for the development of novel treatment strategies that not only halt seizures progression but also minimize their burden [6]. Despite the clinical availability of more than 25 anti-epileptic drugs (AEDs) that

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provide symptomatic relief, more than 33 percent of epileptic patients suffer from pharmacoresistant epilepsy [7]. This reflects an immediate need for developing novel treatment strategies that could modify disease progression and prevent seizure-associated neurobehavioral comorbidities.

Unfortunately, despite extensive experimental and clinical investigation, no disease-modifying therapy against epilepsy has yet been registered for clinical purposes. On top, the drug development process is rather complex, involving hefty amounts of funds, stringent regulatory requirements, and a long clinical testing procedure. Hence, a logical alternative would be the drug repurposing/repositioning of USFDA approved drugs, that are not only safe for humans and used for non- epileptic disorders but also possess the ability to ameliorate the pathways and cellular processes that are disrupted in epilepsy. Based on this approach, anti-epileptic potential has been explored earlier for several drugs used to treat non-epileptic diseases such as Metformin [8-10], Rapamycin [11, 12], Statins [13], Losartan [14, 15] and Celecoxib [16, 17]. These drugs were shown to prevent epileptogenesis, diminish the epileptic pathological changes, through a mechanism that is different from the mainstream AEDs, and encourage researchers to broaden their outlooks in the quest to develop novel AEDs [18]. Interestingly, repurposable drugs have been considered more effective at restoring the dysregulated cellular pathways underlying epilepsy pathogenesis as compared to the currently available AEDs [19].

The agent of interest in the present review is Fingolimod (FTY720), a first-line drug against Relapsing-Remitting Multiple Sclerosis (RRMS) [20] which has already demonstrated neuroprotective effects against neurological disorders such as Alzheimer's disease (AD) [21, 22], Parkinson's disease (PD) [23, 24], Brain injury [25, 26], Subarachnoid haemorrhage (SAH) [27], Stroke [28] and Intracerebral hemorrhage [29]. However, in the perspective of epilepsy, Fingolimod has been shown to exert disease-modifying anti-epileptic effects through anti-inflammatory mechanisms, neuroprotective effects, attenuation of reactive astrogliosis, neuronal loss, and immune cell infiltrates as well as through myelin protection and enhancement of remyelination [30-32]. In addition to the above evidence, the current review will provide an update on the anti-epileptic effect of Fingolimod, by addressing the main aspects of Fingolimod biochemistry and the underlying the molecular crosstalk.

2. FINGOLIMOD BIOCHEMISTRY

Fingolimod (2-amino-2-propane-1,3-diolhydrochloride, FTY720, trade name: Gilenya ® registered under Novartis, Basel, Switzerland) is an analogue of sphingosine-1-phosphate (S1P) [21], obtained through a chemical derivatization procedure of the natural product ISP-I (myriocin) from the ascomycete *Isaria sinclairii* [33].

S1P is a compelling bioactive sphingolipid which controls several cellular processes, including growth, survival, as well as differentiation [34]. Extracellular S1P usually acts in both autocrine and paracrine ways by interacting with different S1P receptor subtypes (S1PR1, S1PR2, S1PR3, S1PR4 and S1PR5) [35] of the G protein-coupled receptor (GPCR) family [36, 37]. FTY720-Phosphate (FTY720-P), which is the bioactive form obtained by SPHK2 phosphorylation, is an S1P analogoue that targets all the S1P receptors (S1P1-5), except S1P2 [38, 39].

These receptors (S1PR1/3/4/5) mediate a myriad of physiological processes, including immunity, cell migration, and inflammation [40, 41]. Furthermore, Fingolimod has been shown to exert diverse biological activities, including the arrest of lymphocyte egress from the secondary lymphoid tissues, inhibition of neuroinflammation, attenuation of microgliosis, enhancement of oligodendrocyte differentiation, and potent neuroprotection [42].

2.1. Fingolimod Exerts Disease-modifying Anti-epileptic Effects

The disease-modifying anti-epileptic effects of Fingolimod are mainly demonstrated by pre-clinical studies. When Fingolimod (0.3 or 1 mg/kg, I.P.) was administered 1 h prior to Pentylenetetrazol (PTZ) (36.5 mg/kg, I.P.)-induced kindling in naval medical research institute (NMRI) mice, decrease seizure behaviors were observed followed by reduced burst activity detected by electroencephalography (EEG) recordings. PTZ was further shown to increase the electrocortical activity, which was reversed by Fingolimod. Moreover, treatment with Fingolimod (0.3 mg/kg, I.P.) was shown to effectively reduce the seizure stage and duration compared to the PTZ-treated group. In addition, behavioral analysis of post-treatment with Fingolimod on fully kindled animals showed that lower doses (0.3 mg/kg, I.P.) reduced effectively seizure stages as well as the duration and increased S2 latency compared to higher doses (low dose FTY720 versus PTZ group; $p < 0.05$ and low dose FTY720 versus high dose; $p < 0.01$) [31].

Similarly, in an animal model of Status Epilepticus (SE) of male Sprague-Dawley (SD) rats induced by Lithium chloride (127 mg/kg, I.P.)-Pilocarpine (30 mg/kg, I.P.) injection, Fingolimod (1 mg/kg, I.P.) treatment significantly reduced ($p < 0.01$) the duration, frequency, and severity of spontaneous convulsions (SCs) at 21-34 days post-SE as compared to Lithium-Pilocarpine induced-SE groups [32].

Fingolimod has also demonstrated its anti-epileptic effects in a well-established genetic model of epilepsy and epileptogenesis of Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats. Early long-term treatment (ELTT) (1 mg/kg/day p.o.) exerted significant anti-epileptogenic effects ($p < 0.05$), as evidenced by the reduction in seizures frequency and duration compared with untreated rats [43]. Similarly, in a recent study, Fingolimod (2 and 6 mg/kg, I.P.) exerted anti-epileptic and anti-convulsive effects when administered in a pre-clinical model of Temporal lobe epilepsy (TLE) in male C57BL6/N mice. Fingolimod was administered on day 47-60 to test anti-convulsive effects, treated 1 h post-SE induction for 2 weeks to test disease-modifying, anti-epileptogenic effect, and was treated with 6 mg/kg/day for 2 weeks starting early from 1 h post-Kainic Acid (KA) injection to study the impact of early intervention. Fingolimod treatment significantly decreased the seizure frequency in the suprahippocampal KA (70 nl)-induced TLE (2 mg/kg, $p = 0.02$, and 6 mg/kg, $p < 0.0001$, Sidak's post hoc test), confirming its

anti-convulsive properties [30]. On the contrary, Fingolimod treatment starting immediately after Pilocarpine-induced SE does not exhibit any beneficial effect on the SE phase. Moreover, epileptic EEG features but not behavioral SE were provoked after treatment with Fingolimod at the later stage of SE. This observation speculates that an anti-epileptic effect demonstrated by Fingolimod against chronic recurrent seizure activity might not be due to attenuation of its effects in the SE stage [30]. Therefore, Fingolimod stands as a disease-modifying, anti-convulsive therapeutic alternative in "pharmacoresistant" TLE patients.

These findings reflect that Fingolimod exerts disease-modifying anti-epileptic effects, as evidenced by a reduction in seizure frequency, duration and severity, suggesting its usability as a possible anti-epileptic treatment therapy.

2.2. Fingolimod Modulates S1P Receptors in Epilepsy

Disrupted sphingolipids metabolism is an important characteristic of several brain diseases, often presented with a lack of specific known defects of sphingolipid metabolic enzymes and/or intracellular traffic [44]. This evidence has revealed sphingolipid metabolism as an emerging target against several brain disorders. Sphingolipids such as S1P play a critical role in the CNS [45] and it can be therefore suggested that the S1P signaling pathway could be a plausible therapeutic target against neurological disorders, including epilepsy [46]. Moreover, S1P1 signaling could exert an important role in astrocytes proliferation during KA-induced excitotoxicity as evident by the localization of S1P1-immunostained astrocytes and neurons in the dentate gyrus (DG) and cornu ammonis 3 (CA3) hippocampal area after intraperitoneal KA (30 mg/kg) administration in male ICR mice [47]. Inhibition of S1P1-induced signaling by Fingolimod was shown to reduce reactive astrogliosis, as evidenced by less glial fibrillary acidic protein (GFAP) positive cells in the hippocampal area (CA1, CA3 and hilus) in the Lithium-Pilocarpine model of SE in male SD rats [32]. Modulation of the S1P pathway might represent a potential therapeutic target against epileptogenesis based on the established role of neuroinflammation in epileptogenesis [48] and the inhibitory potential of Fingolimod in neuroinflammation [49].

Treatment with Fingolimod (1 mg/kg, I.P) in an experimental SE model of male SD rats induced by Lithium-Pilocarpine administration, was shown to attenuate seizure-induced hippocampal overexpression of P-glycoprotein (P-gp), compared to the SE group. This reduction of seizure-induced P-gp, was mediated by the activation of SP1R1, as evident by the decreased effect of Fingolimod on P-gp expression by the selective antagonist of S1PR1, W146. Since neuroinflammation plays an important role in the regulation of P-gp [50-52], Fingolimod suppressed seizure induced hippocampal upregulation of inflammatory markers (NF-κB, TNF-α and COX-2) in a SP1R1-dependent fashion [53].

Furthermore, Fingolimod (2 and 6 mg/kg, I.P.) treatment in 2 experimental models of SE (KA and Pilocarpine-induced SE) in male C57BL6/N mice, modulated the S1PR subunits in several hippocampal areas (CA1, CA3, and DG). Precisely, S1PR1 exhibited a significant upregulation in CA3 after KA-induced SE as well as in CA3 in Pilocarpine-induced SE, whereas it was significantly reduced in DG after KA-induced SE. Moreover, S1PR3 was upregulated after KA-induced SE in all hippocampal areas. On the contrary, the increased expression was recapitulated only in the CA3 and DG areas after Pilocarpine-induced SE [30]. These findings reflect the modulating potential of Fingolimod in SP1R1 receptors in a diverse model of epileptic seizures.

2.3. Fingolimod Inhibits Neuroinflammation after Epilepsy

Although the precise pathomechanisms of epileptogenesis are not well understood, there is increasing evidence of the contribution of neuroinflammation [2, 6]. Intriguingly, there is also a growing discussion of whether brain inflammation contributes to epilepsy or epilepsy which leads to brain inflammation [54]. The leaky blood-brain barrier (BBB) has been implicated in brain inflammation, which has been speculated to take place in epileptogenesis [55]. The compromised BBB allows the entry of the pro-inflammatory cytokines into the brain area [56]. Moreover, glial cells, neurons and endothelial cells from the BBB contribute to the initiation and continuation of the inflammatory signalling in the epileptogenic tissue, mainly by releasing several inflammatory mediators, including danger signal molecules such as high mobility group box 1 (HMGB1), prostaglandin E2 (PGE2), cytokines (IL-1β, TNF-α,) and TGF-β [57]. The contribution of inflammation in epileptogenesis is also evident by the activation of inflammatory mediators such as interleukins, interferons (IFNs), COX-2, NF-κB, as well as of downstream inflammatory mediators (IL-1β, IL-6, TNF-α), chemokines and PGE2 in epileptic conditions [58-62]. Therefore, targeting neuroinflammation might represent a novel treatment strategy against epileptogenesis [63].

In this context, a range of experimental studies indicates that Fingolimod can be a suitable candidate against epileptic seizures due to its anti-inflammatory activities [64, 65]. Indeed, Fingolimod treatment has been demonstrated to downregulate the expression of inflammatory markers after epilepsy.

In a Lithium-pilocarpine SE model of SD rats, Fingolimod treatment (1 mg/kg, I.P.) was shown to significantly downregulate the hippocampal expression of TNF-α and IL-1β compared to the SE group. This reflects that Fingolimod inhibited neuroinflammation during epileptogenesis, which in turn decreased neuronal hyperexcitability in the chronic epileptic state [66].

Moreover, neuroinflammation is characterized by the reactivity of astrocytes and microglia [67], which is prevalent in both patients with epilepsy [68] as well as in experimental models of epilepsy [69]. Epileptic seizures have been shown to induce activation of astrocytes and microglia, contributing to brain injury [70]. Ultimately, activated astrocytes and microglia release several inflammatory particles, mainly IL-1β, high mobility group box 1 (HMGB1) and TNF-α, leading to the promotion of seizures and epileptogenesis [60], thus suggesting that novel anti-epileptic therapeutic agents should be able to reduce the activation of astrocytes and microglia [71].

Fingolimod treatment (1 mg/kg, I.P.) was shown to decrease the hippocampal activation (in CA1, CA3 and the hilus) of astrocytes (as evident by decreased GFAP-positive cells) and microglia (as evident by decreased IBA1-positive cells) post-SE induced by Lithium-Pilocarpine injection in male SD rats [66]. Similarly, in a PTZ kindling model in male NMRI mice, high levels of activated astrocytes and microglia were observed, indicating an inflammation hallmark. In turn, Fingolimod treatment (0.3 or 1 mg/kg, I.P.) decreased the levels of astrocyte and microglia activation, mediated by astrocyte S1PR1 modulation [31].

The anti-inflammatory potential of Fingolimod has been further strengthened by the downregulation of hippocampal NF-κB activity in the experimental SE induced by Lithium-Pilocarpine in male SD rats. In addition, a similar reduction in pro-inflammatory markers (TNF-α and COX-2) was observed upon Fingolimod treatment. These findings suggest that Fingolimod diminishes the hippocampal upregulation of TNF-α and COX-2, which is, in part, mediated by the S1PR-dependent manner in SE rats [53]. Therefore, it may down-regulate seizure-induced overexpression of inflammatory markers *via* S1PR1 activation, thus reflecting its inhibitory potential over neuroinflammation. A pre-clinical study evaluating Fingolimod in pro-inflammatory effects related to KA-induced (0.5 μg/2μl, I.C.V.) seizure-like behaviour and hippocampal degeneration in male SD rats, in respect to the effectors of neuroinflammation in the brain (microglial cells), revealed the reduced amount of $IBA1^+$ cells in the CA3 region of the Fingolimod-treated group [49].

2.4. Fingolimod Exerts Neuroprotection after Epilepsy

Neuronal loss is acknowledged as the key feature of epileptogenesis, which occurs early after the onset of SE [72, 73]. Moreover, neuronal cell death, astrogliosis, as well as Mossy fiber sprouting (MFS) have been reported in a rodent epileptic model induced by Pilocarpine [74]. Thus, any novel anti-epileptic candidate should at least, in part, reduce/inhibit neuronal cell death. Fingolimod, in this regard, has been shown to exert neuroprotection by reducing neuronal cell death in an experimental epileptic model.

In an animal model of SE of male SD rats induced by Lithium-Pilocarpine injection, the number of NeuN-positive cells was found considerably upregulated in the Fingolimod-treated (1 mg/kg, I.P.) animals (CA1, CA3, and the hilus) compared to the SE (CA1-44%, CA3-35%, and the hilus-54%). On the contrary, Fingolimod-treated animals demonstrated decreased numbers of the FJB-positive cells (in CA1, CA3 and the hilus) as compared to the SE groups [66]. This increase in NeuN-positive cells and a reduction in FJB-positive cells in the hippocampal areas after Fingolimod treatment reflects its neuroprotective effect against SE.

Similarly, in a PTZ-induced kindling in male NMRI mice, Fingolimod treatment (0.3-1 mg/kg, I.P.) showed a significant elevation of cell numbers upon Nissl staining as compared to PTZ kindling group. Moreover, the treatment decreased neuronal cell death in the hippocampal CA3 and CA1 areas, compared to the PTZ group, as evident by NeuN immunostaining [31]. Furthermore, Fingolimod attenuated segmental neuronal cell loss in the hippocampal area (only in the ipsilateral and not in the contralateral area), whereas quantification of neuronal cell loss demonstrated neuroprotection only in CA3 but not in CA1 area [30].

Although the precise underlying mechanism behind Fingolimod's neuroprotective activity is still enigmatic, we can speculate that it may be attributed to both direct and indirect mechanisms. This is evident by the fact that neuronal cells mainly express S1PR1 and S1PR3 [75] and that Fingolimod inhibited neuronal cell death through activation of protein kinase B (AKT) and extracellular receptor kinase (ERK) signaling axes [76].

2.5. Fingolimod in KA-induced Neuronal Cell Death

Abnormal neuronal cell death has been detected in epilepsy. Neuronal excitotoxicity includes extreme excitatory neurotransmission mediated by glutamate [77]. A high concentration of extracellular glutamate leads to the inactivation of the N-methyl-D-aspartate (NMDA) receptor allowing the entry of Ca^{2+} into neuronal cells [78]. The successive addition of Ca^{2+} stimulates the production of reactive oxygen species (ROS) that activates several cell death processes, including apoptosis, through the opening of mPTP. Experimental evidence of the contribution of neuronal excitotoxicity in the seizure onset and/or epileptic conditions emerges from studies reporting the elevated concentration of glutamate in both epileptic animal models and patients [79].

Overstimulation of glutamate causes neuronal tissue damage resulting in cell death [80]. The administration of KA resulted in a significant loss of hippocampal cells, specifically in the CA1, CA3 and DG regions [81]. Of importance, hippocampal neuronal death induced by the administration of KA is proposed to be mediated by excessive glutamate release [82]. Hence, KA is extensively used to investigate the pathomechanisms of neurodegeneration induced by excitotoxicity to detect pharmacological agents with potential neuroprotective potential [83].

Fingolimod has exerted its protective effects against KA-induced excitotoxic neuronal cell death and neuroinflammation in both *in vitro* and *in vivo* studies. Precisely, primary neuronal and organotypic cortical cultures were treated with NMDA (25 and 100 μM) to produce excitotoxic cell death *in vitro*, whereas intracerebroventricular (ICV) injection of KA (0.5 μg/2 μl) in SD rats was performed *in vivo*. Fingolimod (10 to 1,000 nM) administered to the cell cultures 24 h prior NMDA was shown to reduce the release of lactate dehydrogenase (LDH) and inhibited neuronal damage. On the contrary, in the organotypic cultures, a higher dose of Fingolimod (100 nM) did not report any reduction in neuronal death.

Repeated treatment with Fingolimod (day -1 to day 2) decreased the seizure score when compared to the KA-treated group and exerted neuroprotective effects against KA-induced neurodegeneration *in vivo* as evidenced by low FJC^+ degenerating neurons and higher $NeuN^+$ cells in the CA3 region of Fingolimod-treated groups. On the contrary, a single dose of Fingolimod (1 μg/2 μl, I.C.V.) did not induce any significant changes between KA- and Fingolimod-treated groups, neither in the seizure-score nor in neuronal cell death at CA3 region, as evaluated by the quantification

of Nissl's stained sections. Moreover, it reduced the activation of microglial cells, as evident by the lower $IBA1^+$ cells in the CA3 of the Fingolimod-treated animals [49].

Therefore, Fingolimod exerts a protective effect in the KA model of excitotoxicity by inducing significant hippocampal neuronal death mainly in ipsilateral CA3, thus reflecting its potential as an anti-epileptic therapeutic agent.

2.6. Molecular Mechanisms Underlying the Antiepileptic Effects of Fingolimod

The mammalian target of the rapamycin (mTOR) signaling axis has been previously associated with several cellular processes such as protein synthesis, cell growth, and proliferation, as well as synaptic plasticity that impacts neuronal excitability and contributes to epileptogenesis [84]. This data suggest that manipulation of the mTOR signaling axis may prove beneficial in different types of epilepsy, including TLE, absence epilepsy, cortical dysplasias, tuberous sclerosis complex, *etc* [85, 86].

Fingolimod has been shown to exert similar beneficial effects in a genetic (absence) epilepsy model of WAG/Rij rats. ELTT with Fingolimod (1 mg/kg/day for 17 weeks) was demonstrated to temporarily reduce the activity of mTOR signaling as denoted by the decreased levels of p-mTOR and p-p70S6k and upregulated p-AKT levels. However, after the termination of Fingolimod treatment (after 5 months), the mTOR pathway activation reverted to the control levels together with the appearance of absence seizures. These findings speculate that inhibitory properties of Fingolimod ELTT might be indirect and associated with its anti-epileptogenic effects (reduction of absence seizures), which would, in turn, decrease the activation of the mTOR pathway. This statement is based on the fact that sub-chronic treatment of Fingolimod (1 mg/kg/day for 1week) neither decreased mTOR pathway activation nor the absence of seizures in adult WAG/Rij rats [43].

Although myelin sheath has not been acknowledged as a crucial contributor to the pathomechanism of epilepsy, myelin damage (hippocampus and cerebral cortex) has been detected at the early period of PTZ-induced epileptic seizures [87]. Furthermore, CNS myelin sheaths are affected in the epileptic patients [88-90], reflecting that myelin repair might represent a crucial target for anti-epileptic drugs. Nevertheless, the pathological understanding of epileptic seizures in the CNS demyelinating diseases remains unravelled, but there is growing evidence supporting the relationship between demyelination and epileptic seizures, thus offering an interesting perspective in investigating novel therapeutic strategies against currently enigmatic and uncontrolled epilepsy types [87].

Fingolimod, in this regard, has demonstrated its myelin repairing potential in a PTZ kindling model in male NMRI mice. Pre-treatment with 2 doses of Fingolimod (0.3 or 1 mg/kg, I.P.) increased their myelination, compared to the PTZ-kindled group as detected by luxol fast blue (LFB) staining. Moreover, both doses of Fingolimod exhibited enhanced intensity of hippocampal myelin staining. Furthermore, immunostaining against NG2 showed increased quantities of oligodendrocyte precursor cells (OPCs) in animals treated with Fingolimod and even greater in animals receiving a reduced dose [31]. Moreover, similar findings were obtained on Fingolimod post-treatment, suggesting that it caused myelin protection as well as increased hippocampus remyelination in the fully kindled animals.

In addition to the T-cell infiltration, activation of innate immunity has been reported in a pre-clinical TLE model induced by unilateral stereotaxic injection of KA (70 nL, 5 mM) [91]. This evidence suggests that activation of the innate immune system contributes to the pathogenesis of epilepsy, and reduction in the infiltration of cytotoxic T cell might be crucial for the potential anti-epileptic effects of any therapeutic alternatives. A decrease in the infiltration of CD45 was also observed in the hippocampi (ipsilateral and contralateral) of KA-induced SE mice treated with Fingolimod. Moreover, upon quantification of CD45 positive cells, decreased immunoreactivity was observed in the Fingolimod-treated animals. A decreased quantity of cytotoxic T cells stained as CD8 positive was also observed in the animals treated with Fingolimod [30], further suggesting that the treatment reduced immune cell infiltrates during late chronic epileptic seizures.

2.7. Treatment of Epilepsy in Multiple Sclerosis (MS): Therapeutic role of Fingolimod?

MS is a demyelinating CNS disorder that occurs commonly in the younger adult and ultimately progresses chronically in older adults [92, 93]. The well-acknowledged MS hypothesis involves autoreactive peripheral T cells that access CNS and initiate an inflammatory process, leading to the destruction of the myelin sheath, reduced axonal transmission, and ultimately neurodegeneration [94]. Not surprisingly, people with MS possess an increased risk of developing epileptic seizures. However, the association between subtypes of MS, the disease severity, and the impact of MS treatment on seizures generation is not yet completely known [95]. People with MS are at a 3-fold higher risk of developing epilepsy [96, 97]. Moreover, the occurrence of epileptic seizures ranges between 0.5% to 8.3% in MS patients, depending on different studies [98, 99]. A recent meta-analysis suggested that the occurrence of epilepsy might be correlated with greater expanded disability status scale (EDSS) scores when compared to MS-patients without seizures and with similar disease duration [96]. MS patients with epilepsy have a greater mortality risk when compared to MS patients without epilepsy [100]. In fact, the prevalence of seizures has been recognised as part of the MS spectrum [101]. The relationship between MS and epileptic seizures has been reported by a pre-clinical study where cuprizone-mediated chronically demyelinated mice (male Thy1-YFP mice) exhibited seizures and disrupted intrahippocampal EEG activity [102].

Epileptic seizures exhibited extreme and hypersynchronous brain activity, indicating that cortical and subcortical lesions in MS might plausibly contribute to the higher rate of epilepsy in MS [103, 104]. Earlier neuroimaging analysis suggested that the epileptic seizures in MS are correlated with a more extensive inflammatory cortical pathology

[105]. However, the precise underlying cause of the concurrent presence of both conditions is still unknown [101] and the pathomechanism untangling this association is an emerging subject of research [106]. However, it is still enigmatic whether and up to what extent the appearance of seizures and epilepsy in MS patients impact the clinical course as well as the long-term disease prognosis [107-109].

Although seizures affect only a minor population of MS patients, they are still a serious problem deserving further attention [98]. Moreover, the adverse side effect of AEDs presents a crucial parameter for the selection of suitable AEDs to treat seizures in MS patients [110]. Therefore, there is a high demand to explore novel treatment alternatives in order to treat epilepsy in patients with MS. Fingolimod in this regard, could be a potential candidate that can reduce epileptic seizures in MS patients. Unfortunately, no evidence supporting this notion is yet available [20, 111], highlighting the importance of performing future clinical studies with MS patients exhibiting epilepsy in order to assess its effectiveness.

3. DISCUSSION

Epilepsy is a devastating neurological disorder affecting ~70 million of the global population [112]. It is caused by the aberrant synchronized firing of neurons, mainly due to the imbalance in excitatory and inhibitory neurotransmission [113]. The mainstream AEDs are unable to control seizures in 30% of the patients, thus reflecting the need to identify novel AEDs. In this regard, drug repositioning, which refers to new indications of approved drugs, has gained significant scientific attention by saving time and reducing costs [114]. Moreover, several drugs approved for non-epileptic disorders have demonstrated anti-epileptic efficacy in experimental models of epilepsy [10, 12, 13]. A recent review has systematically reviewed several molecules and their relevance

Table 1 Studies reporting anti-epileptic effects of fingolimod.

S.N.	Interventions	Model	Treatment Protocol	Observations	Refs.
1	Fingolimod (2 and 6 mg/kg, I.P.) administered with different treatment protocols	Suprahippocampal (left CA1) KA (70 nl) induced SE in male C57Bl6/N-mice and Pilocarpine hydrochloride (335 mg/kg, S.C.)	Treated day 47-60 Treated 1h after SE induction for 2 weeks 2 mg/kg started at day 47 post-SE for 1 week and continued with 2 mg/kg for next week	Fingolimod exerted anti-epileptogenic, disease-modifying effect which might be due to augmentation of Fingolimod target molecules S1PR1 and S1PR3 in CA3 and downregulation of S1PR1 and S1PR3 in DG. Fingolimod treatment exerted neuroprotective and anti-gliotic effects and decreased infiltration of cytotoxic T cell.	[30]
2	FTY720 (S1P analogue) (1 mg/kg I.P.),	Lithium chloride (127 mg/kg, I.P.) - Pilocarpine (30 mg/kg, I.P.) induced SE in male SD rats	Administered immediately, once a day after termination of SE.	FTY720 administration reduced seizure-induced overexpression of P-gp *via* reducing S1PR1-mediated inflammation (reduced TNF-α, COX-2, NF-κB) in rat hippocampus.	[53]
3	Fingolimod (FTY720) (0.3 or 1 mg/kg, I.P.)	PTZ (36.5 mg/kg, I.P.) induced kindling in NMRI mice	Pre-treatment with FTY720 for 1 week, 1 h prior to each PTZ injection	FTY720 significantly reduced the number and duration of PTZ induced seizures. FTY720 attenuated PTZ induced inflammation as evidenced by reduced expression of GFAP and IBA1 in CA1 and CA3 hippocampal region. Fingolimod treatment demonstrated myelin protection in PTZ kindling model as evident by the increase in the intensity of hippocampal myelin staining.	[31]
4	Fingolimod (1 and 3 mg/kg/day, I.P. and oral route)	Genetic (absence) epilepsy model in WAG/Rij rats	Fingolimod early long-term treatment (ELTT) (17 weeks)	Fingolimod treatment initiated before onset of absence seizure exerted anti-epileptogenic and anti-depressant-like effects in WAG/Rij rats. Fingolimod ELTT downregulated mTOR signaling cascade as evident by decreased p- levels of mTOR and p-p70S6k	[43]
5	Fingolimod (FTY720) (1 mg/kg, I.P.)	Lithium chloride (127 mg/kg, I.P.) - Pilocarpine (30 mg/kg, I.P.) induced SE in male SD rats	Administered 24 h after SE onset and continued once daily up to 2 weeks	Treatment with FTY720 alleviates the incidence, frequency, duration as well as severity of spontaneous convulsions (SCs). FTY720 decreased neuronal loss and reduced microglial and astrocytes activation in hippocampus as well as restrained over expression of TNF-α and IL-1β in hippocampus.	[66]

FTY720, Fingolimod; SE, Status Epilepticus; KA, Kainic Acid; PTZ, Pentylenetetrazol; CA, Cornu Ammonis; SD, Sprague Dawley; ELTT, Early long-term treatment; WAG/Rij, Wistar Albino Glaxo/Rijswijk; GFAP, Glial fibrillary acidic protein; SCs, Spontaneous convulsions; I.P., Intraperitoneal; S.C., Subcutaneous; S1PR, Sphingosine 1-Phosphate receptors; IL, Interleukin; IBA1, ionized calcium-binding adapter molecule 1; mTOR, Mammalian target of rapamycin; COX-2, Cyclooxygenase-2; NF-κB, Nuclear factor κ light chain enhancer of activated B cells; TNF-α, Tumor necrosis factor-α.

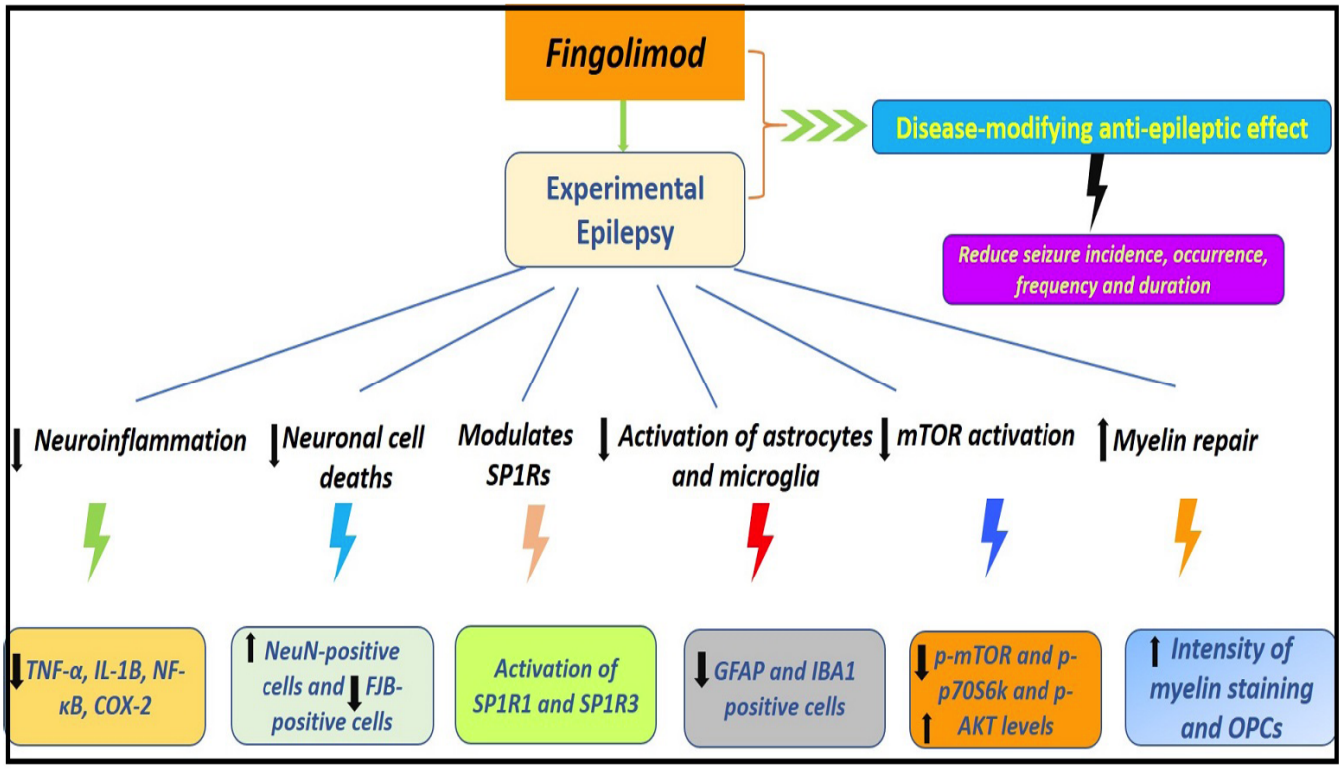

Fig. (1). Molecular mechanisms associated with the disease-modifying anti-epileptic effects of Fingolimod. Experimental evidence indicates the disease-modifying anti-epileptic effects of Fingolimod against epileptic seizures. The underlying molecular mechanisms involve primarily its anti-neuroinflammatory effects as evident by a reduced level of TNF-α, IL-1B, NF-κB, and COX-2. Moreover, Fingolimod confers significant neuroprotection by reducing neuronal cell loss as evident by increased NeuN-positive cells and decreased FJB-positive cells. It was further shown to activate/modulate S1PR1 and SP1R3 during epileptic seizures as well as reduce the activation of astrocytes and microglia (as evident by GFAP and IBA1 positive cells). Moreover, Fingolimod can downregulate the activation of mTOR pathway leading to decreased p-mTOR, p-p70S6k and elevated p-AKT levels. Increased staining of myelin staining, as well as OPCs, have also been observed upon treatment with Fingolimod reflecting its potential for myelin repair. GFAP, Glial fibrillary acidic protein; IL, Interleukin; IBA1, Ionized calcium-binding adapter molecule 1; COX-2, Cyclooxygenase-2; NF-κB, Nuclear factor κ light chain enhancer of activated B cells; TNF-α, Tumour necrosis factor-α; OPCs, Oligodendrocyte precursor cells; S1P, Sphingosine-1-phosphate; S1PR1, S1P receptor 1; S1PR3, S1P receptor 3; mTOR, Mammalian target of rapamycin; AKT, Protein kinase B. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

against epileptogenesis, strengthening the therapeutic potential of the repurposed molecule [115].

Fingolimod, an immunomodulatory drug, has exhibited anti-epileptic effects in a diverse range of pre-clinical epileptic models such as Pilocarpine and KA-induced SE, non-SE absence epilepsy model and PTZ-induced kindling, indicating its potential as a promising candidate for drug repurposing (Table **1**). The therapeutic effect of Fingolimod against epileptogenesis is mainly based on its potential to reduce the incidence, occurrence and duration of the seizure by two-fold [66]. In addition, a 3-fold reduction in the seizure frequency was demonstrated upon Fingolimod administration (immediately 1 h post-SE onset and up to 2 weeks) [30]. Among the several studies discussed herein, the dose and treatment strategy of Fingolimod against epileptogenesis are different and it is worth noting that in the closest practical clinical settings, the drug administration starts at the advanced stage of SE rather than immediately after SE [30]. Regarding the underlying mechanism, Fingolimod has been shown to exert its anti-epileptic effects *via* anti-neuroinflammatory function, reduction of neuronal cell death, reduced activation of astrocytes and microglia by modulating SP1R, decreased mTOR activation, enhanced myelin repair and reduced cytotoxic T cell infiltrates (Fig. **1**). Despite the neuroprotective effects of Fingolimod, there is a room for discussion regarding the treatment strategy as pre-treatment with Fingolimod (*in vitro*) and treatment with repeated dose of Fingolimod exerts protection against neuronal death (*in vivo*), however single dose Fingolimod does not reduce neuronal cell death (*in vivo*) [49]. This finding reflects the need of deeper exploration and find the best practical treatment strategy for Fingolimod that could exert a potent neuroprotection against SE.

Though Fingolimod demonstrated the promising anti-epileptic effect of in rodents model, it is worth to know that the data are supported with a very limited number of findings, reflecting the further need of investigating the anti-epileptic effect of Fingolimod in several models of epileptogenesis which will hopefully pave the way for its clinical implication. In addition, though the therapeutic effect of Fingolimod has not been yet registered in post-traumatic epi-

lepsy (PTE), acknowledging the contribution of BBB disruption as a mechanism of PTE [116] and owing to the Fingolimod potential in restoring BBB permeability [45, 117], further studies in an additional model of brain injury *i.e*., traumatic brain injury (TBI) and PTE are needed [115].

Of importance, Fingolimod is well tolerated and has a safety profile [118] that makes it a good choice for further investigation in clinical settings, and possibly clinical trials. However, an earlier study has reported that patients treated with Fingolimod might experience bradycardia at the beginning of treatment [119]. Therefore, clinical administration of Fingolimod in epilepsy must be carefully designed to monitor side effects, possibly given at the beginning of SE and not at the more advanced stages [30].

4. SEARCH METHODOLOGY

Several databases, such as PubMed, Scopus, and Cochrane Library were searched. Keywords included Fingolimod, Anti-epileptic effect, Epilepsy, Seizures, and Multiple sclerosis and they were used in various combinations. Only the peer-reviewed full-length articles dealing with *in vitro*, *in vivo* aspects and published until 2020, were incorporated in the final manuscript. Moreover, we have screened the bibliography of the primary literature to include all relevant articles. Articles published in a non-English language, unpublished work and conference papers were excluded.

CONCLUSION

The experimental evidence discussed herein provides the proof-of-concept that repurposing/repositioning of Fingolimod might overcome the limitation of currently available AEDs and can confer disease modification.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's diseases
AEDs	=	Anti-epileptic drugs
AKT	=	Protein kinase B
BBB	=	Blood-brain barrier
CA	=	Cornu ammonis
CNS	=	Central Nervous System
DCs	=	Dendritic cells
DG	=	Dentate gyrus
EDSS	=	Expanded disability status scale
EEG	=	Electroencephalography
ELTT	=	Early long-term treatment
ERK	=	Extracellular receptor kinase
FDA	=	Food and drug administration
GFAP	=	Glial fibrillary acidic protein
GPCR	=	G-protein-coupled receptor
IBA1	=	Ionized calcium-binding adapter molecule 1
IL	=	Interleukin
LFB	=	Luxol fast blue
MBP	=	Myelin basic protein
MFS	=	Mossy fiber sprouting
MS	=	Multiple sclerosis
mTOR	=	Mammalian target of rapamycin
NF-κB	=	Nuclear factor-κ light chain enhancer of activated B cells
NMDA	=	N-methyl-D-aspartate
OPCs	=	Oligodendrocyte precursor cells
PD	=	Parkinson's diseases
PWE	=	People with epilepsy
ROS	=	Reactive oxygen species
RRMS	=	Relapsing-remitting multiple sclerosis
S1P	=	Sphingosine-1-phosphate
S1PR	=	S1P receptor
SPHK	=	Sphingosine kinase
TLE	=	Temporal lobe epilepsy
TNF-α	=	Tumour necrosis factor-α

AUTHOR'S CONTRIBUTION

YNP conceptualized carried out the literature review and drafted the manuscript. EA, CP, VG, IO and MFS provided critical revisions and contributed to the final manuscript. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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