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From Heatwaves to Brainwaves: Climate-Driven Microplastics Promote Epstein–Barr Virus Reactivation and Female-Biased Risk for Alzheimer's Disease and Multiple Sclerosis

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Abstract

Background

Climate change accelerates plastic degradation, increasing human exposure to microplastics and their associated endocrine-disrupting additives, thereby reshaping the chemical exposome. Many of these compounds, including bisphenols and phthalates, act as xenoestrogens capable of perturbing hormonal, immune, and oxidative stress pathways within the internal biological exposome. Persistent viral infections such as Epstein–Barr virus (EBV), which dynamically interact with immune and redox regulation, further shape the biological exposome. We hypothesized that climate-associated microplastic compounds may converge with EBV-related molecular networks within the exposome that are implicated in Alzheimer's disease (AD) and multiple sclerosis (MS).

Methods

We developed a computational exposome modelling framework integrating network toxicology and systems bioinformatics to map known and predicted human targets of microplastic-derived compounds with EBV–host protein–protein interactions and AD- and MS-associated proteins. Integrated interaction networks were constructed, and pathway enrichment analyses were performed to identify molecular points of convergence across environmental, viral, and disease-associated networks.

Results

Microplastic-responsive targets were enriched in immune, oxidative stress, and endocrine signalling pathways within both AD and MS networks and overlapped extensively with viral infection–associated pathways, including EBV. EBV interfaced with a greater number of AD-associated proteins than MS-associated proteins, whereas immune-related pathways predominated in MS. A conserved set of 20 EBV–microplastic "dual-hit" host proteins was identified across both diseases. In AD, the dual-hit neighbourhood was enriched for neuronal, metabolic, and hormone-responsive pathways, including neurotrophin signalling, dopaminergic synapse, estrogen signalling, apoptosis, and cellular senescence. In MS, enrichment was dominated by innate and adaptive immune pathways, including Toll-like receptor, IL-17, TNF, and JAK–STAT signalling. Estrogen signalling emerged as an AD-specific enriched pathway, while progesterone-mediated oocyte maturation was enriched in both diseases.

Conclusions

These findings provide systems-level, hypothesis-generating evidence that climate-associated microplastic exposure may intersect with endocrine and EBV-related host pathways relevant to neurodegenerative and autoimmune disease vulnerability. Although experimental validation is required,

this exposome-based framework highlights molecular convergence points through which environmental and viral factors may jointly modulate disease-relevant biological networks, with potential implications for sex-related differences in susceptibility.

1. Introduction

Climate change is increasingly recognized not only as an environmental crisis but also as a modifier of the human exposome [1]. Rising global temperatures, intensified ultraviolet radiation, and increased mechanical weathering accelerate the fragmentation and degradation of plastic materials, leading to enhanced production of microplastics and increased leaching of associated chemical additives [2]. Experimental studies demonstrate that elevated temperature and UV exposure significantly increase additive release from plastics, including bisphenols and phthalates, compared to baseline environmental conditions [3,4]. Thus, climate-associated processes do not introduce novel toxicants but amplify the environmental dispersion, chemical bioavailability, and chronic exposure burden of existing plastic-derived compounds, thereby reshaping the chemical domain of the exposome. Microplastics (< 5 mm) have now been detected in food, water, air, blood, stool, breast milk, urine, semen, and human brain tissue [2,5], highlighting their systemic distribution and integration into the internal biological exposome.

The exposome framework provides a systems-level lens through which such cumulative and interacting exposures can be understood [6]. The exposome encompasses the totality of environmental influences across the lifespan, including external chemical exposures, biological agents such as persistent viral infections, and the internal biological responses they elicit, such as immune activation, oxidative stress, and endocrine signalling perturbations [6,7]. Rather than considering exposures in isolation, the exposome emphasizes dynamic interactions between environmental factors and host molecular networks that collectively shape disease susceptibility [8]. Emerging translational exposomics leverages multi-omics and systems-level modelling to better characterize exposure–response relationships and disease vulnerability, offering a new paradigm for understanding health and informing precision medicine [9]. Within this framework, climate change functions as an upstream modifier of exposure patterns, altering both the chemical and biological domains of the exposome and reshaping the internal regulatory milieu through which these exposures exert their effects.

Beyond their physical presence, microplastics function as sustained-release vectors of endocrine-disrupting chemicals (EDCs). Many plastic additives, including bisphenols and phthalates, are not covalently bound to polymer matrices and are increasingly released under elevated temperature and ultraviolet exposure [3,4]. These compounds exhibit structural similarity to endogenous estrogens and can bind estrogen receptors (ERα, ERβ, and GPER) with varying affinities [10,11]. Estrogen signalling extends far beyond reproductive biology and acts as a central regulator of immune tolerance, cytokine production, mitochondrial bioenergetics, oxidative stress responses, and synaptic plasticity [12–14]. Dysregulation of estrogen receptor signalling has been associated with chronic low-grade inflammation, redox imbalance, and altered immune homeostasis [15,16]. Importantly, estrogen receptor activity modulates antiviral

immune pathways, including type I interferon signalling and B-cell function [17,18]. Thus, climate-associated increases in microplastic-derived xenoestrogen exposure may alter endocrine–immune cross-talk in ways that reshape host–virus equilibrium and immune system homeostasis.

Latent viral infections represent an additional component of the human exposome and provide a biologically plausible context in which such perturbations may exert downstream effects, as even subtle alterations in immune regulation can disrupt host–virus equilibrium. Epstein–Barr virus (EBV), a ubiquitous human herpesvirus infecting over 95% of adults worldwide [19,20], establishes lifelong latency primarily within memory B cells. The persistence of viral latency depends on tightly regulated immune surveillance, oxidative balance, and cellular stress-response mechanisms. Disruptions in immune tone, redox status, or hormonal signalling can influence host–virus molecular interactions and inflammatory signalling cascades [21,22]. Large longitudinal cohort studies have demonstrated that EBV infection precedes the development of multiple sclerosis (MS) [23,24]. Growing systems-level analyses, including network-based and transcriptomic studies, further implicate EBV-related host pathways in Alzheimer's disease (AD), with enrichment observed in female-specific hippocampal signatures [25–27]. These findings support a model in which EBV acts as a modulator of disease-relevant biological networks, however, the precise mechanisms underlying these interactions in each disease context remain unclear.

AD and MS share overlapping pathological features despite their distinct clinical trajectories. Both conditions involve neuroinflammation, mitochondrial dysfunction, oxidative stress, and blood–brain barrier (BBB) disruption [27–29]. MS is characterized by autoimmune demyelination driven by dysregulated adaptive and innate immune responses, whereas AD involves progressive synaptic failure, metabolic decline, and neuronal loss. Increasing evidence suggests that inflammatory and stress-response pathways intersect across these disorders, reflecting shared vulnerability modules within the internal exposome. Notably, both diseases exhibit pronounced sex biases, with women disproportionately affected. Sex differences in immune regulation, glial activation, BBB physiology, and hormonal signalling are well documented [27–29]. Estradiol has been shown to modulate gene expression in EBV-infected B cells in a sex-dependent manner [17], and hormonal fluctuations across the lifespan influence antiviral immune responses and inflammatory regulation [30]. These observations suggest that endocrine signalling may shape how environmental and viral components of the exposome intersect within disease-associated molecular networks, potentially contributing to sex-biased vulnerability.

While microplastic exposure, endocrine disruption, and EBV infection have each been investigated independently, their potential convergence at the systems level, and their integration within an exposome framework, remains insufficiently characterized (see Fig. 1). Environmental exposures often exert modest but chronic effects that may not manifest as overt pathology in isolation. Similarly, latent viral infections may remain clinically silent unless host regulatory mechanisms are perturbed. Capturing such multi-factorial interactions requires analytical frameworks capable of integrating heterogeneous biological datasets across environmental toxicology, virology, and disease biology, since experimental

approaches alone rarely capture the combined, chronic, and context-dependent nature of these interactions.

Systems biology and network toxicology approaches provide a means to identify molecular convergence points among environmental chemicals, host–pathogen interactions, and disease-associated proteins. Network-based studies have successfully elucidated how microplastic-associated compounds may intersect with cardiometabolic and renal disease pathways [31–33] and similar approaches have uncovered viral-mediated mechanisms in neurodegenerative and autoimmune diseases [25,26,34–36]. Rather than establishing causation, these integrative methods map shared nodes, pathways, and interaction modules that may represent potential vulnerability interfaces.

In the present study, we apply a computational exposome modelling framework that integrates network toxicology and systems bioinformatics to investigate how climate-associated microplastic-derived compounds intersect with EBV–host interaction networks and molecular pathways implicated in AD and MS (see Fig. 2). We hypothesize that climate-amplified chemical exposures and persistent viral components of the exposome converge on shared immune-, redox-, and endocrine-sensitive molecular networks relevant to neurodegenerative and autoimmune vulnerability. By identifying shared and disease-specific convergence points, this hypothesis-generating analysis aims to define molecular interfaces through which environmental and viral factors may jointly modulate neuroimmune and neurodegenerative vulnerability, with particular attention to endocrine-related signalling pathways.

2. Methods

2.1 *In Silico* Toxicology Analysis of Climate-Relevant Microplastic-Derived Compounds

To investigate how microplastic-derived pollutants may influence host pathways linked to EBV reactivation and the pathogenesis of AD and MS, we employed an integrated *in silico* toxicology and systems biology approach. The study focused on six environmentally relevant compounds commonly leached from plastics under elevated temperature and ultraviolet (UV) conditions: bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), bisphenol AF (BPAF), di(2-ethylhexyl) phthalate (DEHP), and dibutyl phthalate (DBP) (Table 1). These compounds were selected for their widespread environmental occurrence, endocrine-disrupting potential, and reported neurotoxic or immunomodulatory properties via induction of oxidative stress [37–41], features relevant to both viral reactivation and neurodegenerative risk.

Table 1
Microplastic-derived Compounds

Compound Name	Abbreviation	Compound Class	SMILES
Bisphenol A	BPA	Bisphenol	CC(C)(C1 = CC = C(C = C1)O)C2 = CC = C(C = C2)O
Bisphenol F	BPF	Bisphenol	C1 = CC(= CC=C1CC2 = CC = C(C=C2)O)O
Bisphenol S	BPS	Sulfone-based Bisphenol	C1 = CC(= CC=C1O)S(= O)(= O)C2 = CC = C(C = C2)O
Bisphenol AF	BPAF	Bisphenol (fluorinated)	C1 = CC(= CC=C1C(C2 = CC = C(C = C2)O)(C(F)(F)F)C(F)(F)F)O
Di(2-ethylhexyl) phthalate	DEHP	Phthalate (plasticizer)	CCCCC(CC)COC(= O)C1 = CC = CC=C1C(= O)OCC(CC)CCCC
Dibutyl phthalate	DBP	Phthalate (plasticizer)	CCCCOC(= O)C1 = CC = CC=C1C(= O)OCCCC

The Simplified Molecular Input Line Entry System (SMILES) identifiers for the seven compounds were collected from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). *In silico* pharmacokinetic profiling based on molecular structure (SMILES input) was predicted using the SwissADME online tool (http://www.swissadme.ch/) to determine gastrointestinal absorption and blood–brain barrier (BBB) permeability, to assess the compounds' potential to affect both gut and brain physiology. These parameters also allow assessing the potential of each compound to reach both immune and neural processes, which are relevant to EBV latency and neuroinflammation.

Table 2
Predicted Gastrointestinal Absorption and BBB Permeability.

Compound	GI absorption	BBB permeant
BPA	High	Yes
BPF	High	Yes
BPS	High	No
BPAF	Low	No
DEHP	High	No
DBP	High	Yes

Because the primary objective of this study was to investigate molecular convergence relevant to brain-associated pathologies (AD and MS), downstream disease-network integration emphasized compounds with predicted systemic bioavailability and potential CNS accessibility. ADME predictions (Table 2) of gastrointestinal absorption and BBB permeability was therefore used as prioritization criteria to guide

depth of disease-network integration rather than as strict indicators of biological activity. BPAF, which showed low predicted gastrointestinal absorption and no predicted BBB permeability, was not advanced to the CNS-focused disease-network integration step. In contrast, BPS and DEHP were retained despite limited predicted BBB permeability due to their high absorption and documented immunomodulatory and endocrine-disrupting effects, which may influence neuroinflammatory pathways indirectly via systemic immune mechanisms and modulation of host control over latent EBV.

Importantly, this prioritization does not imply that BPAF lacks biological or systemic relevance. Rather, it reflects a study design focused on compounds with a higher predicted capacity to intersect, directly or indirectly, with EBV- and CNS-associated molecular networks within the scope of the present analysis. Future investigations incorporating broader systemic exposure models may expand upon these findings.

This network toxicology framework is dose-agnostic and is designed to identify shared molecular targets and pathways rather than to model quantitative exposure levels or mixture ratios. Real-world microplastic exposure involves heterogeneous chemical mixtures and variable concentrations influenced by environmental conditions, geography, polymer composition, and exposure route. Accordingly, the present analysis focuses on qualitative molecular convergence across chemical, viral, and disease-associated networks.

2.2. Collection of Compound–Protein Interactions of Microplastic-Derived Compounds

To identify potential human protein targets modulated by microplastic-derived compounds relevant to endocrine and immune disruption, we analyzed BPA, BPF, DBP, DEHP, and BPS. Known compound–protein interactions were retrieved from the STITCH database [42] via the Cytoscape app, In parallel, predicted compound–target interactions were obtained from SwissTargetPrediction [43]. To minimize false-positive interactions inherent to predictive databases and ensure biological relevance, only high-confidence STITCH interactions (score ≥ 0.7) and SwissTargetPrediction targets with probability ≥ 0.1 were retained. Predicted and experimentally supported targets were merged after de-duplication to generate conservative compound–protein interaction sets. These targets formed the basis for downstream integration with EBV–host interaction proteins and AD/MS-associated protein networks to identify potential molecular overlap between microplastic exposure, viral reactivation, and neurodegenerative pathways.

2.3 Network Construction of Microplastic Compound–Protein–Disease Interactions

2.3.1 Construction of microplastic compound–protein networks in AD and MS

To investigate how microplastic-derived compounds may modulate molecular pathways involved in AD and MS, we constructed integrated compound–protein–disease networks. High-confidence compound–

protein interactions were obtained from STITCH [42] and SwissTargetPrediction and merged with AD- and MS-associated proteins. The top 200 disease-associated proteins were retrieved from the STRING disease plugin in Cytoscape [44] (Disease Ontology IDs: DOID:10652 for AD and DOID:2377 for MS) and selected to balance network coverage with specificity, capturing core high-confidence disease nodes while avoiding excessive inclusion of low-relevance peripheral associations. The top 200 disease-related proteins with the highest relevance scores. All five microplastic-derived compounds (BPA, BPF, DBP, DEHP, and BPS) were included to capture both direct and indirect molecular interactions potentially linking environmental exposure to neurodegenerative processes. PPI data were obtained by querying the STRING database [45] (human, taxonomy ID 9606) via its API. A confidence threshold of 0.7 was selected to prioritize high-confidence protein–protein interactions and reduce spurious edge inclusion. The resulting datasets were used to construct two integrated networks: a compound–protein–AD network and a compound–protein–MS network.

2.3.2 Pathway Enrichment and Comparative Functional Analysis

From each integrated network, the common targets shared between microplastic compounds and disease-associated proteins, together with their first-neighbour proteins, were extracted to perform enrichment analysis. This analysis aimed to identify molecular pathways potentially modulated by microplastic exposure within the AD and MS networks. Importantly, enrichment of viral infection pathways reflects shared host proteins annotated within KEGG viral modules and does not imply active viral replication or induction. Pathway enrichment analysis was performed using clusterProfiler [46] with the KEGG database, retaining only statistically significant pathways with an adjusted $p < 0.01$ (Benjamini–Hochberg correction). Because the KEGG database includes both disease-related and mechanistic categories, we focused exclusively on biological and mechanistic pathways, specifically those classified under *Metabolism*, *Cellular Processes*, *Environmental Information Processing*, and *Organismal Systems*, while excluding all other subcategories. A comparative enrichment analysis (*compareCluster*) was then conducted to identify pathways that were shared or differentially modulated between AD and MS.

Additionally, given the established involvement of EBV and other viral infections in MS, and their emerging links to AD, we also performed a focused KEGG subset analysis of viral infection pathways. Using the *compareCluster* output, pathways annotated under the KEGG *"Infectious disease: viral"* subcategory were extracted, retaining only those with an adjusted $p < 0.01$.

2.4. Integration of the EBV-Host Interactome with the Compound–Protein–Disease Networks

2.4.1 Identification and Mapping of EBV–Host Interactions Within AD and MS Networks

To incorporate viral perturbations into the compound–protein–disease framework, experimentally validated EBV–host PPIs were retrieved from VirHostNet 3.0 [47] and PHISTO [48] databases. In total, 7073 EBV–host PPIs were collected, covering three major EBV strains: *Human herpesvirus 4 strain B95-8* (taxid: 10377), *EBV strain AG876* (taxid: 82830), and *EBV strain GD1* (taxid: 10376). After integration and de-duplication, the dataset contained 7,073 high-confidence PPIs involving 153 EBV proteins interacting with 1,256 unique human host proteins across three major EBV strains (B95-8, AG876, and GD1). Human protein symbols were standardized and intersected with all non-compound nodes in the AD and MS integrated networks.

These EBV-targeted host proteins were then used to construct EBV–host–microplastic–disease subnetworks for AD and MS. Each node was annotated according to its functional category within the existing networks, including “EBV protein,” “Compound,” “Disease protein,” “Common target” (shared microplastic–disease target), or “Other protein” (microplastic target protein only). This classification enabled assessment of whether EBV preferentially interfaces with disease-associated proteins, microplastic-responsive targets, or shared dual-hit nodes. The resulting subnetworks provided a mechanistic framework to identify viral interface proteins positioned at the intersection of EBV infection, microplastic exposure, and host pathways relevant to AD and MS. EBV–host interactions represent documented physical or functional associations and do not encode directionality (e.g., activation vs inhibition), cellular context, or temporal dynamics.

2.4.2 Identification of EBV–Microplastic Dual-Hit Proteins and First-Neighbour Expansion for Pathway Enrichment

To identify host proteins positioned at the intersection of EBV–host interactions and microplastic compound targets, dual-hit proteins were defined as human proteins that were both direct EBV targets and microplastic compound targets. Dual-hit proteins were identified separately for AD and MS, yielding 20 dual-hit host proteins in each subnetwork. To contextualize these shared EBV–microplastic interfaces within each disease system, first neighbours of the dual-hit proteins were extracted from the full integrated AD and MS networks, from Section 2.3. All human protein interactors directly connected via edges were included, while EBV protein nodes and compound nodes were excluded to ensure enrichment focused solely on host biology. The dual-hit proteins and their first neighbours were merged to create two protein sets representing the EBV–microplastic dual-hit neighbourhood in AD and MS. These sets were converted to Entrez IDs using *org.Hs.eg.db*, and KEGG pathway enrichment was performed with clusterProfiler [46] (adjusted $p < 0.01$, Benjamini–Hochberg correction). As in Section 2.3, analysis was restricted to mechanistic KEGG categories, Metabolism, Cellular Processes, Environmental Information Processing, and Organismal Systems, excluding all KEGG disease pathways. This approach enabled identification of the signalling networks most strongly associated with EBV–microplastic convergence within each disease context, providing a mechanistic basis for different patterns of vulnerability in AD and MS.

2.4.3 Identification of Dual-Hit Protein Overlap with Estrogen and Progesterone Signalling Pathways

Because several microplastic-derived compounds act as xenoestrogens, and endocrine dysregulation is implicated in both AD and MS, we evaluated whether EBV–microplastic dual-hit proteins directly mapped to hormone-related KEGG pathways. KEGG enrichment results from the dual-hit neighbourhood analysis (Section 2.4.2) were first screened for the presence of the *Estrogen signaling pathway* and *Progesterone-mediated oocyte maturation*. The resulting hormone-pathway protein sets were intersected with the dual-hit protein lists (i.e., proteins simultaneously targeted by EBV and by at least one microplastic compound within each integrated disease network). This allowed identification of dual-hit proteins that were annotated components of KEGG estrogen or progesterone signalling modules. All intersections were performed separately for AD and MS using base R intersect(), and protein counts were recorded to quantify hormone-pathway membership. This procedure enabled a focused assessment of whether EBV–microplastic convergence points (dual-hit hubs) lie within established endocrine signalling pathways, providing a molecular link between xenoestrogen exposure, viral reactivation, and disease-specific network perturbation. It worth noting that presence within KEGG hormone signalling modules reflects annotation-based pathway membership and does not indicate pathway activation state.

Because this framework integrates heterogeneous datasets of chemical–protein interactions, disease associations, and viral host interactions, identified convergence reflects structured molecular overlap within integrated networks. While directionality and causal dynamics require experimental investigation, the present analysis defines specific molecular interfaces through which environmental and viral factors may intersect in AD and MS.

3. Results

3.1 Network Integration and Pathway Enrichment of Microplastic Compound–Protein Interactions in AD and MS

To explore how microplastic-derived compounds may contribute to the molecular mechanisms underlying neurodegenerative diseases, we constructed two integrated networks: a compound–protein–AD network and a compound–protein–MS network. Each network combined experimentally validated and computationally predicted compound–target interactions with disease-associated proteins to capture both direct and indirect molecular relationships.

3.1.1 KEGG Enrichment Analysis of Microplastic-Integrated AD and MS Networks

KEGG enrichment analysis of the common compound–disease targets and their first-neighbour proteins revealed that microplastic exposure may influence key cellular and signaling pathways involved in

neurodegeneration. In the AD network, the top-ranked pathways were dominated by cell death and stress-response modules (Apoptosis, Cellular senescence) and inflammatory signaling (IL-17 signaling, TNF signaling, C-type lectin receptor signaling) (Fig. 3A). Major signal-transduction hubs, including the PI3K–Akt, Ras, and HIF-1 pathways, were also among the most enriched, together with immune-related Osteoclast differentiation and Th17 cell differentiation. Notably, several neuronal and endocrine regulatory pathways appeared within the top 15, including Neurotrophin signaling, Dopaminergic synapse, and Estrogen signaling, emphasizing the intersection between microplastic compound targets, immune and stress signaling, and hormonal or synaptic regulation relevant to AD pathogenesis.

In the MS network, the top 15 enriched KEGG pathways were strongly dominated by immune and cytokine signaling modules (Fig. 3B). The most significant terms included Cytokine–cytokine receptor interaction, TNF signaling, and JAK–STAT signaling, alongside Toll-like receptor, NOD-like receptor, C-type lectin receptor, Chemokine signaling, and T cell receptor signaling pathways, highlighting broad activation of both innate and adaptive immune axes. Additional highly ranked categories such as PI3K–Akt signaling, Apoptosis, NF-κB signaling, and Osteoclast differentiation, together with Th17 cell differentiation and IL-17 signaling, indicate convergence on inflammatory, survival, and effector T cell functions. Notably, the pathway “Viral protein interaction with cytokine and cytokine receptor” was also among the top hits, suggesting that microplastic-responsive targets in the MS network are embedded within cytokine circuits that are central to antiviral responses and chronic neuroinflammation.

3.1.2 Comparative KEGG Pathway Enrichment Between AD and MS

Comparative KEGG pathway enrichment analysis of the integrated microplastic compound–protein networks revealed extensive functional overlap between AD and MS. Out of all statistically significant pathways, 70 pathways were shared, while 37 were unique to AD and 6 were unique to MS. The comparative analysis ranked the most significant pathways across both networks, highlighting shared immune and stress-related mechanisms as well as distinct molecular signatures specific to each disease (Fig. 4A). The shared pathways were dominated by inflammatory and stress-response processes, including Apoptosis, Cellular senescence, IL-17 signaling, TNF signaling, and NF-κB signaling, together with core signaling hubs such as PI3K–Akt, Ras, MAPK, and HIF-1. Immune differentiation and response modules such as Th17 cell differentiation, Toll-like receptor signaling, and T-cell receptor signaling were also among the most enriched. Notably, several endocrine and neurotrophic regulatory pathways, including Estrogen signaling, Prolactin signaling, Neurotrophin signaling, and Serotonergic synapse, were shared, highlighting cross-talk between hormonal, immune, and neuronal signaling in both diseases.

In contrast, the AD-specific pathways were predominantly neuronal and signaling related, including Dopaminergic synapse, Glutamatergic synapse, Long-term potentiation, Circadian entrainment, Calcium signaling, Wnt, Hippo, and Oxytocin signaling pathways, alongside energy and lipid metabolism modules such as Cholesterol metabolism and Glutathione metabolism. These enrichments suggest microplastic-

targeted disruption of synaptic and neurotransmission processes central to AD pathogenesis. The MS-specific pathways were more immunological in nature, encompassing Intestinal immune network for IgA production, RIG-I-like receptor signaling, Phagosome, Regulation of actin cytoskeleton, and Tryptophan metabolism, consistent with enhanced immune activation and barrier dysfunction mechanisms typical of MS pathology.

3.1.3 Viral Infection Pathway Enrichment in Microplastic-Integrated Networks

To investigate whether microplastic-derived compounds could modulate pathways involved in viral infection and reactivation, we performed a focused KEGG enrichment analysis restricted to the *"Infectious disease: viral"* subcategory (Fig. 4B). Both the AD and MS microplastic-integrated networks were enriched for the same 12 viral infection pathways, including *Epstein–Barr virus (EBV) infection*, *Kaposi sarcoma–associated herpesvirus infection*, *Human cytomegalovirus infection*, *Herpes simplex virus 1 infection*, *Human papillomavirus infection*, *Human T-cell leukemia virus 1 infection*, *Human immunodeficiency virus 1 infection*, *Measles*, *Influenza A*, *Hepatitis B*, *Hepatitis C*, and *Coronavirus disease (COVID-19)*.

Although the repertoire of enriched pathways was identical, the strength of enrichment and protein involvement differed between the two diseases. Notably, the Epstein–Barr virus infection pathway was significant in both networks but exhibited higher enrichment in MS than in AD, highlighting a shared molecular interface between microplastic targets and EBV-associated host signaling. Together, these findings indicate that microplastic-responsive targets intersect extensively with viral infection networks, particularly those associated with herpesvirus biology, suggesting that environmental microplastic exposure may influence molecular processes linked to viral reactivation and chronic neuroinflammation in both AD and MS.

3.2 Integrated Network Analysis of EBV–Host–Microplastic–Disease Interactions

To evaluate the convergence of viral perturbation, environmental toxicants, and host susceptibility pathways, we integrated the EBV–host interactome with the microplastic–target–AD/MS networks. This framework allowed us to distinguish (i) direct viral interactions with disease-associated proteins, and (ii) viral interactions with microplastic-responsive host proteins, thereby identifying molecular nodes through which climate-amplified environmental pressures may intersect with viral reactivation and neuroimmune dysfunction.

3.2.1 EBV Directly Targets a Larger Set of AD Proteins Than MS Proteins

Mapping the EBV–host PPIs onto the full integrated networks revealed that EBV directly targets more AD-network proteins (n = 40) than MS-network proteins (n = 33), out of the 200 disease-associated

proteins included in each network. Within the AD network, 20 of the EBV-target proteins correspond to AD-associated proteins, including regulators of amyloid processing (*ADAM10, BACE2*), synaptic integrity (*HTT*, *NEFL*), mitochondrial and metabolic stress (*GAPDH*, *GRN*), and apoptosis (*BAX*, *TP53*). These results suggests that EBV has the potential to influence multiple key AD processes, including neuronal survival, proteostasis, and neuroinflammation. In contrast, the MS network contained 13 MS-associated proteins that are directly targeted by EBV, including key mediators of antigen presentation (*HLA-DQA1, HLA-DRB1, HLA-A*), immune cell adhesion (*ICAM1, CD44*), and cytokine/JAK–STAT signalling (*NFKB1, TYK2*). This are consistent with the well-established role of EBV in MS pathogenesis through primary modulation of immune processes rather than direct neuronal influence. Together, these results demonstrate that EBV influences pathways linked to neuronal function in AD but engages more immune-centric pathways in MS, indicating disease-specific viral–host interactions.

3.2.2 EBV Directly Targets a Conserved Set of Microplastic-Responsive Host Proteins in Both AD and MS Networks

To isolate the mechanisms by which microplastics and EBV converge on shared host pathways, we examined the overlap between direct EBV targets and microplastic compound targets. Within both the AD and MS networks, we identified 20 EBV–microplastic dual-hit proteins that were identical in AD and MS, despite the diseases having distinct pathogenic signatures. Although the same 20 proteins appeared in both conditions, their classification within each disease network differed. The 18 proteins were classified as compound targets, while the remaining two proteins in each network were “common targets,” meaning that they were simultaneously microplastic targets and disease-associated proteins. Notably, these disease-overlapping proteins differed between AD and MS.

The dual-hit proteins include regulators of xenobiotic and endocrine signalling (*AHR, ESRRG*), stress-activated kinases (*SRC, RPS6KA3*), cytoskeletal and metabolic regulators (*ACTB, SLC2A1*), immune signalling components (*LCK, S1PR3*), and apoptosis-associated factors (*PRKCA, CAPN1*). The disease-specific common targets, where *HSP90AA1* and *CTSB* in AD, and *AHR* and *S1PR3* in MS, represent potential mechanistic entry points through which microplastic exposure and EBV reactivation may interact with AD- or MS-specific pathways.

The presence of a shared, identical 20-protein EBV–microplastic subnetwork across AD and MS highlights a conserved, climate-sensitive viral–host stress module that may modulate susceptibility to neuroinflammatory and neurodegenerative processes across distinct diseases.

3.2.3 KEGG Enrichment Reveals Neuronal, Endocrine, and Stress-Response Pathways Underlying EBV–Microplastic Dual-Hit Effects in AD

KEGG enrichment analysis of the EBV–microplastic dual-hits and their first neighbors was enriched for key processes included cellular senescence, apoptosis, and the PI3K–Akt and p53 signalling pathways, reflecting strong engagement of neuronal survival, stress-response, and damage-repair mechanisms

(Fig. 5A). Several neurobiological pathways were prominent, including neurotrophin signalling, dopaminergic synapse, and inflammatory mediator regulation of TRP channels, highlighting enrichment within pathways governing synaptic plasticity, neurotransmission, and inflammatory signalling. Endocrine and metabolic regulation also emerged prominently through estrogen signalling, prolactin signalling, progesterone-mediated oocyte maturation, and oocyte meiosis, pointing toward hormone-sensitive vulnerability of neuronal circuits. Additional enrichment of HIF-1, IL-17, C-type lectin receptor, and osteoclast differentiation pathways indicates that immune–metabolic crosstalk and hypoxic/inflammatory stress contribute to how EBV and microplastic targets intersect within the AD network. Overall, the AD enrichment profile suggests that dual-hit perturbation is embedded primarily in pathways governing neuronal resilience, synaptic function, endocrine regulation, and age-related cellular decline.

3.2.4 KEGG Enrichment Reveals Immune, Cytokine, and Autoimmune Signalling Pathways Underlying EBV–Microplastic Dual-Hit Effects in MS

In MS, the EBV–microplastic dual-hit neighbourhood showed dominant enrichment for immune and inflammatory regulatory pathways. Highly represented pathways included Toll-like receptor, NOD-like receptor, TNF, Th17 cell differentiation, T cell receptor, IL-17, and C-type lectin receptor signalling, collectively reflecting strong engagement of pathogen-sensing, cytokine-driven inflammation, and adaptive immune activation (Fig. 5B). Core cell-state and stress pathways such as cellular senescence, apoptosis, FoxO, and PI3K–Akt signalling were also enriched, indicating that EBV–microplastic convergence influences survival, activation, and exhaustion states of immune cells central to MS pathology. Endocrine-immune interactions were represented through prolactin signalling and progesterone-mediated oocyte maturation, consistent with hormonal modulation of inflammatory activity in MS. Additional enrichment of osteoclast differentiation and JAK–STAT signalling highlights interactions between immune effector cells, cytokine responses, and tissue-remodelling processes. Altogether, the MS enrichment profile indicates that the dual-hit module is positioned within the heart of autoimmune signalling networks, particularly pathways governing innate pathogen recognition, T-cell activation, and pro-inflammatory cytokine cascades.

3.2.5 Dual-Hit Nodes Connecting EBV, Microplastic Targets, and Female Hormone Signalling

To identify hormone-related convergence points between EBV and microplastic exposure, we examined the overlap between EBV–microplastic dual-hit proteins and KEGG estrogen and progesterone pathways. In line with the enrichment results, estrogen signalling was among the Top 15 enriched pathways only in AD, whereas it did not appear in the Top 15 for MS. By contrast, progesterone-mediated oocyte maturation was strongly enriched in both AD and MS, indicating that progesterone signalling represents a shared hormonal axis within the dual-hit neighbourhood across the two diseases. The two dual-hit

proteins, SRC and HSP90AA1, were associated with the estrogen signalling pathway in AD. These same proteins were also present in the estrogen pathway in MS, but the pathway did not reach Top-15 enrichment significance there. This suggests that estrogen signalling plays a more prominent mechanistic role in AD than in MS in respect to the EBV–microplastic dual-hit interface, indicating stronger hormone-linked vulnerability in AD.

Three dual-hit proteins (RPS6KA3, CDK1, and HSP90AA1) were present in both AD and MS in the progesterone-mediated oocyte maturation pathway. These proteins respectively regulate growth-factor–driven kinase signalling (RPS6KA3), cell-cycle progression and stress checkpoints (CDK1), and hormone-receptor chaperoning under cellular stress (HSP90AA1). Overall, the results indicate that EBV and microplastic compounds converge on the estrogen and progesterone signaling pathways.

Overall, our findings identifying these enrichment patterns reflect shared network positioning within integrated interactomes and do not imply directionality or activation state of individual pathways.

4. Discussion

This is the first study, to our knowledge, providing an integrative systems-level analysis demonstrating structured molecular convergence between climate-associated microplastic-derived compounds and EBV–host interaction networks within pathways relevant to AD and MS, grounded in an exposome-informed framework. By integrating microplastic-derived chemical targets, EBV–host interactions, and disease-associated proteins, our analysis identifies shared host modules and pathways positioned at the interface of external environmental exposures and internal biological components of the exposome, through which environmental microplastic toxicants and viral reactivation may jointly shape neuroimmune vulnerability. The findings suggest that exposure to microplastics, accelerated by global warming and plastic degradation, may not act as a direct cause of AD or MS, but rather as an amplifier of underlying biological processes that modulate disease risk within a cumulative exposure framework.

Our analyses revealed that the molecular targets of microplastic-derived compounds are strongly enriched in immune, oxidative stress, and endocrine signaling pathways [49]. These pathways are also central to the maintenance of EBV latency within host B cells, highlighting convergence between chemical exposures and persistent viral components of the internal exposome. Xenoestrogen bisphenols and phthalates, released more readily from plastics under elevated temperatures, interact with estrogen receptors and disrupt hormone-regulated immune homeostasis [50,51]. Indeed, it was shown that overactivation of estrogen receptors disrupts immune homeostasis by shifting balance towards inflammation and autoimmunity, as estrogen enhances immune responses, impacting B and T cells, antibody production, and potentially worsening autoimmune conditions [52,53]. Importantly, estrogen can also regulate type-I Interferon (IFN) responses which affects how the body fights viruses and overactivation might suppress beneficial IFN production [18]. Altogether, these findings suggest that such dysregulation can weaken antiviral control, potentially increasing the likelihood of EBV reactivation[54]. As

EBV reactivation is known to elevate inflammatory cytokines, promote oxidative stress, and lead to immune system dysregulation [55], and propagation of downstream neuroinflammatory processes.

Despite sharing a conserved set of 20 EBV–microplastic “dual-hit” proteins, AD and MS exhibited distinct pathway-level molecular signatures, suggesting disease-specific organization of exposome-sensitive network modules. In MS, the enrichment analysis of the EBV–microplastic dual-hit proteins and their first neighbours within the integrated network was dominated by innate and adaptive immune processes, including Toll-like receptor, NOD-like receptor, IL-17, and Th17 signaling, indicating a stronger immunological signature in MS. These pathways are well-established contributors to EBV-associated MS risk and align with recent evidence that EBV acts as a prerequisite for MS development, through the modulation of immune system processes in the early MS clinical types [35]. Thus, dual targeting by microplastics can act as a synergistic factor amplifying these immune processes, reinforcing the autoimmune and pro-inflammatory mechanisms that underlie MS pathogenesis within an exposome-modulated immune landscape.

By contrast, AD showed stronger enrichment in neuronal, metabolic, and hormone-responsive pathways, particularly estrogen and neurotrophin signaling. The prominence of PI3K-Akt, apoptosis, and cellular senescence pathways indicates that EBV–microplastic interactions may affect neuronal survival, synaptic regulation, and age-related stress responses. Estrogen can activate the PI3K-Akt pathway through activation of its receptors, and it is believed to be beneficial against AD by promoting neuron survival [56–58]. EBV can also activate this pathway, potentially influencing both cancer and neurodegeneration, with studies suggesting EBV might drive genomic instability that impairs DNA repair via PI3K-Akt, contrasting with estrogen's potentially protective pathway-activating role [58–60]. These observations are in line with emerging transcriptomic data demonstrating female-specific enrichment of EBV-related pathways in AD brains [27]. Thus, although microplastic–EBV intersections are present in both diseases, the downstream biology diverges, reflecting predominant immune amplification in MS versus neuroendocrine susceptibility in AD.

A key finding of the present study is the identification of endocrine pathways, particularly estrogen and progesterone signaling, as central convergence points for EBV–microplastic interactions within the exposome framework. Several dual-hit proteins, including *SRC, HSP90AA1*, and *RPS6KA3*, act as hormone-responsive regulators of cellular stress and immune signaling, positioning them at the interface of endocrine and antiviral pathways. Notably, estrogen signaling emerged as a more prominent pathway in AD than in MS, aligning with clinical and molecular evidence that AD exhibits heightened hormonal sensitivity and disproportionately affects women [61]. Although estrogen signaling is also involved in MS, where it modulates immune responses, T-cell differentiation, and neuroprotection [62], in our enrichment analysis results it was less pronounced than in AD. This is consistent with the view that estrogen plays a regulatory rather than primary mechanistic role in MS, whereas in AD it has more a more direct contribution through effects on synaptic function, mitochondrial stability, and neuroinflammatory regulation. In contrast, the progesterone-mediated oocyte maturation pathway was

enriched and part of the top 15 pathways in both diseases, indicating a broader endocrine influence on EBV–microplastic convergence. Together, these findings support a model in which microplastic-derived xenoestrogens disrupt estrogen and progesterone homeostasis, thereby weakening immune control of latent EBV, an embedded biological component of the internal exposome. Women experience cyclical, menopausal, and pregnancy-related hormonal shifts, each associated with altered EBV activity [17,63], thus environmental endocrine disruptors may further increase susceptibility. This mechanistic interplay offers a biologically plausible explanation for the marked sex biases observed in both AD and MS, and how the combinatorial action of different environmental factors could contribute to this vulnerability. Beyond estrogen receptor signaling, sex differences in immune cell composition, microglial activation states, blood–brain barrier integrity, and antiviral interferon responses have been documented in both AD and MS [64–66]. These sex-dimorphic immune and neurovascular features may influence how environmental endocrine-active compounds and EBV–host interactions are integrated within disease-associated networks. Therefore, the observed enrichment of hormone-related pathways should be interpreted within a broader framework of sex-specific immune and neuroinflammatory regulation rather than as a singular estrogen-driven mechanism.

EBV directly targeted a larger number of AD-related proteins than MS-related proteins, including regulators of amyloid processing, synaptic integrity, mitochondrial function, and proteostasis [26]. This broader footprint within the AD network suggests that EBV reactivation may influence multiple neuronal processes associated with neurodegenerative progression. Conversely, EBV's interaction with MS proteins was more immunological in nature, aligning with its well-established role in initiating aberrant immune responses and driving autoimmune demyelination [34,35]. These patterns reinforce the hypothesis that EBV acts not as a universal cause but as a network amplifier, interacting with environmental pressures, such as microplastic exposure, to reshape disease-relevant molecular landscapes.

While this computational framework reveals compelling molecular intersections, several limitations should be acknowledged. All *in silico* predictions require experimental validation, and real-world exposure levels and temporal dynamics were not incorporated, despite substantial variation in microplastic exposure across geography, age, occupation, and climate, which represent additional layers of exposome heterogeneity. Additionally, the disease associated data are not tissue-specific or sex-specific. Future integration of longitudinal exposure data, tissue and sex-specific data, hormone profiling, and experimental single-cell models will be important for validating and refining the proposed microplastic–EBV neuroimmune interactions. Additionally, because PPI and chemical–protein interaction databases do not encode activation state or transcriptional directionality, the present findings reflect shared targeting potential within integrated networks rather than coordinated up- or down-regulation of specific pathways.

5. Conclusion

Our findings support a model in which climate-driven microplastic exposure, acting through endocrine and immune disruption, may increase susceptibility to EBV reactivation and thereby contribute to female-

biased vulnerability to AD and MS. Collectively, this study delineates a conserved molecular interface linking climate-associated microplastic-derived endocrine-active compounds and EBV–host interaction networks within immune, metabolic, and hormone-responsive pathways implicated in AD and MS. By positioning environmental and viral components within shared disease-associated interactomes, this analysis provides a systems-level framework for understanding how multifactorial exposures may converge to shape neurodegenerative and autoimmune vulnerability.

Rather than implicating a single exposure as causal, these findings support an exposome-based model in which climate-amplified chemical exposures and persistent viral components jointly reshape internal regulatory networks, altering host–virus equilibrium and endocrine–immune balance. This integrative perspective underscores the importance of considering cumulative, interacting exposures within the exposome across the lifespan when investigating complex autoimmune and neurodegenerative diseases.

Declarations

Competing Interests

The author declares no competing interests.

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Data Availability Statement

All data used in this study are publicly available from the resources and references cited within the Methods section.

Code Availability Statement

The code used in this study may be shared upon reasonable request, subject to intellectual property considerations, by contacting the corresponding author.

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Figures

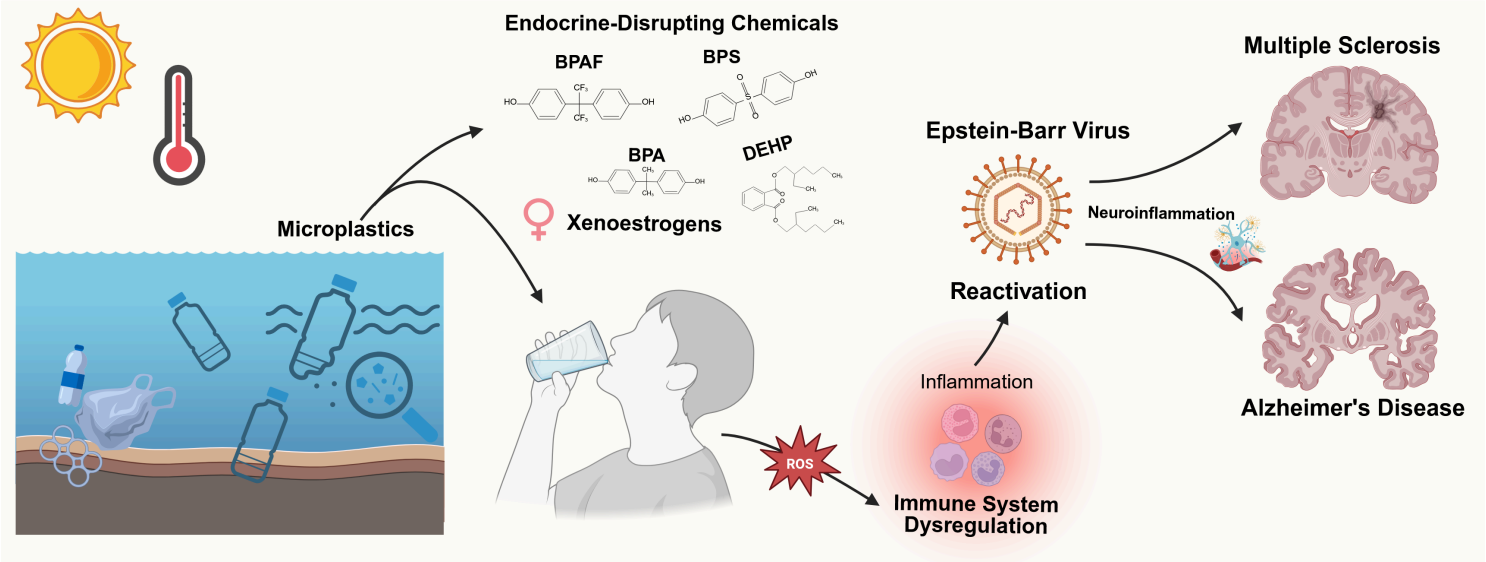


Figure 1

Proposed mechanism linking exposure to climate-driven microplastic to EBV reactivation and increased neurodegenerative risk. *Rising global temperatures accelerate the degradation of plastics, leading to the release of microplastics that enter the food and water supply. These particles release endocrine-disrupting chemicals such as bisphenols (BPA, BPF, BPS, BPAF) and phthalates (DEHP), which exert xenoestrogen effects when consumed by humans through contaminated water and food. Once inside the body, microplastics promote oxidative stress (ROS production) and immune dysregulation, leading to chronic low-grade inflammation. Chronic inflammation may impair antiviral immune responses that are essential for maintaining viral latency, thereby facilitating EBV reactivation, which in turns result to neuroinflammation which is implicated in the pathogenesis of MS and AD.*

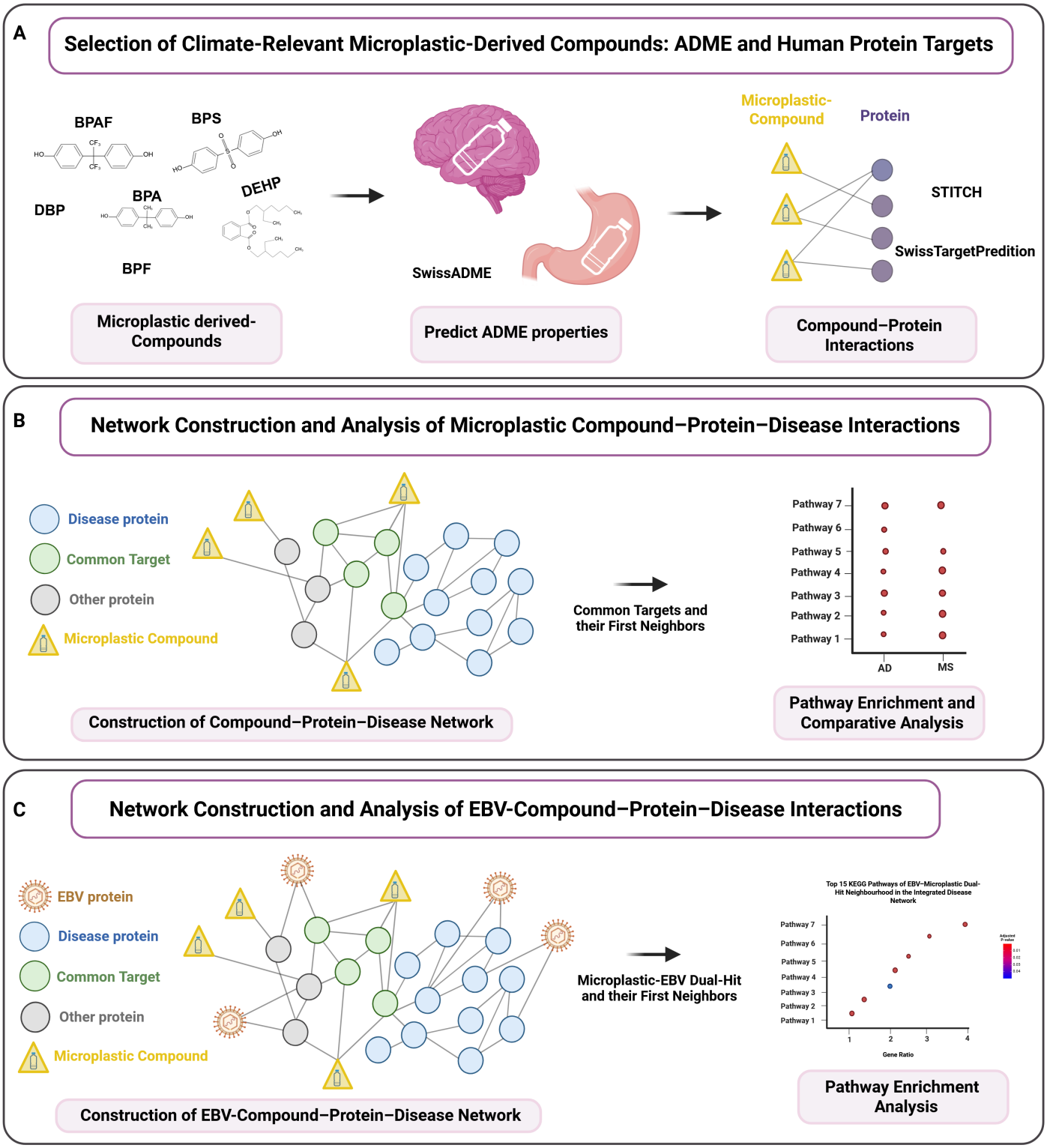
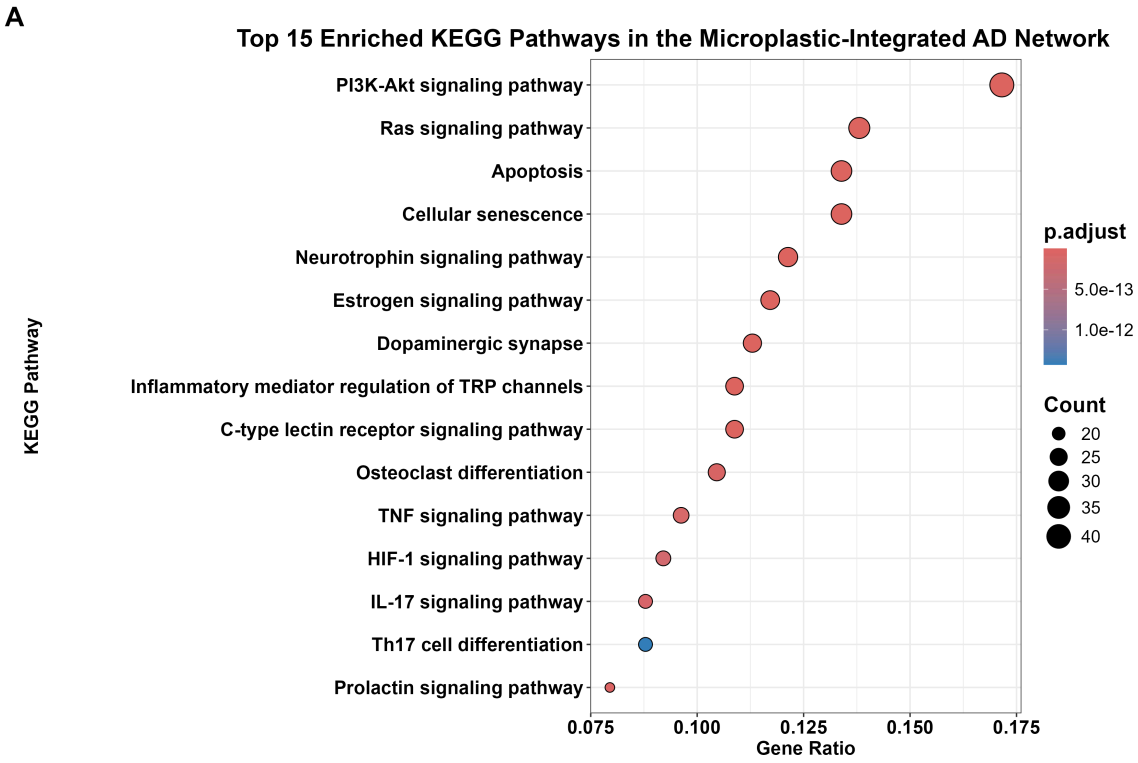


Figure 2

Schematic illustration of the methodology used in this study. (A) Selection and characterization of climate-relevant microplastic-derived compounds. *Six compounds (BPA, BPF, BPS, BPAF, DBP, DEHP) were evaluated for ADME properties using SwissADME, followed by identification of known human protein targets from STITCH and predicted targets from SwissTargetPrediction.* ***(B) Network construction and analysis of microplastic compound–protein–disease networks.*** *Microplastic-derived*

compound targets were integrated with AD and MS disease-associated proteins to generate compound–protein–disease networks. Common targets that is disease proteins and microplastic compounds targets and their first neighbours were subjected to KEGG pathway enrichment analysis. ***(C) Network construction and analysis of EBV-microplastic compound–protein–disease networks.*** *EBV-host PPIs were integrated into the compound–protein–disease networks to identify dual-hit nodes, genes targeted by both EBV and microplastic compounds. Enrichment analysis was then performed on the dual-hit genes and their first neighbours.*



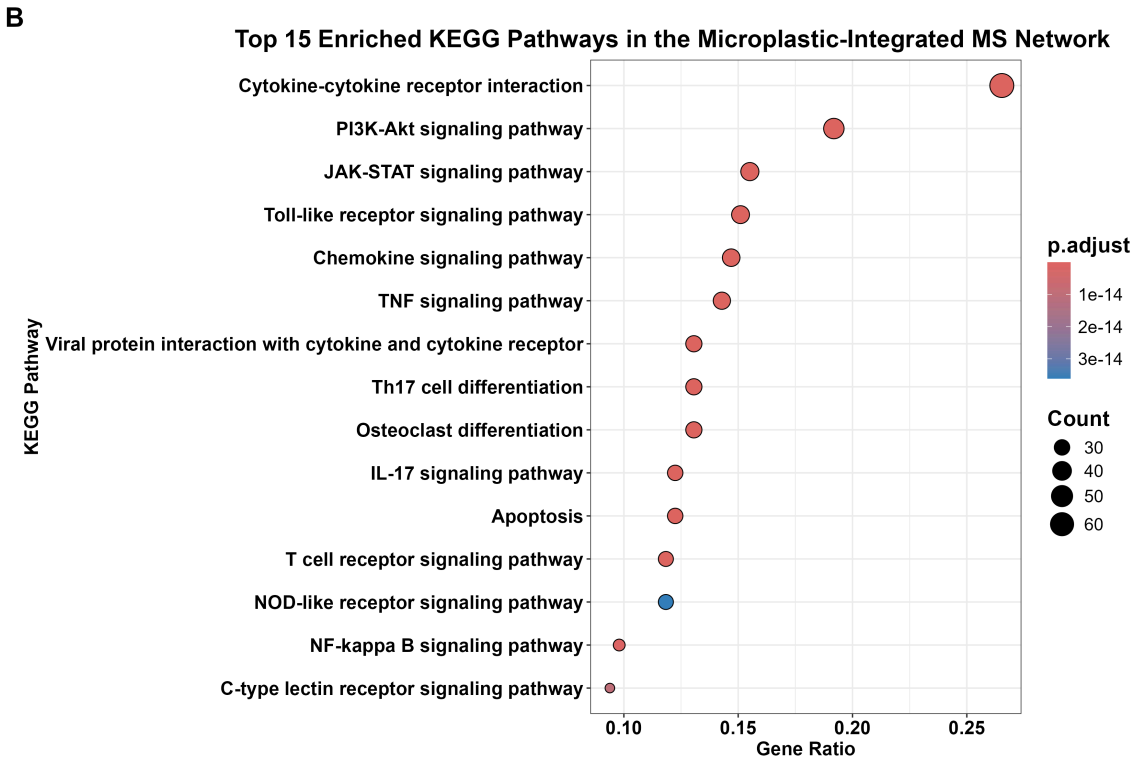


Figure 3

(A) Top 15 enriched KEGG pathways identified from the microplastic–protein–AD integrated network. (B) Top 15 enriched KEGG pathways from the microplastic–protein–MS integrated network.

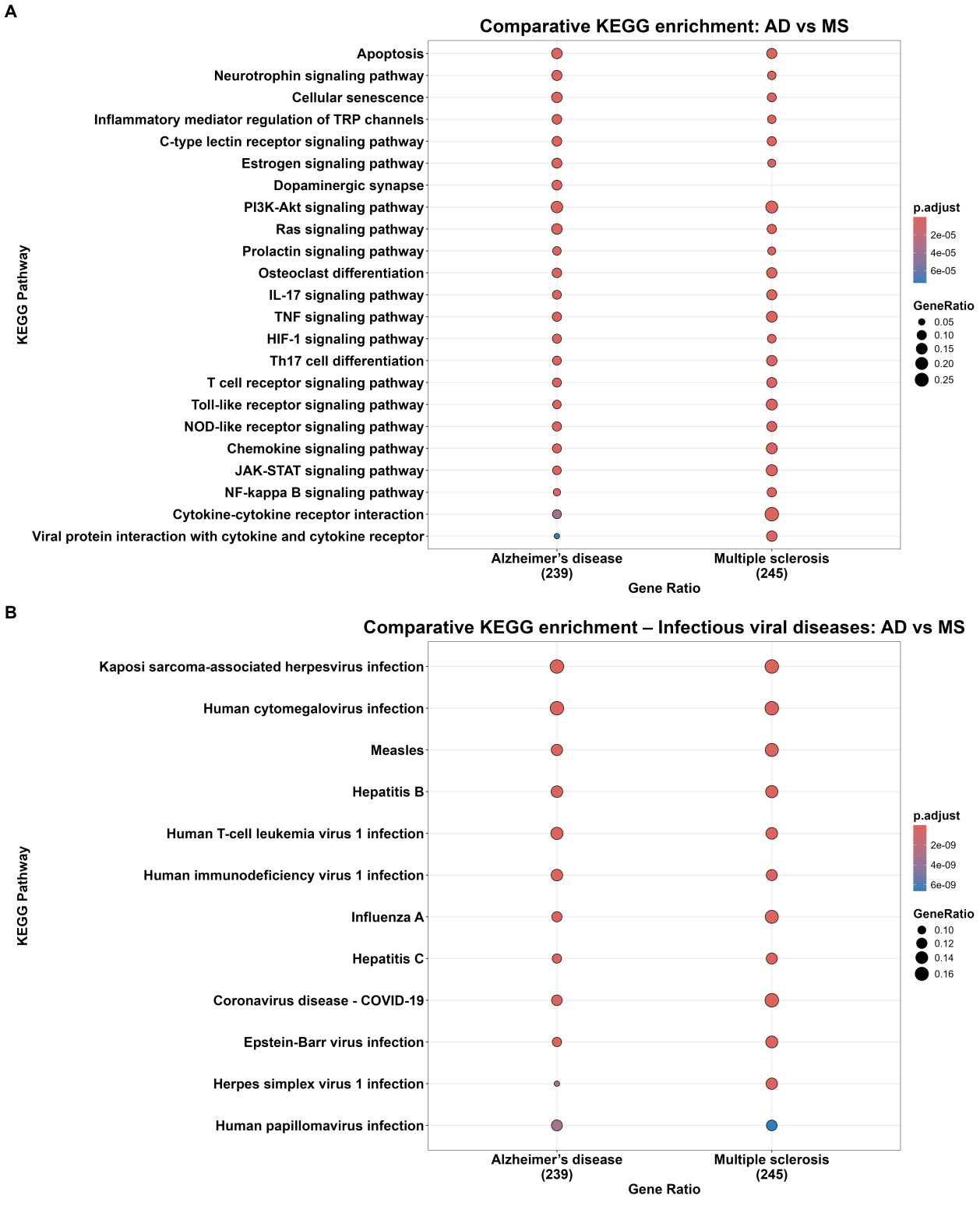


Figure 4

Comparative KEGG pathway enrichment analysis of microplastic-integrated AD and MS networks. (A) *Comparative enrichment of biological KEGG pathways in AD and MS based on shared microplastic–protein targets and their first-neighbour interactors.* ***(B)*** *Focused comparative KEGG enrichment for infectious viral disease pathways in AD and MS.*

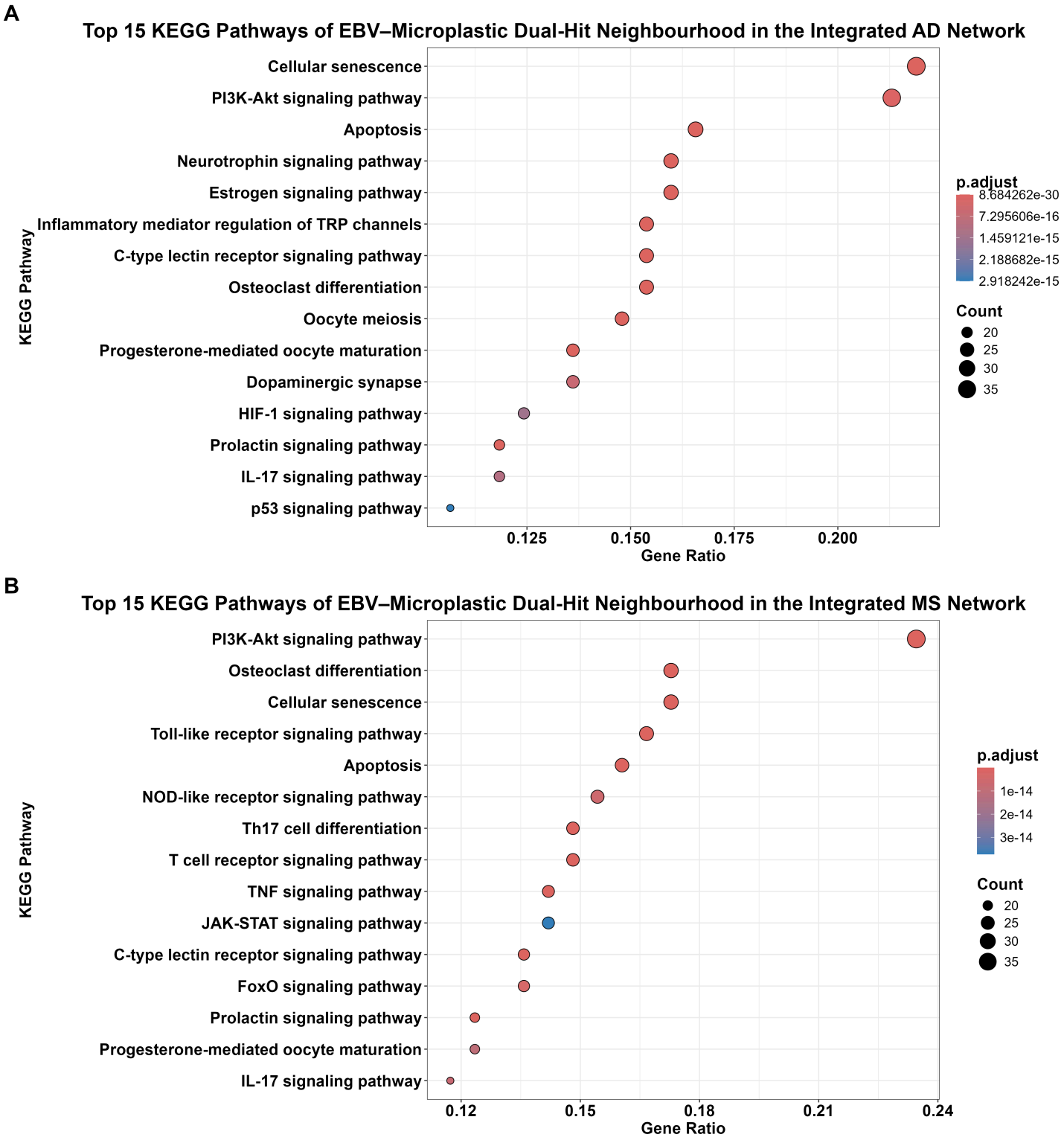


Figure 5

(A) *Top 15 KEGG Pathways of EBV–Microplastic Dual-Hit Neighbourhood in the Integrated AD Network.*
(B) *Top 15 KEGG Pathways of EBV–Microplastic Dual-Hit Neighbourhood in the Integrated MS Network.*