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RESEARCH ARTICLE

THE GUT–MICROBIOTA–BRAIN AXIS IN NEURODEGENERATIVE DISORDERS: MOLECULAR MECHANISMS, IMMUNE INTERACTIONS, AND THERAPEUTIC OPPORTUNITIES

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Abstract

Neurodegenerative diseases (NDDs), such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and Amyotrophic Lateral Sclerosis (ALS) are an increasing global health concern with progressive neuronal loss and inadequate curable treatments. In recent years scientists have discovered a pathway connecting neurodegeneration and the gut microbiota–brain axis (GMBA). This review examines how gut microbiota dysbiosis—characterized by low microbial diversity due to depletion of beneficial bacteria and overgrowth of pathogenic species—favours disease progression. Dysbiosis has been associated with intestinal barrier integrity disruption, consequent permeability and systemic translocation of microbial products, including lipopolysaccharides (LPS) triggering pro inflammatory cytokine release, and neuroinflammation. These inflammatory processes are linked to an impaired blood–brain barrier, activated microglia, and neuronal injury. Moreover, a reduction in the production of short-chain fatty acids (SCFAs), particularly butyrate, impairs immune regulation, and neuroprotection, while disrupted microbial metabolism affects neurotransmitter synthesis and signaling. There are several modulatory factors that influence gut microbial taxonomy like diet, aging, medication use, and lifestyle. The review further explores therapeutic techniques and their possibilities which include dietary interventions, probiotics, prebiotics, fecal microbiota transplantation, and some new psychobiotics approaches.

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Introduction:-

Neurodegenerative diseases like Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and Amyotrophic Lateral Sclerosis (ALS) are a rising concern worldwide. Studies estimate over 152 million individuals to be affected by 2050, highlighting the urgency to better understand such conditions (Gadhav & Sugandhi, 2024). However, the progressive loss of neuronal makeup and function in the brain renders these diseases incurable. As a result, neuroscience research is focused on identifying modifiable risk factors and novel therapeutic targets that address these conditions. One such rapidly increasing area of research is the relationship between gut microbiota and

neurodegenerative diseases. The gut microbiota refers to the trillions of microorganisms, including bacteria, viruses, fungi, and archaea, that live in the gastrointestinal tract, primarily in the large intestine (ScienceDirect). Patients with neurodegenerative diseases experience a worsening pattern of gut microbial composition, with decreased beneficial microbes and increased opportunistic pathogens (V, 2023). This microbial imbalance known as gut dysbiosis appears to be a popular pattern amongst the elderly population. The elderly undergo age-related changes, including diminished intestinal motility, limited production of digestive enzymes, and gradual deterioration of the gut lining. These changes are associated with increased intestinal permeability, commonly referred to as “leaky gut.” In addition to this, excessive or prolonged medication use has also been found to destroy good bacteria, thus promoting the proliferation of pathogenic species.

In contrast, under healthy conditions, this microbial community plays a vital role in host gene expression, immune system development, resistance to pathogen colonisation, nutrient absorption and the synthesis of vitamins and neurotransmitters (Sender & Fuchs, 2016). Yet, when dysbiosis takes place, this balance is disturbed, and harmful bacterial derivatives, including lipopolysaccharides (LPS), enter the bloodstream. This leads to a systemic immune response, characterized by the secretion of pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6 (Hill & Round, 2021). These inflammatory signals may contribute to blood-brain barrier disruption, trigger microglial cells causing neuroinflammation and neuronal injury. These processes are mediated through the gut–brain axis, which is a bidirectional communication network between the central nervous system (CNS) and the gastrointestinal tract. The axis transmits signals through neural (the vagus nerve), endocrine (the hypothalamic-pituitary-adrenal axis), immune, and metabolic pathways (Sender & Fuchs, 2016). The existence of this axis highlights the less explored interconnection between gut and brain health. Furthermore, it suggests that gut dysbiosis may not merely accompany neurodegeneration, it may actively contribute to it. The present study aims to explore the potential of maintaining a healthy gut microbiota in slowing the progression of neurodegenerative diseases. To understand this relationship, it is critical to first look at the composition and the functional roles of the gut microbiota in maintaining the physiological homeostasis.

Methodology of the Review:-

Systematic literature searches were conducted in PubMed, ScienceDirect, and Google Scholar using search strings of "gut microbiota AND neurodegeneration," "gut-brain axis AND Alzheimer's disease," "dysbiosis AND Parkinson's disease," and "short-chain fatty acids AND neuroinflammation" within the range of (January 2015-January 2026).

Inclusion Criteria:-

- Peer-reviewed original articles
- Mechanistically relevant studies to the gut-brain axis

Exclusion Criteria:-

- Case reports involving less than five subjects
- Publications not in the English language
- Publications not mechanistically relevant to the gut-brain axis

Study Selection (PRISMA-style Flow Chart):-

- Total number of initial records identified: 190
- Number after removal of duplicates and irrelevant records: 180
- Number of full texts screened: 110
- Number of studies included in analysis: 50

All records that failed the exclusion criteria during full-text screening (n = 60) were discarded because of no relation to the mechanism under study or poor quality of methodology used. The criteria used for selecting studies were based on appropriate sample size and power, use of control groups and reproducibility, longitudinal and intervention studies, incorporation of multiple omics (e.g., metagenomics and metabolomics), and direct quantification of microbial metabolites, not prediction. Meta-analysis could not be performed due to heterogeneity among study methods. This study is a review paper and does not require ethics approval.

Composition and Functional Metabolism of the Gut Microbiota:-

The gut microbiota refers to the diverse community of microorganisms that inhabit the human gastrointestinal tract, primarily composed of bacteria from the phyla Firmicutes, Bacteroidetes, Verrucomicrobia, Actinobacteria, and Proteobacteria, along with fungi, viruses, and archaea (Romero et al). These microbes perform essential functions such

as digestion of complex polysaccharides, synthesis of K and B vitamins, regulation of immune responses, and protection against pathogenic invasion (Health). These microbes are primarily essential for the fermentation of undigested dietary compounds like fiber, proteins and lipids, as well as for the production of metabolites. Short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate are the key metabolites. They reinforce intestinal barrier function, exert anti-inflammatory effects, regulate metabolism, and influence host immune responses. Studies have shown that butyrate serves as a major energy source for colonocytes and imparts approximately 10% of the colonic energy requirements (Araújo). Propionate is involved in the production of glucose in the liver and small intestine. Acetate is vital for energy production and synthesis of lipids. A diet consisting of soluble and insoluble dietary fibers (non-digestible polysaccharides of cell walls of plants) influences the production of the SCFAs. The table below shows the classification of the dietary fibers, distinguishing between soluble and insoluble type with their associated compounds and dietary resources:

Fibre	Compound	Food Sources
Soluble	Galactomannan	Guar bean
	Pectin	Apples, citrus fruits, carrots
	Psyllium husk	Psyllium
	Galacto-oligosaccharides (GOS)	Legumes
	Fructo-oligosaccharides (FOS)	Bananas (Chin et al) ⁹
	Inulin	Garlic, onions
	Beta-glucans	Oats, whole grains
	Arabinoxylans	Whole grains
	Resistant starch	Green raw potatoes
	Wheat dextrin	Wheat-based foods
Other soluble fibres	Beans, lentils, chickpeas, algae, mushrooms	

Insoluble	Cellulose	Plant cell walls (vegetables, grains)
	Hemicellulose	Whole grains, vegetables
	Chitin / Chitosan	Mushrooms, crustaceans
	Lignin	Seeds, woody plant parts
	Suberin	Plant skins
	Cutin	Fruit & vegetable outer layers (Sankarganesh et al) ¹⁰

Structure Of The Intestinal Barrier In Maintaining Systemic And Neural Integrity:-

The intestinal barrier is a multilayered defense system located along the inner wall of the gastrointestinal tract, primarily in the small and large intestines. It forms a critical interface between the gut lumen, which contains the digested food particles, microorganisms, and microbial products, and the internal environment of the body. The barrier initiates the interactions between the gut microbiota and the host to maintain immune balance and prevent invasion of pathogens, toxins, and microbial components into the systemic circulation thereby helping to protect the central nervous system (CNS).

By regulating permeability and immune responses, the intestinal barrier maintains homeostasis, preserving the stability of the gut microenvironment (Gou et al). This function is achieved through several coordinated layers within the intestinal barrier. First, the mucus layer secreted by goblet cells is organised into two layers: an outer loose layer, which is occupied by the intestinal bacteria and a dense inner layer that is free of bacteria. This mucus layer acts as a physical barrier by trapping microbes and separating the intestinal lumen from the underlying tissue. The outer layer of the mucus acts as a nutrient source for commensal microbiota, stabilizing the balance of intestinal flora (Sergi). Beneath the mucus layer lies a single layer of intestinal epithelial cells, including enterocytes, goblet cells, Paneth cells, and enteroendocrine cells. These cells are tightly connected by tight junction proteins, which prevent toxic bacterial products such as lipopolysaccharides (LPS) from entering the bloodstream and causing systemic inflammation (Dmytriv et al)¹³. Paneth cells produce antimicrobial peptides (AMPs) that kill harmful bacteria while allowing the beneficial commensal microbes to inhabit the mucus layer.

Below this lies the gut-associated lymphoid tissue (GALT), which contains immune cells such as macrophages and dendritic cells. In this layer, the intestinal barrier cooperates with the immune system by releasing secretory Immunoglobulin A (sIgA), a primary antibody that coats beneficial bacteria for protection (Tommaso et al). It also regulates the immunogenicity of intestinal antigens as a part of the innate immune system by inducing T cell differentiation and activating the adaptive immune responses (Ogino et al), while supporting the anti-inflammatory properties of dendritic cells, and contributing to immune homeostasis (Fu et al).

Microbiota-Mediated Neurosignalling:-

Neurosignalling occurs via the bidirectional gut-brain axis, conveying sensory information—such as nutrition detection and mechanical changes—from gut enteroendocrine cells to the brain. It enables motor control (brain-to-gut), regulating digestion and immune responses through the vagus nerve. Gut microbiota are essential for neurosignalling, as they stimulate vagal afferent neurons, produce neurotransmitters, and modulate signals transmitted from the gut to the brain (Kim et al). Microbes also produce neuroactive compounds, including neurotransmitters and their precursors, which influence mood and cognition, such as serotonin, dopamine, and gamma-aminobutyric acid (GABA). Certain gut bacteria, including *Staphylococcus* and *Clostridial* species, have been implicated in modulating serotonin production, which plays a role in regulating intestinal motility. Some gut microbes, including *Staphylococcus* species, are associated with dopamine production and modulation which influences gastric secretion, stomach motility, peristalsis and gastric emptying. This also impacts blood circulation in the stomach lining, playing a role in nutrient delivery and maintaining tissue integrity. GABA is produced by *Bifidobacterium*, *Bacteroides fragilis*, *Parabacteroides* and *Eubacterium*, and it modulates synaptic transmission in the enteric nervous system while regulating intestinal motility.

and inflammatory responses (Chen et al). Although experimental studies support the role of this pathway, further research is required to establish the precise underlying mechanisms.

Determinants of Gut Microbiota Composition:-

The function and composition of the gut microbiota are influenced by several factors, including diet, genetics, age, stress levels, lifestyle habits (such as exercise), environmental factors, mode of birth, infant feeding practices and use of medication use (Wen and Duffy).

A diet rich in fiber and plant-based foods, such as the Mediterranean diet (vegetables, fruits, olive oil, and whole grains), acts as a source of prebiotics that support beneficial bacteria such as Bifidobacterium and Lactobacillus. This increased microbial diversity regulates inflammation, reduces free radicals, and improves metabolic health. Additionally, probiotic foods such as yogurt, kefir, and kimchi introduce functional beneficial microbes directly into the gut (Slavin). In contrast, diets high in refined sugars and saturated fats (the Western diet) are associated with an increased abundance of potentially harmful species like *E. coli*, *Salmonella*, and *Shigella* (Statovci et al). Furthermore, food additives such as sweeteners (saccharin, sucralose, and aspartame) and emulsifiers (carboxymethylcellulose and polysorbate 80) negatively impact the microbiota by promoting glucose intolerance, reducing mucus thickness, and impairing the intestinal barrier (Gultekin et al). Medications also influence gut microbiota composition, especially antibiotics, which reduce microbial diversity by eliminating both beneficial and harmful bacteria (Ramirez). Other drugs, such as proton pump inhibitors, laxatives and certain antipsychotics, further alter the gut environment by affecting gastrointestinal pH (Imhann et al). Furthermore, the mode of delivery plays an essential role in early microbiota development. Vaginally born infants are exposed to their mother's vaginal and fecal bacteria, promoting greater microbial diversity, whereas infants delivered by caesarean section are primarily exposed to skin microbes, resulting in lower diversity (Zhang et al).

Breastfeeding further supports microbial development, as breast milk contains Human Milk Oligosaccharides (HMOs), which selectively promote the growth of beneficial bacteria (Wickramasinghe). Lifestyle factors, such as physical exercise, stress and sleep patterns, also influence microbial diversity. Regular exercise increases production of the beneficial SCFAs, thereby enhancing microbial diversity (Varghese et al) 27. In contrast, stress alters gut motility and hormone levels, leading to microbial imbalance through the GBA, changes in the proportion of major microbial phyla and increased intestinal permeability. Sleep deprivation results in a reduction in *Lactobacillus* and *Bifidobacterium*, while increasing pro-inflammatory cytokines like IL-6 and TNF- α (Foster et al). Exposure to environmental toxins such as heavy metals and pesticides further disrupts the gut microbiota by increasing pro-inflammatory Proteobacteria and reducing beneficial SCFA-producers (Ma et al).

The Gut–Microbiota–Brain Axis:-

The Gut-Microbiota-Brain Axis (GMBA) is a bidirectional communication network that functionally connects the gut and its microbiota with the central and enteric nervous systems through neural, endocrine and immune signals. This communication occurs through several main pathways: neural (vagus nerve), immune, microbial-metabolite mediated (SCFAs), and endocrine tryptophan-associated signalling. These interactions are mediated by the release of neurotransmitters, cytokines, microbial metabolites, and other signalling molecules. Immune signalling in the GBA involves both direct pathways, such as activation of immune cells in the brain and indirect pathways through circulating cytokines and microbial metabolites, which influence physiological and behavioural changes in the brain (O'Riordan et al). In response to microbial stimuli, peripheral immune cells release pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β , which can cross the blood-brain barrier (BBB) or enter through circumventricular organs, influencing neuronal activity and trigger neuroinflammation (Lucerne and Kiraly).

Immune signalling is also regulated by microbial metabolites, specifically tryptophan and SCFAs. SCFAs such as acetate and butyrate, produced through bacterial fermentation in the gut, can cross the BBB and influence microglia maturation, function, and gene expression in brain cells. Tryptophan is an amino acid that can be metabolized into serotonin, kynurenine metabolites and indole derivatives, which affect neurotransmission, immune regulation and neuroinflammation. Indole derivatives produced by gut bacteria such as *E. coli* activate aryl hydrocarbon receptors (AHR) on astrocytes and microglia thereby suppressing neurotoxic inflammation (Parker et al). Endocrine signalling within the microbiota-gut-brain axis links the gut and brain, regulating stress, mood and sleep through the release of hormones and neurotransmitters including cortisol, serotonin and melatonin (Rusch et al).

Cortisol, a stress hormone regulated by the hypothalamic–pituitary–adrenal (HPA) axis, becomes elevated in cases of microbiome imbalance, as this system becomes overactive, and is associated with anxiety and depression (Lu et al). Melatonin is a sleep hormone produced in both the brain and the gut, is influenced by the gut microbiota, and helps

regulate the circadian and sleep-wake cycles (X et al). Approximately 90-95% of serotonin is produced by enterochromaffin cells, which regulate mood, sleep, digestion and appetite. Gut bacteria *Lactobacillus* and *Bifidobacterium* enhance serotonin synthesis by increasing the availability of tryptophan (Wei et al). Overall, gut-derived hormones and neurotransmitters, including serotonin and GABA, support emotional regulation, and cognitive function while suppressing stress responses (Chadaram et al).

Microglial Dynamics In Neuroinflammation:-

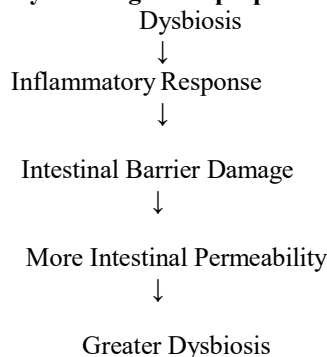
Microglia are tissue-resident macrophages that constitute around 5–15% of total brain cells and perform several functions in the central nervous system (Sender and Fucas). They develop through three stages: early, pre-, and adult. During early brain development, early and pre-microglia play important roles in synaptic remodelling, shaping neural circuitry, and regulating neuron numbers through programmed cell death (PCD) (Pelvig and Pakkenberg). A few weeks after birth, microglia transition into the adult stage, where they maintain homeostasis by releasing pro- and anti-inflammatory signals, clearing pathogens, and repairing tissue damage (Sierra and Encinas). However, persistent pro-inflammatory signalling can lead to chronic microglia overactivation, which is associated with neurodegenerative diseases. This dominance of pro-inflammatory responses over anti-inflammatory signalling, results in neuronal damage, as it impairs neuroprotective and wound-healing properties of microglia (Haq and Schlachetzki). Furthermore, genetic risk alleles linked to neurodegenerative and behavioural diseases influence genes that are highly expressed in microglia. Disruptions in gut microbial balance can also alter microglial function, highlighting the significance of gut dysbiosis.

Gut Microbiota Dysbiosis As A Driver Of Neurodegenerative Pathology:-

Gut dysbiosis is the imbalance in the composition, diversity and function of the gut microbiota, characterised by loss of beneficial bacteria, overgrowth of pathogenic microbes, and reduced microbial diversity (DeGruttola et al). This disrupts gut homeostasis by impairing the intestinal barrier, altering immune regulation and increasing intestinal permeability. The abundance of beneficial bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* decreases, resulting in reduced SCFA production—especially butyrate, a necessary energy source for gut cells. This weakens anti-inflammatory signalling and reduces support for epithelial integrity.

Conversely, there is an expansion of harmful bacteria, particularly Proteobacteria, including pathogenic *E.coli* and *Clostridium* species. These microbes produce toxic metabolites and degrade the protective mucus layer, promoting inflammation (Martín et al). As the dysbiosis progresses, gut defence mechanisms weaken, with reduced production of mucus, SCFAs, antimicrobial peptides (AMPs), and secretory IgA (sIgA) leading to decreased pathogen neutralisation. Simultaneously, levels of the lipopolysaccharides (LPS) and bacterial toxins increase, disrupting epithelial tight junctions and promoting leakage into the bloodstream (Shen et al). Altered microbial metabolites, such as SCFAs, impair immune regulation, barrier integrity and gut-brain signalling. Elevated levels of LPS, ammonia, and hydrogen sulfide further drive the systemic inflammation, oxidative stress, and neuroinflammation (Tan et al). The disrupted barrier allows microbial components such as LPS to translocate into the bloodstream, where they bind to toll-like receptors (TLRs) on immune cells, activating inflammatory signalling pathways such as NF-κB (Perros). This activation increases pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, leading to chronic low-grade systemic inflammation (Zhang et al). Reduced SCFA levels also decrease regulatory T cell (Treg), impairing immune tolerance and promoting persistent immune activation (Liu et al).

Dysbiosis worsens the disease progression by creating a self-perpetuating cycle:



Inflammatory mediators spread systemically to organs including the liver, metabolic tissues, the immune system, and the brain (Li et al). Inflammation reaches the brain through three primary pathways: blood circulation (cytokines and LPS), neural signalling via the vagus nerve, and immune cell activation, leading to microglial activation, blood-brain barrier disruption, and neuroinflammation within the CNS (O’Riordan et al.).

Dysregulation of the ultimately contributes to neurodegeneration, including:-

- Alzheimer's disease (AD): associated with Escherichia/Shigella and H. pylori, fostering amyloid-beta accumulation and neuroinflammation.
- Parkinson's disease (PD): linked to Enterobacteriaceae and Desulfovibrio, contributing to α -synuclein aggregation and motor dysfunction (Wu et al).
- Multiple Sclerosis (MS): characterized by altered T-cell responses and microbial shifts involving Akkermansia and Acinetobacter (Cekanaviciute et al).

However, it remains unclear whether gut dysbiosis is a primary cause of neurodegenerative diseases or a consequence of disease progression, emphasizing a major limitation in current research.

Therapeutic Strategies Targeting the Gut–Microbiota–Brain Axis:-

Therapeutic interventions focusing on the gut microbiota may help maintain gut health and reduce the risk of neurodegenerative diseases. Firstly, diet is a major factor shaping gut microbiota composition and GABA function. Beneficial dietary patterns such as Mediterranean, DASH and MIND diets are rich in fiber, polyphenols, and omega-3 fatty acids, which promote butyrate-producing bacteria and increase SCFA levels. This results in a reduction of inflammation, amyloid-beta accumulation, and cognitive decline. The ketogenic diet may also be beneficial, as ketosis provides an alternative energy source for the brain, modulates gut microbiota, reduces inflammation, and alters microglial activation. Secondly, microbiota-based therapies include probiotics, prebiotics, synbiotics, and postbiotics (PPSP). Probiotics such as Lactobacillus and Bifidobacterium help enhance gut barrier integrity, reduce inflammation, and increase SCFA production.

Prebiotics are non-digestible carbohydrates (e.g., inulin and dietary fiber) that promote the growth of beneficial bacteria and enhance SCFA production. Postbiotics are non-living microbial metabolites with anti-inflammatory and immunomodulatory effects, although their efficacy varies across diseases, with limited impact observed in conditions such as Huntington’s disease. Thirdly, Fecal microbiota transplantation (FMT) involves transferring microbiota from a healthy donor to restore gut balance. It has shown potential in improving cognitive function in AD and motor symptoms in PD, along with protecting dopaminergic neurons. However, there is a risk of infection and gastrointestinal side effects. Fourthly, emerging therapies include phytochemicals, such as curcumin, resveratrol, and ginseng, which exhibit anti-inflammatory, antioxidant, and microbiota-modulation properties, although their bioavailability remains low. Photobiomodulation (light therapy) has also been explored for its ability to alter gut microbiota composition and increase the SCFA-producing bacteria. (Izzeddine et al) (Li et al).

Limitations:-

Variations in the gut microbiome due to factors like diet, genetics, age, and geographical location make it difficult to categorize and necessitate personalized treatments. Such variations also complicate scientific studies, as it remains unclear whether microbiome imbalance is a cause or an effect of neurodegenerative diseases.

Future Perspectives:-

Future-orientated approaches include psychobiotics, which target brain function through microbiota modulation, as well as microbiome engineering for targeted therapeutic interventions. Future research should place greater emphasis on personalized microbiome-based therapies tailored to individual microbiome profiles, the integration of multi-omics approaches (such as metagenomics and metabolomics), and the identification of microbiome-based biomarkers for early detection.

Conclusion:-

In conclusion, the evidence presented in this review emphasizes the role of gut microbiota in the pathophysiology of neurodegenerative diseases, impacting the immune function, intestinal barrier integrity, and neuroinflammatory processes. The gut-brain axis plays an important role by facilitating neuronal damage associated with gut dysbiosis during the initiation and progression of barrier disruption, neuroinflammation, and microbial imbalance. This mechanism is driven by a reduction of the beneficial microbial metabolites such as SCFAs and an increase in

pro-inflammatory mediators like LPS, contributing to microglial overactivation and blood–brain barrier (BBB) dysfunction. Furthermore, existing evidence supports an association between gut microbiota imbalance and neurodegeneration, although a definitive causal relationship has yet to be firmly established. There is also substantial inter-individual variability and incomplete mechanistic understanding, which limit the effectiveness of microbiome-targeting therapeutic approaches. Future research should focus on personalized medicine approaches, longitudinal studies, and enhanced multi-omics techniques that can help elucidate the relevant mechanisms and produce specific interventions. Ultimately, the alleviation of neurodegenerative diseases may be achieved through the promising strategy of maintaining gut microbial homeostasis.

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