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Review

Impact and Advances in the Role of Bacterial Extracellular Vesicles in Neurodegenerative Disease and its Therapeutics

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Review

Impact and Advances in the Role of Bacterial Extracellular Vesicles in Neurodegenerative Disease and its Therapeutics

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Abstract: Bacterial Extracellular Vesicles (BEVs) generated from the bacteria has high feasibility of intracellular interactions with other cells, can be used as a cargo to deliver any therapeutic substances like monoclonal antibodies, proteins, plasmids, siRNA and small molecules for the treatment of neurodegenerative diseases (NDs). BEVs have a high ability for delivering therapeutic molecules across the blood-brain barrier to treat Alzheimer's Disease (AD) via various mechanisms. In this review, we have sum up in-depth research details of the role and advancement of BEVs in NDs, AD and its Therapeutics. Moreover, details about offensive and defensive functions of BEVs in ND pathogenesis and examine the critical BEV networks in the microbiome-gut-brain axis and their role in neurodegenerative disorders. Additionally determining the roles of BEVs in the neuroimmune system and their interaction with neurodegenerative disorders and exploring the risk factors of BEVs in the autophagy-lysosomal pathway and their possible effects on neurodegenerative disorders are summarised in detail. In conclusion, this review seeks to contribute to a better understanding of the potential function of BEVs in NDs and to identify new therapeutic intervention strategies.
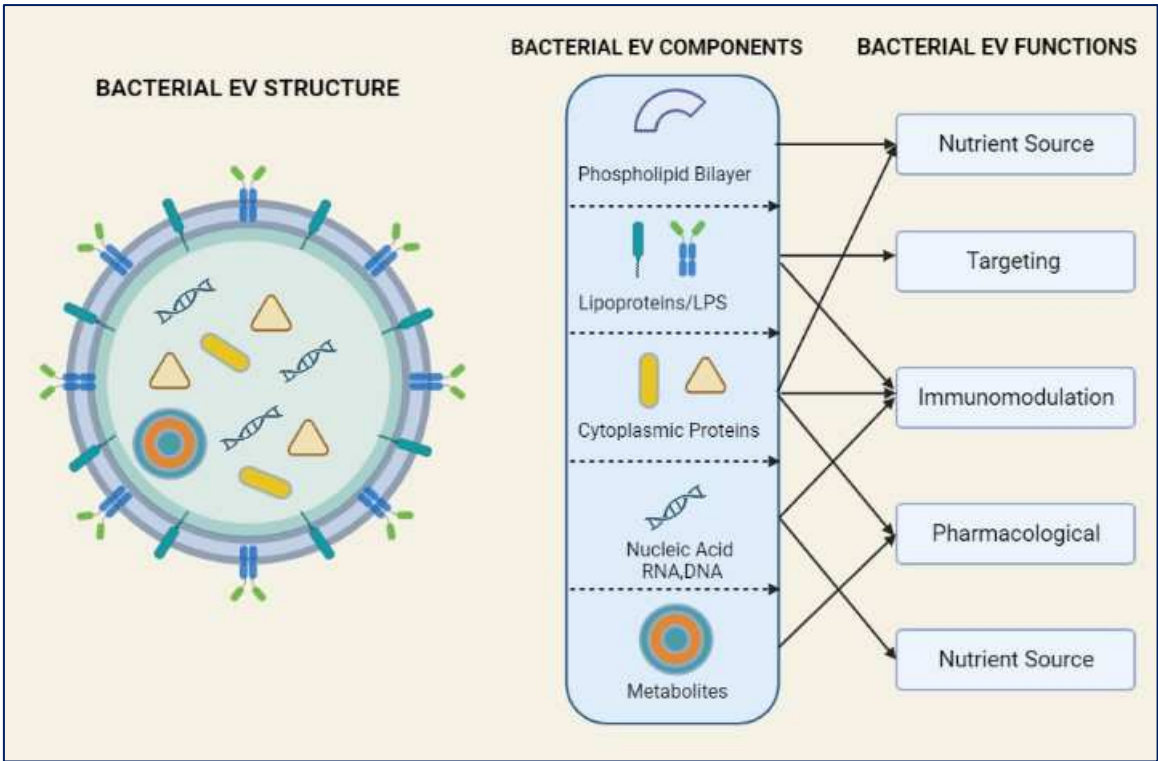
Keywords: Bacterial Extracellular Vesicles; Therapeutics; Neurodegenerative Disease; Alzheimer's Disease; Nanocarriers

1. Introduction

Neurodegenerative diseases (NDs) are a group of progressive disorders that affect the central nervous system and result in the gradual degeneration and mortality of neurons [1]. Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) are among these conditions of NDs [1]. Alzheimer's Disease International estimates that 50 million people worldwide are afflicted by dementia alone [2]. Consequently, neurodegenerative disorders (NDs) pose a significant threat to public health and a significant burden on society [2,3]. Despite significant efforts to develop treatments, no known cures for NDs are presently available [4].

Researchers have begun to investigate the function of bacterial extracellular vesicles (BEVs) in the pathogenesis of NDs in recent years [5,6]. BEVs are small, membrane-bound particles released by bacteria (Figure 1) that contain a variety of bioactive molecules, such as proteins, lipids, and nucleic acids [5,6]. It has been demonstrated that these vesicles serve an essential role in bacterial

communication, adaptation, and virulence [7]. In addition, recent studies indicate that BEVs may also add to the development and progression of NDs, potentially presenting novel therapeutic targets [6,7].

Figure 1. Bacterial Extracellular Vesicles (BEVs) structure and its components used for its therapeutic function and defensive mechanisms.

The potential function of BEVs in NDs has been the subject of intensive research over the past few years [8]. According to studies, BEVs can play both offensive and defensive functions in the context of NDs, including regulation of immune responses, modulation of the microbiome-gut-brain axis, and induction of autophagy-lysosomal pathway dysfunction [6,8,9]. In addition, recent advancements in BEV isolation, characterization, and engineering have paved the way for the development of novel therapeutic strategies [5,9].

This review's objective is to provide an overview of the current literature on the role of BEVs in NDs and to investigate recent developments in the field of BEV therapeutics. Specifically, this analysis seeks to:

Focus on the offensive and defensive functions of BEVs in ND pathogenesis.

Examine the critical BEV networks in the microbiome-gut-brain axis and their role in neurodegenerative disorders.

Determine the roles of BEVs in the neuroimmune system and their interaction with neurodegenerative disorders.

Explore the risk factors of BEVs in the autophagy-lysosomal pathway and their possible effects on neurodegenerative disorders.

Emphasize the potential uses of BEVs in developing new drug for neurodegenerative diseases.

Suggest future prospect of the study of the role of BEVs in neurodegenerative diseases.

This review seeks to contribute to a better understanding of the potential function of BEVs in NDs and to identify new therapeutic intervention strategies.

1. Offensive and Defensive roles Bacterial Extracellular Vesicles in Neurodegenerative Disease

Latest research has shown that bacterial extracellular vesicles [10], also known as BEVs, can cause neuroinflammation and affect neuronal function [11], which points to the potential neurotoxicity of these particles in the context of neurodegenerative disorders [11,12]. (Kim et al., 202; Kumar et al., 2020). BEVs tend to yield the inflammatory cytokines and chemokines after activating microglia and astrocytes with virulence factors such lipopolysaccharides, peptidoglycans, and proteins [13–15]. Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), among others, have all been associated to the activation of neuroinflammatory pathways [12,15].

BEVs generated from Pseudomonas aeruginosa were discovered in a recent study (Figure 2) to induce inflammation and mortality of dopaminergic neurons in the substantia nigra [11,12,16]. Inflammation and mortality of dopaminergic neurons in the substantia nigra is a defining hallmark of Parkinson's disease (PD) [11,15]. It was discovered that BEVs generated from Escherichia coli caused neuronal death and impaired memory in an Alzheimer's disease mice model [15,16]. By inducing neuroinflammation and impairing neuronal function, BEVs may contribute to the pathogenesis of NDs, according to these findings [16,17].
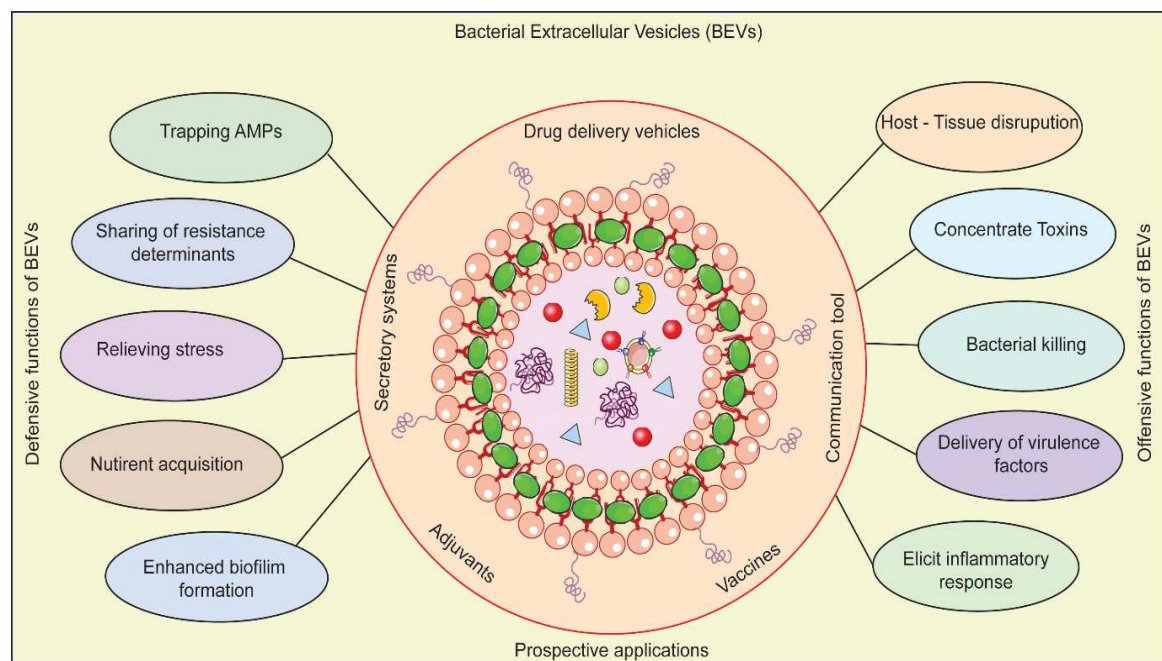
Figure 2. Offensive and Defensive roles Bacterial Extracellular Vesicles in Neurodegenerative Disease and its prospective applications in therapeutics.

In addition to their potential neurotoxicity [17], it has been demonstrated that BEVs serve a protective role in NDs [17]. Several studies have demonstrated, for instance, that BEVs can exert neuroprotective and immunomodulatory effects [17,18]. Specifically, it has been demonstrated that BEVs from commensal gut bacteria enhance cognitive function and reduce neuroinflammation in mouse models of NDs [18,19]. These results suggest that BEVs may also have therapeutic applications for the treatment of NDs [18,19]. The neurotoxicity of BEVs necessitates caution in their use as therapeutics, but their neuroprotective and immunomodulatory properties present opportunities for the development of novel treatments for NDs [10,18]. To thoroughly comprehend the mechanisms underlying the offensive and defensive roles of BEVs in NDs, additional research is required [10,17].

Recent research suggests that BEVs can also play a defensive function in NDs due to their neuroprotective and immunomodulatory properties [17,18]. Multiple studies have demonstrated, for instance, that BEVs derived from specific bacterial strains can improve neuronal survival and function in neurodegenerative conditions [19]. In the mouse model of Alzheimer's disease, Haney et al. [20] found that BEVs from the probiotic Lactobacillus rhamnosus GG could reduce amyloid-beta

(A) deposition and enhance cognitive function [21]. Wang et al. [21] demonstrated that BEVs from *Bifidobacterium infantis* could reduce inflammation and oxidative stress in a mouse model of Parkinson's disease [22], resulting in enhanced motor function [18,19,22].

BEVs have been shown to possess immunomodulatory properties in the context of NDs, in addition to their neuroprotective effects [15,22]. By modulating the gut-brain axis [23], found that BEVs from *Akkermansia muciniphila* could reduce neuroinflammation and enhance cognitive function in a mouse model of Parkinson's disease [15,24]. Similarly, demonstrated that BEVs from Lactobacillus plantarum PS128 modulated microglial activity to enhance cognitive function and reduce neuroinflammation in an Alzheimer's disease mouse model [22,25]. These studies suggest that BEVs may serve a dual role in NDs by possessing both offensive and defensive characteristics [15,25]. Some BEVs can induce neuroinflammation and impede neuronal function, whereas others can prevent neurodegenerative processes and modulate the immune system [18,21]. To thoroughly comprehend the mechanisms underlying the defensive properties of BEVs and to investigate their potential as therapeutic agents for NDs, additional research is required.

1. Critical Networks of Bacterial Extracellular Vesicles in the microbiome-gut-brain axis

The microbiome-gut-brain axis (MGBA) is a complex network of bidirectional communication between the gastrointestinal tract, the central nervous system (CNS), and the gut microbiota [19,26]. Recent evidence suggests that this axis regulates a variety of physiological and pathological processes, such as neuroinflammation and neurodegeneration [26,27]. The gut microbiota has a vast array of microorganisms inhabiting the human gastrointestinal tract, and it has been shown to influence brain function and behaviour via multiple mechanisms [27]. These include the production of neurotransmitters and short-chain fatty acids, modulation of the immune system, and regulation of the hypothalamic-pituitary-adrenal axis [28,29]. Multiple NDs, such as Parkinson's [28], Alzheimer's [29,30], and multiple cerebral sclerosis (Table 1), have been linked to abnormalities in the gastrointestinal microbiota in their pathogenesis [30–32]. Additionally, it has been demonstrated that bacterial extracellular vesicles (BEVs) produced by intestinal microbiota can cross the blood-brain barrier and directly affect the CNS function [22,31]. BEVs from the gut commensal *Bacteroides fragilis* have been shown to facilitate the differentiation and maturation of oligodendrocytes, which are essential for the production of myelin in the CNS [6,33]. In a mouse model of Alzheimer's disease, BEVs from *Akkermansia muciniphila* have been shown to protect against neuroinflammation and cognitive decline [23,24,33].

The above discussed results point out that the microbiota-gut-brain axis (MGBA) plays an important role in the pathogenesis of NDs, and that BEVs produced by intestinal microbiota may represent a novel drug delivery system for such conditions [34]. It has also been demonstrated that the gut microbiome can influence brain function and behaviour via multiple mechanisms, including the production of neurotransmitters, regulation of the immune system, and modulation of the gut-brain axis signalling pathways [35]. Bacterial extracellular vesicles (BEVs), that are produced by numerous bacteria in the microbiome of the gut, have been identified as potential mediators of this communication between the gut and the brain [6,35]. The effects of BEVs on the microbiome-gut-brain axis and their potential function in NDs have been studied and discussed in animal models [18]. In cell cultures and mouse models, BEVs from the gastrointestinal microbiome of Parkinson's disease (PD) patients were able to induce alpha-synuclein aggregation, which is a hallmark of PD pathology [15,22]. In a mouse model of Alzheimer's disease (AD), It was observed that BEVs from a specific gut bacterium, *Akkermansia muciniphila*, reduced neuroinflammation and enhance cognitive function [36].

Table 1. A summary of research findings in relation to the neuro-immune system affecting different types of NDs and their key conclusions of the study.

NDs	Key Finding	Source
Alzheimer's Disease	Microglial activation contributes to amyloid beta deposition and neuronal damage	[37]

Parkinson's disease	T cells infiltrate the substantia nigra and promote neuroinflammation	[38,39]
Multiple sclerosis	Dysbiosis and gut-derived molecules contribute to neuroinflammation and disease progression	[40–42]

Another study identified a group of BEVs produced by gut bacteria that could cross the blood-brain barrier as a result, penetrating the brain, modulating the immune system [43], and potentially playing a significant role in NDs [17,27]. These studies indicate that BEVs can play a significant role in the communication between the gastrointestinal microbiome and the brain, and that their dysregulation may contribute to the development and progression of NDs [36,43]. The mechanisms underlying the effects of BEVs on the microbiome-gut-brain axis and their potential as therapeutic targets for NDs require additional study [27,36].

1. Functions of Bacterial Extracellular Vesicles in Neuro immune system and their crosstalk

The neuro-immune system, which is made up of interactions between the neurological system and the immune system, is critical in neurodegenerative diseases (NDs) [38,44]. This neuro-immune systems help keep the homeostasis in balance. If this balance is distraught, it can lead to chronic inflammation, damage to neurons, and eventually NDs [45,46]. In terms of NDs, the neuro-immune system is made up of immune cells like microglia and astrocytes that become active when there is neuroinflammation [47]. When these cells become active, they release cytokines and chemokines that cause more inflammation and damage to neurons [47,48]. Peripheral immune cells, such as T cells and monocytes, can also promote neuroinflammation by crossing the blood-brain barrier and entering the central nervous system [48,49].

Table 2. Studies that describing how BEVs and the neuro-immune system interact in the pathogenesis and therapeutics of NDs.

Study	BEV Source	Model/System	Key Findings
[21,50,51]	*Bacteroides fragilis*	Mouse model of MS	BEVs promoted the expansion of regulatory T cells, dampening immune responses and preventing autoimmunity
[23,24,52]	*Akkermansia muciniphila*	Mouse model of PD	BEVs reduced neuroinflammation by decreasing pro-inflammatory cytokine levels while raising anti-inflammatory cytokine levels.
[21,22,53]	*Bifidobacterium bifidum*	Mouse model of AD	BEVs reduced neuroinflammation and improved cognitive function

Recent studies have shown how important the microbiome-gut-brain axis is in NDs and how it affects the neuroimmune system [54]. Dysbiosis, which is an imbalance in the gut microbiome, has been linked to the development of NDs [54,55]. This could be because of small molecules from the gut, like lipopolysaccharides, affect the immune system [13,45]. Latest studies have looked at how BEVs and the neuro-immune system interact, which shows how BEVs might be able to change the immune response in NDs [13,17,43]. For example, BEVs made from the gut bacteria *Bacteroides fragilis* suppressed the immune response in a mouse model of multiple sclerosis [56]. It was found that the BEVs helped regulatory T cells grow (Table 2), regulatory T cells are very important for calming down immune responses and preventing autoimmunity [50].

BEVs from the gut bacteria *Akkermansia muciniphila* were demonstrated to diminish neuroinflammation in a mouse model of Parkinson's disease [23,24]. It was found that the BEVs decreased the amount of pro-inflammatory cytokines in the brain and increased the number of anti-inflammatory cytokines [13,15]. This suggests that the BEVs have a neuroprotective effect. A study looked at how BEVs from the gut bacteria Bifidobacterium bifidum might affect the immune system in an Alzheimer's disease animal model [21,53]. The researchers found that giving the BEVs to the

mice led to less inflammation in the brain and better brain function [53]. These studies show that BEVs may be able to change the immune response in NDs, which means they may be a good way to treat these diseases [17,54]. But more research is needed to fully understand the mechanisms behind these effects and to figure out the best ways to use BEVs as medicines.

1. Risk factors of Bacterial Extracellular Vesicles in Autophagy Lysosomal Pathway

The autophagy-lysosomal pathway (ALP) (Figure 3) is a complicated cellular process that gets rid of damaged organelles, misfolded proteins, and invading pathogens by breaking them down and recycling them [57–60]. Dysregulation of the ALP has been linked to neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's [58,61–63].

The ALP has three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy [64,65]. Autophagy or macroautophagy, has been studied the most and it involves the formation of autophagosomes that engulf cytoplasmic parts and fuse with lysosomes to break them down [66,67].
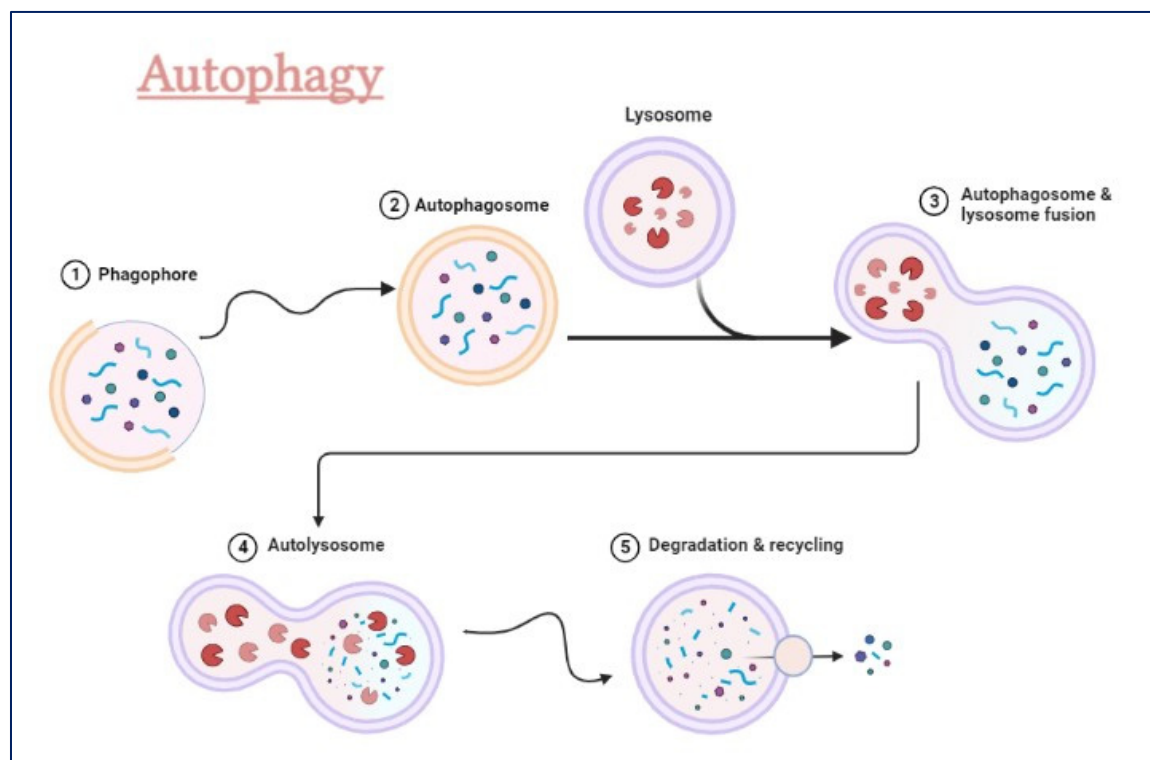

Figure 3. The process of initiation, nucleation and maturation of autophagy including the autophagosome formation and autophagy flux for the formation of autolysosome.

ALP is very important in removing toxic proteins, like alpha-synuclein in PD, Aβ and phospho tau in AD, from building up in the brain and trying to clear this toxic proteins when activated [68–71]. Also, abnormal regulation of the ALP has been linked to the activation of inflammatory pathways and oxidative stress, both of which contribute to the development of NDs [49,72,73]. BEVs may be able to promote the ALP in different NDs, such as PD and AD [13,15,17]. Recent studies have shown that by controlling or promoting the ALP using BEVs [18], suggesting that BEVs could be a promising therapeutic target for treating NDs (Figure 4) focussing on macro autophagy, chaperone-mediated autophagy and micro autophagy [52,53,74].

The ALP is very important for keeping cells in balance, and its malfunction has been linked to the development of several NDs [68,75,76]. More research is needed to fully understand how the ALP works in NDs and to look into the possibility that BEVs could be used as a therapy to control the ALP [65,77,78]. As per the previous studies, BEVs may have an effect on the autophagy-lysosomal pathway, in turn helping or keeping cells in balance by getting rid of damaged organelles and protein

clusters [79,80]. Autophagy is a strictly regulated process that involves the creation of autophagosomes, which are double-membrane vesicles [58,68]. These vesicles take in the toxic cytoplasmic materials and send it to lysosomes by fusing to form autolysosome to clear or broken down the engulfed proteins or organelles [81–83]. There are many hydrolytic enzymes in lysosomes that can break down the contents of autophagosomes into nutrients that can be used to make energy and change the shape of cells [84,85].
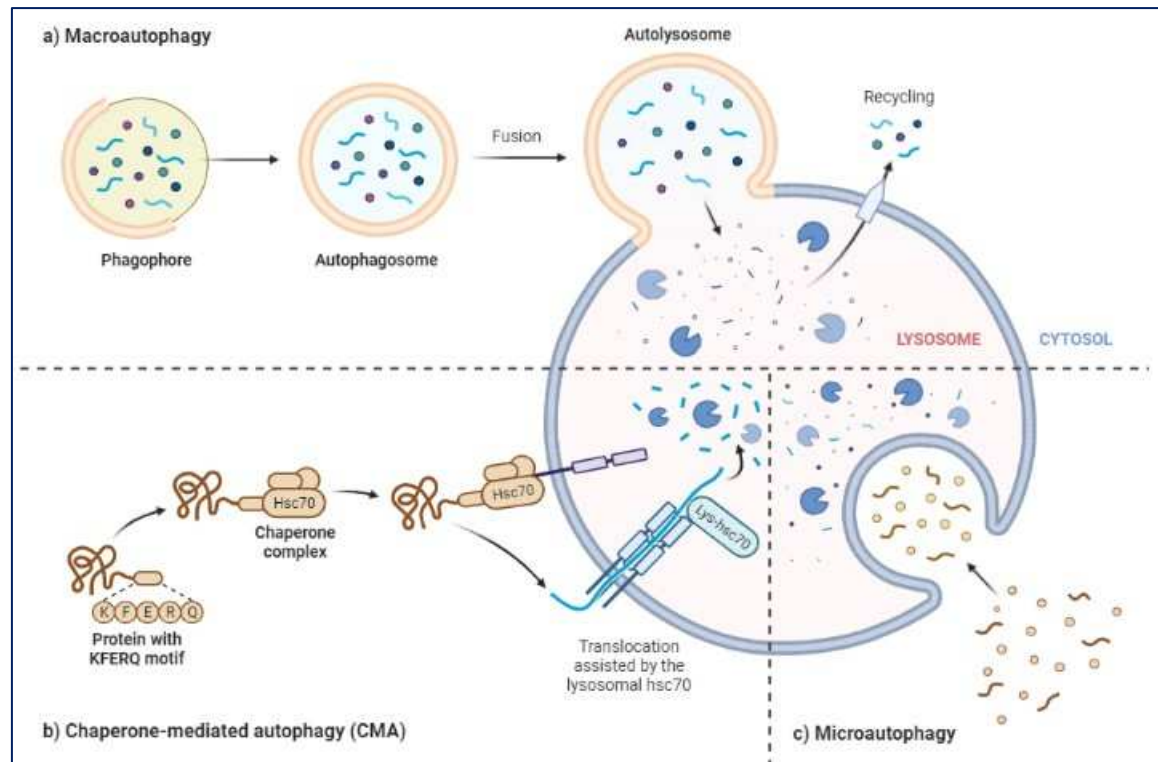
Figure 4. Three major types of autophagy lysosomal pathways in NDs and other brain diseases are macro autophagy, chaperone-mediated autophagy and micro autophagy.

Studies have shown that BEVs can mess up the autophagy-lysosomal pathway, which makes it harder for cells to get rid of waste and causes toxic aggregates to build up [85,86]. For example, a recent study showed that BEVs made from *Porphyromonas gingivalis*, a pathogenic oral bacterium linked to Alzheimer's disease, could stop autophagy by stopping lysosomes from becoming acidic and stopping autophagosomes from breaking down [86–88]. BEVs made from *Bacteroides fragilis*, a common gut bacterium that can change the immune system, could stop autophagy in dendritic cells by stopping the fusion of autophagosomes and lysosomes [27,53,88].

On the other hand, some studies have shown that BEVs may actually be playing a protective role in the autophagy-lysosomal pathway by assisting to make new lysosomes and speeding up autophagic flux [53,84,86]. For example, a recent study showed that BEVs made from Lactobacillus acidophilus, a probiotic bacterium with anti-inflammatory properties, could improve autophagy flux by increasing lysosomal biogenesis and promoting lysosomal acidification [89,90]. It was also found that BEVs made from *Akkermansia muciniphila* linked to better metabolic health, could speed up the removal of misfolded proteins in a mouse model of Parkinson's disease by activating the autophagy-lysosomal pathway [24,90,91]. In neurodegenerative diseases, the connection between BEVs and the autophagy-lysosomal pathway is complicated and needs to be investigated more [24,90,92]. The possibility that BEVs could interfere with or improve this important way for cells to get rid of waste could have big effects on how neurodegenerative diseases start and how they can be treated.

1. Prospective applications of Bacterial Extracellular Vesicles in Therapeutics

In East Asian countries traditional Chinese Medicine (TCM), makes use of herbal concoctions to treat NDs such as AD and PD for many years [60,93,94]. However, BEV can become an effective alternative for such treatment [78,87,90]. Depending on their source and the surrounding environment, exogenous vesicles (EVs) have the potential to both trigger immune responses and induce anti-tumor responses; as a result, they may offer useful tools for the development of innovative cancer treatments [87,95].

Since BEVs can cross the blood-brain barrier, several recent studies have looked into how BEVs could be used to treat NDs [89]. They can change immune responses and protect neurons from damage [77,96]. Evidently, BEVs have the potential to be used as a drug delivery system to treat NDs [89]. BEVs can carry a wide range of cargo, such as proteins, nucleic acids, and small molecules. This makes them an ideal vehicle to deliver active agents to specific cells or parts of the brain [97]. In fact, a number of studies have shown that therapeutic cargo can be delivered by BEVs in nonclinical models of NDs [97–99]. For example, one research study used BEVs made from mesenchymal stem cells to deliver miR-133b to neurons in a mouse model of Alzheimer's disease [97,98] and this study illustrated the tremendous output in cognitive function and lowered the levels of amyloid beta [97–99].

It has been repeatedly found that BEV can not only change the immune system but also protect nerve cells, which makes them a very useful drug delivery system for treating NDs [99]. Reducing neuroinflammation, a characteristic feature of many NDs, has been demonstrated as an effect of BEVs on the brain's immune system [90,98]. Another very interesting and important factor is that BEVs protect neurons from damage by lowering oxidative stress and helping neurons stay alive [90,98].

It's important to remember that while using BEVs to treat NDs has a lot of potentials, there are also risks and challenges. For example, BEVs may interfere with the way lysosomes work and slow down the waste removal system of the cell, which can certainly cause toxic proteins and other cellular debris to build up and cause different kinds of issues [100,101]. Another challenge is the lack of information. While the research has shown some promising results, there is a major possibility that the lack of substantial information about the working of the pharmacokinetics, its safety, and effectiveness of BEVs in humans, especially when it comes to long-term use and possible immune responses can produce some side effects [78,92,101].

Even with these certain and uncertain challenges, the possible uses of BEVs in NDs are an interesting and intriguing area of research that needs more study and development [78,90]. With continued progress in our understanding of how NDs work and how BEVs affect these processes, BEVs may end up being a useful addition to our arsenal of neuroprotective and disease-modifying therapies [84]. Bacterial extracellular vesicles (BEVs) are starting to look like a good way to treat diseases that damage nerve cells (NDs) [90]. Recent preclinical studies on mouse models of NDs have shown that BEVs can change the immune response, lower neuroinflammation, and improve cognitive function [90,99]. Also, BEVs have been shown to protect neurons in the lab by preventing the buildup of misfolded proteins, encouraging autophagy, and improving lysosomal function [68,81,84].

On a practical note, several preclinical studies have looked into the possibility that BEVs could be used to deliver drugs to treat NDs [78,89,98]. BEVs used as drug delivery agents in model organisms have depicted some promising results. For example, BEVs were allowed to carry therapeutic agents like siRNA and drugs to specific brain cells [77,89,98]. The results showed that BEVs made from mesenchymal stem cells can deliver active siRNA that targets the tau protein in the brain and reduce tau phosphorylation and clumping in a mouse model of Alzheimer's disease [77,98]. The use of BEVs to treat NDs in a clinical setting is still in its early stages [101]. Clinical trials and several other studies are being conducted and reports are mostly positive.

1. Future insights of Bacterial Extracellular Vesicles

In recent years, there has been a lot of interest in the new field of research on the role of bacterial extracellular vesicles (BEVs) in neurodegenerative diseases (NDs). Even though we know more about how BEVs might be used in therapy, there is still a lot to learn about how they work. One important

area of future research is to learn more about how BEVs interact with the autophagy-lysosomal pathway, as this may be a key part of how they affect NDs. Also, there needs to be more research on the possible risks of using BEVs as therapeutic agents, such as the possibility of bad immune responses and effects on other biological systems that were not intended.

The development of better and more targeted ways to get BEVs to the brain is another important area of future research. At the moment, not much is known about the factors that affect how BEVs are taken up and distributed in the brain, which may be important for their therapeutic effectiveness. Advances in nanotechnology and other delivery technologies may open up new ways to improve the targeting and delivery of BEVs to certain parts of the brain. Another big problem is that there aren't any standard protocols for isolating and describing BEVs. There are a lot of different ways to isolate BEVs, which can change the purity and make-up of the vesicles that are isolated. Also, because there is no agreement on how to define and group BEVs, it is hard to compare the results of different studies.

Another problem is that we don't know enough about how BEVs affect NDs and how they work. Several studies have shown that BEVs can change how the immune system responds, improve the survival of neurons, and help get rid of misfolded proteins. However, the exact molecular processes that cause these effects are not well understood. This makes it harder to improve BEV-based treatments for NDs. Concerns have also been raised about the ability of BEV to cause immunogenicity and toxicity, as well as effects that are not intended. Before BEVs can be used in clinical settings, these problems show how important it is to test their safety and make sure they are safe.

1. Conclusions

Clearly, bacterial extracellular vesicles (BEVs) have the potential to play an important role in the field of neurodegenerative diseases (NDs) and their therapeutics. According to the studies discussed in this thread, BEVs have immunomodulatory and neuroprotective properties that may be useful in the treatment of NDs. BEVs have demonstrated promise as prospective drug delivery systems for the treatment of neurodegenerative diseases (NDs) due to their ability to cross the blood-brain barrier (BBB) and target specific brain cells. However, there are obstacles and limitations that must be taken into account when researching and implementing BEVs in NDs. A lack of standardisation in BEV isolation and characterization methods, for instance, can result in inconsistent results and hinder the comparability of studies. In addition, a greater understanding of the mechanisms underlying the effects of BEVs on NDs requires more exhaustive research.

To completely realise the potential of BEVs in NDs, future research should focus on addressing these challenges and limitations. To ascertain the safety and efficacy of these therapies in humans, it is necessary to investigate the optimal dose, frequency, and duration of BEV treatment. In addition, additional research is required to better comprehend the underlying mechanisms by which BEVs exert their effects and to identify the BEVs most likely to be effective in treating NDs. In conclusion, BEVs hold great promise as a potential therapeutic approach for NDs, but additional research is required to completely comprehend their potential and overcome their limitations of use. The prospective benefits of BEVs in NDs make them an intriguing research topic that warrants further investigation.

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