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Excitotoxicity In Neurodegeneration: An Therapeutic Approach

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Abstract

Excitotoxicity, a pathological phenomenon defined by excessive glutamate signaling and calcium influx, plays an important role in the pathological course of several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). This review discusses the multiple molecular and cellular processes involved in excitotoxicity - glutamate accumulation, excessive activation of ionotropic receptors, impairment of mitochondrial function, oxidative nitrosative stress, and apoptotic signaling - and how they culminate in synaptic failure and eventually cell death. The disease-specific perspectives highlight how excitotoxicity intersects with a variety of proteinopathies and transporter dysfunctions. To date, therapeutic approaches have been focused on mitigating excitotoxicity by using NMDA and AMPA receptor antagonists, elevating glutamate clearance, blocking calcium channels, and antioxidants, each demonstrating partial neuroprotection and symptom relief. At the same time, promising approaches including gene- and RNA-based therapies, stem cell transplantations, nano-medicine-based drug delivery, and multi-target regimens highlight the need for neuroprotective and personalized treatments available in the clinic. A more comprehensive mechanistic understanding and integrated approaches will be essential to halt or reverse excitotoxicity-mediated neural degeneration.

Keywords: Excitotoxicity, Glutamate, Neurodegeneration, NMDA Receptor, Oxidative Stress, Calcium Dysregulation, ALS, Alzheimer's Disease.

1. INTRODUCTION

Neurodegeneration is the term used to describe the slow loss and subsequent death of the nervous system basic building blocks, which are neurons, resulting in such chronic neurological disorders as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis (ALS) [1]. Such disorders are characterized by a decline in cognition, motor deficit, and serious limitations in the quality of life. Common shared pathways are oxidative stress, mitochondrial failure, inflammation and excitotoxicity. Excitotoxicity is a disease in which a neuron is destroyed by overstimulation by such excitatory neurotransmitters as glutamate.

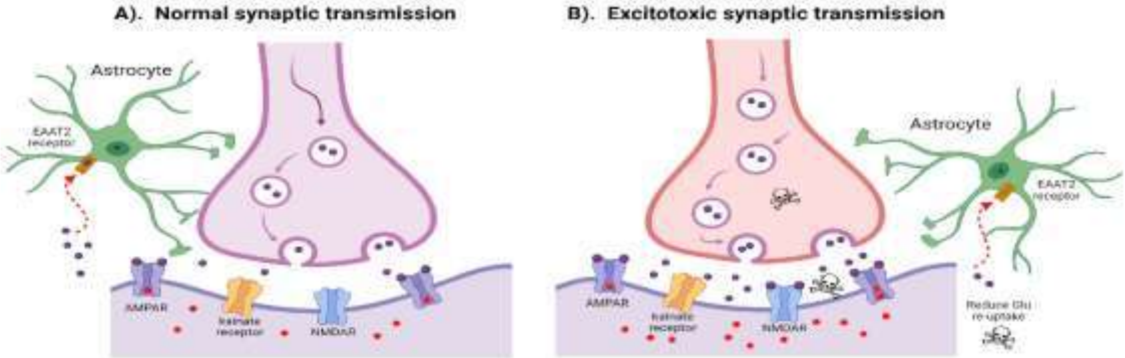

Figure 1: Excitotoxicity in Neurodegeneration [2]

In case of glutamate dysregulation, such an overstimulation of ionotropic receptors, including NMDA and AMPA, cause unregulated movement of excess calcium ions into the neurons, and this results in a cascade of damaging effects. Excitotoxicity in neurodegenerative disorder is not a stand alone phenomenon but one that interacts with other pathological activities. As an example, accumulation of amyloid-beta oligomers in Alzheimer disease also disrupts glutamate uptake and Favors extrasynaptic NMDA receptor activation, whereas in ALS a

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decreased expression of astrocytic glutamate transporters results in maintain glutamate in the synaptic cleft.

The discovery of excitotoxicity in neurodegeneration has resulted in a new direction of therapeutic approaches, where a lot of research has centred in treatments that rebalance glutamate signalling or favour more efficient glutamate removal or inhibition of the injury process with chelation of calcium [3]. Learning more about the mechanisms is one of the keys to the development of effective treatments that may slow, stop or reverse the disease progression of neurodegenerative diseases.

2. MECHANISMS OF EXCITOTOXICITY

Excitotoxicity, results of the excessive accumulation of glutamates in the CNS, elicits the overstimulation of ionotropic receptors, causing the calcium ions influx and the enzymes distorting cellular structures. Mitochondria overwhelmed with this process also lose their membrane potential, generate reactive oxygen species (ROS) and field pro-apoptotic elements [4]. Induced by ROS/RNS and enzymes such as NADPH oxidase, oxidative and nitrosative stress injures essential biomolecules as well as overwhelms antioxidant defenses and results in neuronal dysfunction and cell death.

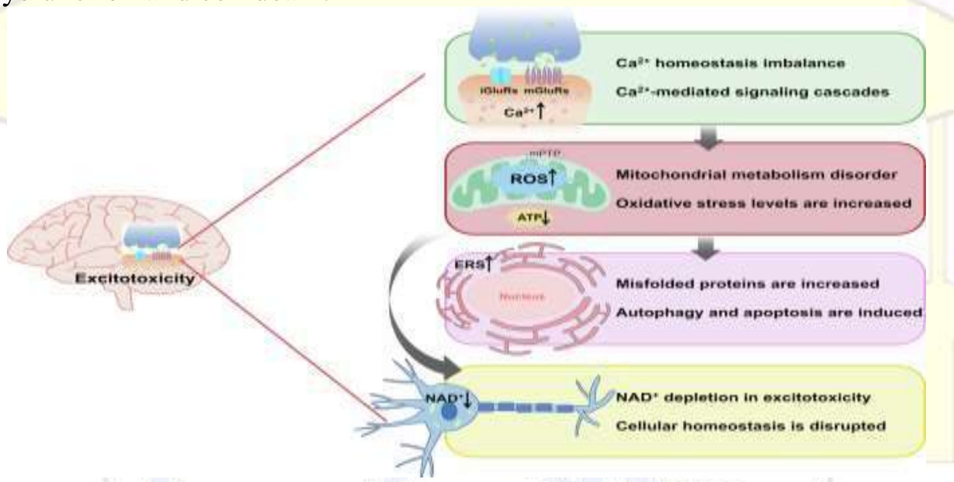

Figure 2: Molecular mechanisms of excitotoxicity [5]

2.1. Glutamate and Synaptic Transmission

The glutamate neurotransmitter plays an important role in the central nervous system, which is an excitatory neurotransmitter that contributes to the process of synaptic transmission, neurodevelopment, learning, and memory as well. It is an ionotropic and metabotropic receptor mechanism, and it affects synaptic effects. Glutamate under physiological condition is removed through excitatory amino acid transporters [6]. But in case of pathological states such as ischemic stroke, traumatic brain injury, neuroinflammation or neurodegenerative diseases such as Alzheimer or Huntington, glutamate release is disrupted where either impaired reuptake or excess glutamate release, both are linked to neuronal dysfunction and neuronal death.

2.2. Ionotropic Receptor Overactivation

- **NMDA Receptors (NMDARs):** NMDARs are highly permeable to calcium-ion channels that are indispensable in synaptic plasticity and long-term memory. Nevertheless, the over-activation, especially of extrasynaptic NMDARs, results in the excessive inflow of calcium ions, which activates the calcium-dependent enzymes, such as nNOS, calpains, and phospholipases. Overactivation breaks cytoskeletal integrity, down-regulates cellular membranes, damages mitochondrial system and activates apoptotic and necrotic forms of cell death [7].
- **AMPA and Kainate Receptors:** These mediate rapid excitatory transmission as they enable entry of both sodium and calcium through binding of glutamate. An altered subunit composition makes calcium permeable in the pathological state and especially when there

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is neurodegeneration, it enhances excitotoxicity, and it also adds to the deleterious activity of an over-activated NMDA receptor.

2.3. Calcium Dysregulation and Mitochondrial Damage

This neuronal secondary [citation needed] messenger calcium is regulated by the sequestration into such organelles as mitochondria and the endoplasmic reticulum (ER). With the introduction of excitotoxic injury, the influx of calcium overloads buffering processes resulting in the overloaded mitochondria, dysfunctional ATP synthesis, increased reactive oxygen species and opening of the mitochondrial permeability transition pore (mPTP). This gives rise to caspase-dependent as well caspase independent pathways of cell death. ER excess calcium blocks protein folding processes, and engulfs the cell through the unfolded protein response (UPR).

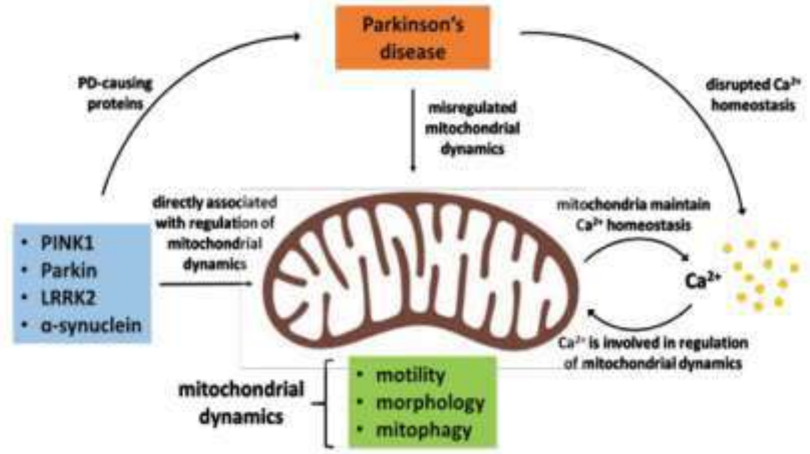

Figure 3: Calcium Dysregulation and Mitochondrial Damage [8]

2.4. Oxidative and Nitrosative Stress

Excitotoxicity depicts a condition of excess formation of types of reactive oxidizing substances (ROS) and reactive nitrogen substances (RNS), which cause oxidative and nitrosative stress. These reactive species harm vital body molecules, which make the cell fall apart. NMDA receptor overactivation activates nNOS leading to a rise in nitric oxide that may produce peroxynitrite. Enzymes such as NADPH oxidase and xanthine oxidase also increase the level of ROS, which uncouples the redox homeostasis, facilitates inflammation and causes a lasting neuronal damage [9]. The antioxidant protective systems of the body such as glutathione, superoxide dismutase and catalase are usually swamped making the damage of cells worse.

3. DISEASE-SPECIFIC ROLE OF EXCITOTOXICITY

The excess activity of glutamate and the failure to control its receptors and transporters, therefore, cause excitotoxicity that is essential in many neurodegenerative disorders. These disorders are characterized by different mechanisms, through which improper glutamate regulation leads to nerve damage and disease advances [10].

3.1. Alzheimer's Disease (AD)

The Alzheimer disease is defined by interference in the glutamate uptake in the astrocytes by soluble oligomers of amyloid-beta, the latter being able to down-regulate excitatory amino acid transporters. This causes build-up of extracellular glutamate and the hyperactivation of NMDA receptors with an enhancing effect of neurotoxic signaling. The tau hyperphosphorylation hampers microtubule dynamics that affect glutamate clearance and the neural transports systems [11]. Early synaptic dysfunction and loss is a primary contributor in early cognitive decline in AD and this excitotoxic cascade is central in this pathology. An NMDA receptor antagonist, memantine, provides symptom relieving effects.

3.2. Parkinson's Disease (PD)

Parkinson disease is a condition that arises because of the destruction of the dopaminergic neurons in substantia nigra pars compacta in the brain resulting into disparities in basal ganglia output. This deficiency makes the subthalamic nucleus (STN) hyperactive and improves glutamatergic excitatory input [12]. Such hyperactivity aids in stress and degeneration of neurons. The antagonists of the NMDA and AMPA receptors could prevent PD and the stimulation of a deep brain could diminish the excessive glutamatergic release and excitotoxicity.

3.3. Huntington's Disease (HD)

Huntington disease is a hereditary disease which occurs as a result of CAG tri-nucleotide repeated sequences in the huntingtin gene. It leads to production of mutant huntingtin protein (mHTT) that interferes with the normal functioning of a cell by causing sensitivity of NMDA receptors, boosting their calcium permeability and excitotoxicity, and compromising the level of glutamate uptake by astrocytes [13]. Of particular concern to such excitotoxicity are striatal medium spiny neuronds, which are rich in NMDA receptors but poor in calcium-buffering with low toleration to excitotoxic insults.

3.4. Amyotrophic Lateral Sclerosis (ALS)

In ALS, motor neuron death is partly caused by chronic excitotoxicity, caused by down-regulation of the EAAT2 astrocytic glutamate transporter resulting in the build-up of extracellular glutamate. This excess glutamate activates AMPA and NMDA receptors on the motor neurons, which are affected mostly because of their expressed higher rates of calcium permeable AMPA receptors, and lower capacity of calcium buffers. First approved ALS drug by FDA is Riluzole, which is effective as a neuroprotective agent at the presynaptic level through the regulation of the release of glutamate and being able to work with sodium channels.

Table 1: Summary of Literature on Excitotoxicity and Neuroprotection

Author(s)	Study	Focus Area	Methodology	Key Findings
Huber et al. (2022) [14]	Deficient neurotransmitter systems and synaptic function in FTLD	Glutamatergic dysfunction and synaptic failure in FTLD	Literature review and analysis of neuropathological and experimental studies	Altered glutamate signaling and synaptic dysfunction are central in FTLD; correcting neurotransmitter deficits may offer therapeutic benefit.
Iovino, Tremblay, & Civiero (2020) [15]	Glutamate-induced excitotoxicity in Parkinson's disease	Role of glial cells in excitotoxicity in PD	Review of experimental and clinical studies	Astrocytes and microglia contribute to impaired glutamate homeostasis; targeting glial dysfunction may reduce excitotoxicity in PD.
Jeon et al. (2021) [16]	Contribution of TRPC channels in neuronal excitotoxicity	Role of TRPC channels in excitotoxicity in neurodegeneration and stroke	Experimental studies with cell models and review	TRPC channel dysregulation increases calcium influx during excitotoxic events; targeting these channels offers neuroprotective potential.
Kim & Baik (2019) [17]	Glutamate dehydrogenase as a neuroprotective target	Role of GDH in glutamate and energy metabolism under stress	Biochemical and molecular biology studies	Enhancing GDH activity may reduce glutamate toxicity and support neuronal survival; GDH is a promising neuroprotective target.

Lemieszek et al. (2018) [18]	Neuroprotective properties of Cantharellus cibarius polysaccharides	Natural compounds as neuroprotectants in excitotoxicity	In vitro cell culture models of neurodegeneration	Polysaccharide fractions reduced glutamate-induced cytotoxicity and oxidative stress; potential as natural neuroprotectants.
Linciano et al. (2023) [19]	Novel S1R agonists counteracting NMDA excitotoxicity	Drug development targeting NMDA excitotoxicity and oxidative stress	Laboratory-based synthesis and neuronal cell assays	S1R agonists preserved neuronal viability by modulating calcium influx and boosting antioxidant defenses; promising multifunctional agents.

4. NEUROPROTECTIVE THERAPEUTIC APPROACHES

Interventions aiming at excitotoxicity are by regulating glutamate receptor activity, glutamate clearance, calcium stabilization, and oxidative stress. Pathological NMDA receptor activation is blocked by receptor antagonists such as memantine and ifenprodil that limit neurotoxicity without altering normal neurotransmission [20]. Perampanel is a regulator of excitatory transmitters in the seizure disorders. Extracellular glutamate clearance is boosted by the use of glutamate transport enhancers such as ceftriaxone and riluzole. Nimodipine and dantrolene, which belong to calcium channel blocking agents, are capable of inhibiting intracellular overload of calcium and hence lead to the excitotoxic injury. Antioxidant such as edaravone, MitoQ, CoQ10, resveratrol, and curcumin reverse oxidative and nitrosative stress protecting the mitochondroid and minimizing on the damage of neurons. Neurotrophic factors and anti-apoptotic and neurotrophic agents such as minocycline, melatonin and neurotrophic factors enhance neuronal survival and regeneration [21].

4.1. Receptor Antagonists

Targeting glutamate receptors directly is a key therapeutic approach to mitigate excitotoxicity:

- The NMDA uncompetitive, low-affinity antagonist, memantine, is approved against Alzheimer disease [22]. It can be described as a well tolerated effective agent with special properties due to which it inhibits excesses of pathological NMDA receptor activity sparing normal synaptic transmission [23] which in turn limits the neuronal damage but not altering the cognitive ability.
- Readily bioactive at the NMDA receptors with NR2B subunit that are mostly found in the extrasynaptic sites with neurotoxic signaling, ifenprodil and MK-801 are more selective [24]. These agents decrease neuronal excitation and excitotoxicity, by selectively suppressing these subtypes, without disrupting normal neurotransmission. Nevertheless, clinically, the potent psychotropic effects of MK-801 restrain its clinical application [25].
- Perampanel is a non-competitive AMPA receptor inhibitor which is used in treatment of epilepsy [26]. it inhibits rapid excitatory synaptic transmission, and limits calcium entry via AMPA receptors, with a possible neuroprotective action in excitotoxic and seizure-related disorders.

4.2. Glutamate Transport Modulation

Improving glutamate clearance and limiting its synaptic accumulation are effective strategies:

- β-lactam antibiotic, such as ceftriaxone, has been found to up-regulate the expression of the major astrocytic glutamate transporter within the CNS, EAAT2 (GLT-1) [27]. This improves the removal of extracellular glutamate, guarding against excitotoxicity in diseases like ALS and spinal cord lesion.

- Riluzole, which is approved against ALS, has several anti-excitotoxic effects: it inhibits the release of glutamate by its presynaptic transmission, increases its reabsorption, and modulates sodium channels to limit their hyperexcitability of neurons [28]. Such processes explain the long-term survival of patients with ALS and the position of riluzole as a prototype model of anti-excitotoxic drugs.

4.3. Calcium Channel Blockers

Calcium dysregulation plays a central role in excitotoxic damage, and agents that block calcium influx can prevent neuronal injury:

- Removal of neuronal injury following subarachnoid hemorrhage has been employed by the use of nimodipine which is a dihydropyridine calcium channel blocker [29]. It is a blocker of L-type voltage-gated calcium channels inhibiting intracellular calcium overloads.
- Dantrolne blocks ryanodine receptor on the endoplasmic reticulum and decreases the release of the calcium release triggers on the intracellular stores [30]. It has demonstrated neuroprotection in animal models of spinal cord injury, stroke and epilepsy via stabilization of intracellular calcium levels and inhibition of mitochondrial dysfunction [31].

4.4. Antioxidants and Free Radical Scavengers

Counteracting oxidative and nitrosative stress is vital to mitigate downstream excitotoxic damage:

- Edaravone, a free radical scavenger that has received regulatory permit to treat ALS in Japan and the U.S. limits oxidative damage in a number of ways including: neutralizing ROS, enhances mitochondrial integrity [32]. It has been demonstrated to slow the progression of the disease as well as enhance motor movement in selected cases of ALS.
- MitoQ and Coenzyme Q10 (CoQ10) are mitochondrial targeting antioxidants that neutralize effects of ROS production at the mitochondrial level. They continue the activity of mitochondria, boost the formation of ATP, and limit the oxidative damage caused by neurodegenerative illnesses [33].
- Resveratrol (found in grapes) and Curcumin, (found in turmeric) as natural compounds are polyphenolic compounds, antioxidants, anti-inflammatory and anti-apoptotic. They may have potential as chronic excitotoxic injury preventives because of their capability to fine-tune signaling via the NF-x B and Nrf2 pathways, but because of their bioavailability this potential may be limited.

4.5. Anti-Apoptotic and Neurotrophic Agents

Long-term neuroprotection can be in terms of protecting neurons against programmed cell death and augmenting survival circuitry:

- Tetracycline antibiotic, minocycline inhibits microglial activation, down-regulates caspase-1, caspase-2 and caspase-9 and stabilizes the mitochondrial membrane. It has been effective in the models of stroke and spinal cord injury, as well as in ALS, as it postpones the initiation of apoptosis and eases inflammation [34].
- The analogs of BDNF (Brain-Derived Neurotrophic Factor) and GDNF (Glial cell line-Derived Neurotrophic Factor) enhance the neuroregeneration, synaptic plasticity and neuronal survival. Despite promising results of preclinical investigation, clinical translation is hampered by a lack of blood-brain barrier (BBB) permeability, and the requirement of a targeted drug delivery mechanism.
- Melatonin is an endogenous neurohormone with effects of a strong antioxidant and regulator of mitochondrial functions. Its BBB permeability and its multiple protective effects also

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appropriate it to be an adjunctive treatment in neurodegenerative disorders associated with excitotoxicity [35].

5. NOVEL AND EMERGING STRATEGIES

New neuroscience and biomedical engineering have currently provided opportunity in recent research to solve the problem of excitotoxicity with greater sensitivity and accuracy [36]. Such new therapies are also seen as a means of escaping the shortcomings of established therapies by attacking the molecular foundations of excitotoxic injury and providing increasingly specific and less systemic toxic therapeutic regimens [37].

5.1. Gene Therapy and RNA-Based Approaches

The future research aims at finding new interventions based on genes and target neurodegenerative diseases caused by excitotoxicity [38]. There is experimental use of methods such as antisense oligonucleotides and small interfering RNAs to silence mutant genes such as HTT in Huntington s disease and SOD1 in ALS. In the same manner, viral-based gene therapy such as adeno-associated viruses (AAVs) is in development to increase levels of EAAT2 expression in astrocytes and of antioxidant enzymes [39].

5.2. Stem Cell Therapy

The Mesenchymal stem cells (MSCs) and the neural progenitor cells (NPCs) have been used to treat neurodegenerative diseases such as ALS and spinal cords and have been proved to be effective [40]. Such treatments are capable of producing neurotrophic factors, anti-inflammatory cytokines, and modulatory molecules and able to repair or combine damaged neuronal circuits and possibly turning excitotoxic damage around. In clinical trials, safety and useful application promises have been demonstrated [41].

5.3. Nanomedicine and Targeted Drug Delivery

Another promising approach to the excitotoxicity treatment is the nanomedicine in which neuroprotective factors become encapsulated by nanoparticles, such as liposomes, dendrimers, polymeric nanoparticles, and solid lipid nanoparticles [42]. They can be surface-ligand or antibody-targeted to damage-afflicted body areas, or to certain neuron-populations, to augment bioavailability of a targeted drug, minimize peripheral side effects and result in more positive therapeutic effects. On-demand therapy in case there was an injury site can also be achieved because drugs may be released in response to local stimuli using some nanocarriers [43].

5.4. Combination Therapy

Excitotoxicity has been observed as multifactorial with overactivation of glutamate receptors, excessive calcium load, oxidative stress, mitochondrial dysfunction, and apoptosis [44]. This cascade is not attained by many monotherapies. The combination therapies are now being made to target at multiple levels such as receptor antagonists, antioxidants, and neurotropic agents. The emergence of personalized medicine that is directed by molecular and genetic biomarkers is permitting increasingly personalized therapeutic regimens among the individual patients [45].

6. CONCLUSION

Excitotoxcity plays an important role in the pathophysiology of such neurodegenerative disorders as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis. This mechanism occurs through inappropriate stimulation of glutamate and calcium overload, which result in dysfunction of mitochondria, oxidative stress, and apoptotic pathways resulting in damage to the neurons and their detrimental degeneration. Current treatments, including NMDA and AMPA receptor antagonists, glutamate transport modulators, calcium channel blockers, antioxidants, and neurotrophic each palliates some stages of the complex process of excitotoxicity, and in many cases the treatments handle only one-half of this cascade. Advancing technologies including gene and RNA-based therapies, stem cells therapy, nanomedicine, and combination therapies attempt to treat excitotoxin damages with greater specificity and comprehensiveness, delay the progression of the disease and the recovery of

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neuronal activities. After all, a more comprehensive knowledge of the phenomenon of excitotoxicity and individual therapeutic preservative might change clinical procedures and enhance patient outcomes.

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