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A Review of Emerging Evidence Linking Bisphenol A to Alzheimer's Disease Pathogenesis

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Abstract: Dementia, a significant neurocognitive disorder, is the seventh most prevalent cause of death worldwide and has a substantial impact on societal costs. Alzheimer's disease (AD), the most common form of dementia, gradually impairs cognitive and functional abilities, resulting in severe memory loss and dependence. Research suggests that the onset and progression of AD may be influenced by environmental factors, such as exposure to bisphenol A (BPA), a chemical that is commonly found in consumer products. A total of 30 relevant publications were retrieved from ScienceDirect, Scopus, and Web of Science for inclusion in this narrative review. This review examines the clinical evidence supporting a correlation between BPA exposure and AD, with a particular focus on how BPA exposure impairs cognitive function, disrupts insulin signaling, induces oxidative stress, and promotes the accumulation of amyloid-beta plaques and tau proteins, which are distinctive features of AD. Additionally, maternal exposure to BPA during pregnancy can have a detrimental impact on the brain development of offspring, thereby enhancing their susceptibility to AD. These findings underscore the necessity of additional research to comprehend the mechanisms that underlie BPA-induced neurotoxicity and to devise strategies to reduce its influence on neurodegenerative disorders.

Keywords: Bisphenol A (BPA); Alzheimer's disease; neurotoxicity; clinical studies.

1. Introduction

The most recent World Alzheimer Report 2021 [1] indicates that dementia is currently the seventh most prevalent cause of death worldwide and one of the costliest illnesses in society. Dementia affects 35.6 million individuals worldwide. According to a report by the World Health Organization (WHO), this population is anticipated to increase by over fourfold by 2050 (115.4 million) and double by 2030 (65.7 million). Dementia is prevalent in all countries; however, over half (58%) of those affected reside in low- and middle-income countries. By 2050, this figure is anticipated tourpass 70% [2]. According to the Alzheimer's

Disease Foundation, Malaysia (ADFM), between 204,000 and 264,000 individuals will have dementia that is in its final stages and will necessitate 24-hour care in 2020 (8.5 percentage points to 11 percentage points). This figure is anticipated to triple by 2050, from 637,500 to 825,000, a 312% increase, in part due to data that illustrates Malaysia's rapid aging [3]. Additionally, the foundation underscored the importance of environmental and lifestyle risk factors in the epidemic of dementia cases. Malaysia has been classified as an aging nation by the United Nations (UN) because 7.3% of the total population is 65 years of age or older, exceedinghe UN's 7% [4].

Dementia, which is also known as a major neurocognitive disorder (MND), is a condition that exhibits a variety of symptoms. There is a substantial negative impact on memory, behavior, reasoning, and social skills, which interferes with daily tasks and social autonomy [5]. Alzheimer's disease (AD) is the most prevalent cause of dementia in adults over the age of 65; however, it is not the sole one [6]. It is crucial to recognize the constraints of the term "dementia," which is frequently employed to describe AD and is typically associated with older individuals. It is important to note that individuals of all ages can be affected by major neurocognitive disorders, and cognitive decline does not necessarily indicate that AD is the underlying cause [5]. This disease destroys brain cells and nerves, disrupting message-carrying transmitters in the brain, particularly those responsible for memory storage, according to the World Health Organization. This is the most prevalent cause of dementia, accounting for 60% to 70% of all cases [7]. Alzheimer's disease is a neurodegenerative disorder that manifests symptoms gradually over time and progressively deteriorates [8]. Research indicates that the onset and progression of AD may be influenced by a range of factors beyond genetics. One area of research that is particularly compelling is the correlation between cognitive decline and metabolic diseases such as diabetes and obesity, as well as vascular conditions such as heart disease, stroke, and high blood pressure [9]. Neurofibrillary tangles, amyloid plaques, chronic inflammation, neuronal connection destruction in the brain, and vascular contribution are the primary disease-related factors in AD, as shown in Figure 1 [8].

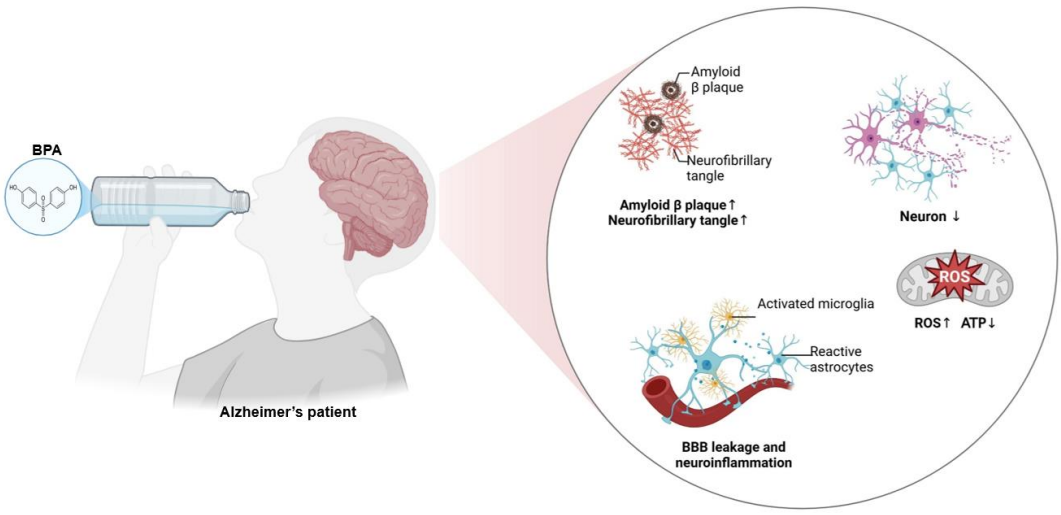


Figure 1. Neuroinflammation and AD progression.

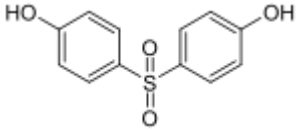
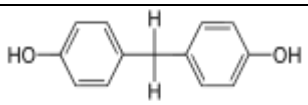
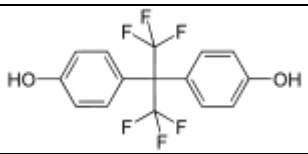
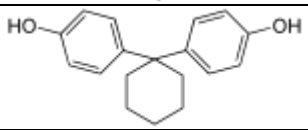
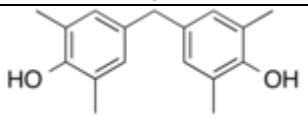
Alzheimer's disease typically progresses in three stages: early or mild, middle or moderate, and late or severe. A progressive pattern of cognitive and functional dysfunction characterizes each stage. The disease's known target is the hippocampus, a brain region that is associated with memory. Memory loss is the initial symptom of this condition. As the disease advances, memory impairment becomes increasingly severe [10]. Mild cognitive impairment

(MCI) is frequently recognized as a transitional phase between dementia and normal aging. Memory loss is the most prevalent symptom of MCI, which is referred to as amnestic MCI [11]. This phase of AD is frequently referred to as the prodromal stage. The probability of a correlation between amnestic MCI and AD exceeds 90% [10]. In the initial stages, wandering and becoming lost, as well as struggling to manage finances and pay bills, asking questions repeatedly, taking longer to complete daily tasks, and altering their personality and behavior, can be problematic [12]. Patients are frequently diagnosed during this period. The middle stage is characterized by the onset of difficulty identifying family and friends as memory loss and confusion worsen. They may experience difficulty adapting to new circumstances, acquiring new skills, or completing intricate tasks, such as dressing. Impulsive behavior, hallucinations, delusions, and paranoia may also be present at this juncture. In the late stage, plaques and tangles eventually engulf the entire brain, and brain tissue undergoes a significant decline [10]. Individuals with severe AD are incapable of communicating and are entirely dependent on others for care [12]. The patient may spend the majority of their time in bed due to the body's shutdown at the end of life.

The National Institute of Environmental Health Sciences (NIEHS) has determined that bisphenol A (BPA) is a chemical widely used in the production of polycarbonate, a hard, transparent plastic found in numerous consumer products. Water bottles, baby bottles, dental fillings and sealants, medical tools, safety devices, compact discs, home electronics, and sports equipment are all potential sources of this substance [13]. It is also present in epoxy resins, which are employed to coat the interior of food and drink cans [14]. People are frequently exposed to minute quantities of BPA through food, beverages, and water supplies, as these substances can migrate from food packaging [15]. The results of general population biomonitoring indicate that individuals are permanently and heavily exposed to BPA, which leads to an increase in internal unconjugated BPA exposure in humans. This has been demonstrated in numerous studies. On the other hand, the remaining free BPA stimulates the production of reactive oxygen species (ROS) through enzymatic and non-enzymatic formation of phenoxyl radicals, despite the fact that the majority of BPA in exposed humans undergoes rapid metabolism, resulting in lower toxic metabolite formation [16]. A study of 41,230 individuals has demonstrated a strong correlation between BPA levels in urine or serum and the development of type 2 diabetes mellitus (T2DM). Insulin resistance and hyperglycemia are the results of BPA exposure [17]. Currently, approximately 415 million adults worldwide are affected by T2DM; however, the International Diabetes Federation anticipates that this figure will increase to as many as 642 million by 2025. Cognitive loss, tau accumulation, and dementia are all associated with late-onset AD, which is caused by the accumulation of amyloid-beta (Aβ) in the brain for more than 15 years. T2DM more than doubles the risk of AD in these individuals [18].

Bisphenol A is a synthetic substance that belongs to the diphenylmethane and bisphenol families and has two hydroxyphenyl groups linked to the carbon atom of the main chain. Its chemical formula is $(CH_3)_2C(C_6H_4OH)_2$ [19]. In response to concerns about the health risks of BPA, some manufacturers have switched to alternative bisphenols such as bisphenol S and bisphenol F. These are made in the same way BPA is, by substituting various ketones for acetone and undergoingimilar condensation processes [20]. These options have also raised health concerns. Table 1 presents the names, structural formulas, and reactants of the BPA analogs.

Table 1. The structural formula of BPA analogs [21].

Structural formula	Name	Reactants	
	Bisphenol S	Phenol	Sulphur trioxide
	Bisphenol F	Phenol	Formaldehyde
	Bisphenol AF	Phenol	Hexafluoroacetone
	Bisphenol Z	Phenol	Cyclohexanone
	Tetramethyl bisphenol F	2,6-xylenol	Formaldehyde

In humans, bisphenol A has been associated with infertility, obesity, heart disease, type 2 diabetes, cancer, and Alzheimer's disease. The US Food and Drug Administration (FDA) declared in a 2014 report that exposure levels of less than 5 micrograms per kilogram of body weight per day are considered safe [22]. The average individual is only exposed to 0.2-0.5 micrograms per kilogram of body weight daily. BPA is still considered a safe food additive, despite the FDA's 2012 prohibition on its use in baby formula cans, baby bottles, and sippy cups. Nevertheless, recent research indicates that BPA exposure, even at "safe" levels, may cause or contribute to a variety of health issues [22,23]. Additional research is required to ascertain whether there is a genuine safety threshold for BPA exposure or whether it can be detrimental at any level of exposure. BPA substantially elevates tau-phosphorylation and oxidative stress in the cortex and hippocampus of AD brain tissue [24].

Additionally, it induces an increase in Aβ and neuroinflammation. Alzheimer's disease, the most prevalent form of dementia, is believed to be the result of the early harmful occurrence of Aβ accumulation in the brain. This condition is characterized by the presence of plaques and tangles in the brain [25,26]. To improve understanding of the molecular mechanisms underlying BPA-induced brain damage, extensive research has been conducted. Thus, the objective of this review is to enhance understanding of the potential involvement of BPA in the onset or development of this neurodegenerative disorder by providing a comprehensive summary of the experimental research on the relationship between BPA and AD.

2. Materials and Methods

The PRISMA flow diagram in Figure 2 outlines the literature search process for bisphenol A and Alzheimer's disease, along with the subsequent screening. ScienceDirect, Scopus, and Web of Science were utilized to retrieve relevant publications for this narrative review. We used search terms like bisphenol A (BPA), BPA analogs, the effects of BPA on health, Alzheimer's disease (AD), dementia, insulin, and clinical evidence. To narrow down the search and get complete and accurate results, Boolean operators like "AND" and "OR" were used. The filter tool was then used to find works that were published between 2008 and 2024. We looked at possible paper titles and abstracts to find them. After getting and reading the full

texts of possible articles, the selection was improved. Reference lists in related publications were reviewed both manually and electronically to uncover potentially overlooked research during initial searches. A number of variables, including the target population, study interventions, research design, outcome measures, methodological quality, and study quality, were used to select which studies to examine in depth.

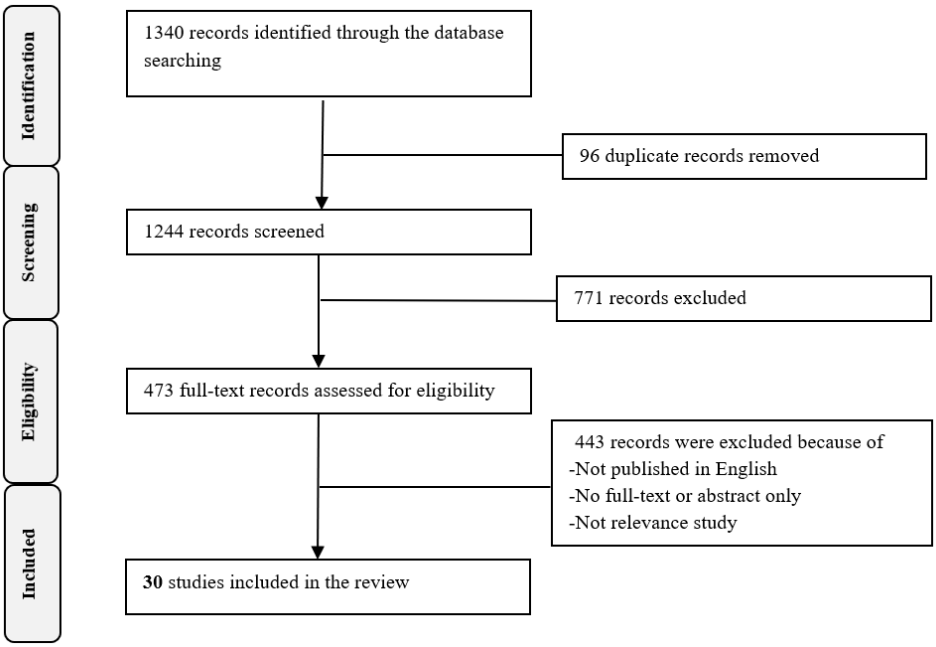


Figure 2. PRISMA flowchart.

3. Results and Discussion

This review synthesized experimental research examining the influence of BPA exposure on the initiation and progression of Alzheimer's disease, emphasizing neuropathological and behavioral consequences. In the studies reviewed, exposure to BPA, whether acute or chronic, was consistently associated with pathological characteristics typical of Alzheimer's disease (AD), such as amyloid-beta (Aβ) accumulation, tau protein hyperphosphorylation, synaptic dysfunction, oxidative stress, and neuroinflammation. Cognitive impairments, comprising spatial learning deficits and diminished memory retention, were frequently documented. These findings indicate that BPA functions not only as an environmental toxicant but also as a potential catalyst for AD pathogenesis via multifactorial disruption of neural homeostasis. However, heterogeneity in experimental design spanning differences in animal models, exposure timing, BPA dosages, and methodological endpoints poses challenges in establishing a unified mechanistic framework.

The objective of the review is to provide a comprehensive summary of the findings from experimental research investigating the potential impact of BPA exposure on the onset or progression of AD. In addition, the study examines the various methodologies used in experimental investigations to investigate the impact of BPA on cognitive function, neuroinflammation, and amyloid-beta build-up in Alzheimer's disease. The review comprises a table that provides a concise summary of the overall findings, which includes experimental research that meets the inclusion criteria. The most significant findings and recommendations derived from the experimental studies examined are emphasized in these tables. It provides a comprehensive examination of the available data and offers suggestions for the future of this field of study.

3.1. BPA-induced hormonal disruption in AD.

The evidence synthesized from the reviewed studies in Table 2 consistently demonstrates that BPA disrupts insulin signaling pathways in the brain, thereby contributing to molecular and pathological changes associated with AD. BPA exposure has been shown to induce insulin resistance, elevate circulating insulin levels, and inhibit downstream signaling targets such as AKT and glycogen synthase kinase-3β (GSK3β), ultimately disrupting glucose homeostasis in the hippocampus [27]. Experimental models indicate that BPA can impair insulin receptor activation both in vitro and in vivo, with murine hippocampal models revealing that BPA disrupts insulin receptor phosphorylation, impedes downstream signal transduction, and promotes pathological accumulation of amyloid-β (Aβ) and hyperphosphorylated tau. Such molecular alterations ultimately result in neuronal loss and measurable cognitive deficits [28]. Moreover, BPA was shown to interfere with insulin receptor binding affinity and synaptic plasticity, further exacerbating neurodegenerative processes. Notably, multiple studies have confirmed BPA's ability to cross the blood–brain barrier (BBB) during critical developmental windows, thereby influencing neuroendocrine homeostasis, neurotransmitter levels, and cognitive performance [29].

Table 2. Summary of findings on how BPA-induced hormonal disruption in AD.

Ref.	Type of bisphenol	Sample	Concentration/ Dosage	Exposure window	Duration of treatment	Endpoint / Findings	Remarks
[27]	BPA	C57BL6 male mice	100 µg/kg/day	Subcutaneous injection	30 days	• BPA interfered with glucose uptake in the CNS • Hyperactivation of the IR/AKT/GSK3β axis was shown in the brain of BPA-treated mice • An increase in phosphorylated tau and APP was observed in BPA-treated mice	The adverse effects of BPA on insulin secretion and insulin sensibility, especially in the brain, on β-APP, p-tau, and glucose transport dysregulation
[28]	BPA	Mice	0.001 µM to 100 µM	Treatments were added with fresh media	14 days	• BPA induced apoptotic cell death in SN56 cholinergic cells from the basal forebrain • Induced oxidative stress, Aβ, and tau generation by insulin pathway downregulation • Induced oxidative stress by the NRF2 signaling pathway downregulation	BPA-induced HDAC2 and PTP1B overexpression led to insulin signaling disruption, producing amyloid-β_{1-42} and p-tau peptides accumulation, and cell death in BFCN
[29]	BPA	Mice	0.01mg/L to 1mg/L	Via drinking water	weeks	• BPA reduced the ratio of T/E2 in male mice • Altered the expressions of 16 genes overlapped with the DEG involved in the AD, PD, HD, and OXPHOs in the hippocampus • Inhibited the mRNA and protein expressions of the OXPHOs	Exposure to BPA decreased learning ability through suppression of mitochondrial OXPHOs

Ref.	Type of bisphenol	Sample	Concentration/ Dosage	Exposure window	Duration of treatment	Endpoint / Findings	Remarks
[30]	BPA	Pancreatic β-cells (Human)	0.5–10 µM	Cells were treated with BPA in 6-well plates	24 hours	• BPA promoted hIAPP aggregation in a dose-dependent manner, which is supported by the enhanced fluorescence intensity • Accelerated transition of hIAPP from unordered structure to β-structure in the presence of BPA	BPA exposure increased T2DM risk may involve the exacerbated toxic aggregation of hIAPP
[31]	BPA	Mice	0.01, 0.1, and 1 µg/mL	Via drinking water	9 weeks	• BPA decreased the cognitive function of F1-male mice • Inhibited the protein and mRNA expressions of the insulin signaling pathway and GLUT4 in the hippocampus	Blood sugar levels of F1-male mice were increased after thirteen weeks of treatment with BPA
[32]	BPA	SH-SY5Y cells (Human)	0, 2, 20, 200, and 2000 nM/L	Cells were incubated with different BPA concentrations	30 min	• BPA disrupted the insulin signaling pathways by decreasing IR tyrosine phosphorylation and increasing IRS1 serine phosphorylation, which leads to reduced AKT phosphorylation	BPA exposure contributes to an increase in intracellular [Ca^{2+}] and ROS, and ATP and mitochondrial membrane potential decrease
[33]	BPA	*Drosophila melanogaster*	0.05, 0.5, and 1 mM	Via a cornmeal diet supplemented	26 days	• BPA-induced over-production of lipid peroxides, ROS, and reduced antioxidant activities • Induced micronuclei formation and impaired nucleoplasm-cytoplasmic transport	CeO_2NPs ameliorate oxidative stress, improve behavioral abnormalities, and reduce pupation abnormalities induced by BPA
[34]	BPA	Mouse astrocyte type I cells (C8-D1A)	30 µM	Cells were treated with BPA in 6-well plates	24 hours	• BPA causes ROS-induced neurotoxicity *in vitro* and *in vivo* • ALA prevents BPA-induced cell death in mouse C8-D1A astrocytes • ALA protected mice from BPA-induced cognition and muscle coordination alterations	Enhancement in the antioxidant levels via ALA prevents the neurotoxicity of BPA
[35]	BPA	Mice	0.001 µM to 100 µM	Cells were treated with BPA in 6-well plates	14 days	• BPA-induced apoptotic cell death in basal forebrain cholinergic neurons • Decreased ACh levels through ChAT activity inhibition • Disrupted cholinergic transmission and NGF/TrkA/$P75^{NTR}$ signaling through HDAC2 overexpression	BPA induced cholinergic neurotransmission disruption through the reduction of ChAT activity and produced apoptotic cell death in BFCN

Ref.	Type of bisphenol	Sample	Concentration/ Dosage	Exposure window	Duration of treatment	Endpoint / Findings	Remarks
[36]	BPA	Mice	0.05, 0.5, 5, or 50 mg/kg body weight	Through a standard rodent chow diet	22 weeks	• BPA increases neuroinflammation and damages the blood-brain barrier function • Caused gut barrier dysfunction and altered the microbiota composition • Decreased 5-HT and its metabolite levels in the serum, hippocampus, and colon	Dietary intake of BPA induces cognitive impairment in male mice but not female mice
[37]	BPA	Human cortical neurons (hCNs)	0.1, 1, and 10 μM	Cells were treated with BPA in 6-well plates	14 days	• BPA upregulated NMDARs and disturbed intracellular calcium homeostasis • Induced mitochondrial dysfunction and endoplasmic reticulum stress • Induced neural apoptosis and neuronal network damage	BPA-triggered excitatory neurotoxicity alleviated by NMDAR antagonists
[38]	BPA	Male and female C57BL6 mice	100 μg/kg/day	Subcutaneous injection	3-8 months	• Perinatal BPA exposure contributed to brain insulin resistance in the adult offspring • BPA downregulated the expression of insulin signaling molecules in the frontal cortex of the male offspring • BPA exposure during the perinatal period decreased expression of the phosphorylated IR Tyr1355 site and AKT Ser473 site.	Perinatal exposure to BPA contributes to the abnormal increase of APP and hyperphosphorylation of tau
[39]	BPA	Mice	100 μg/kg/day	Subcutaneous injection	15 days	• BPA increased fasted blood glucose level and plasma insulin level, leading to insulin resistance in adult mice • Decreased the insulin signaling, AKT, GSK3β, and ERK phosphorylation in the CNS • Impaired glucose uptake by decreasing GLUTs expression in the CNS	BPA exposure perturbs insulin signaling and glucose transport in the brain, which might be a risk factor for brain insulin resistance

Beyond its direct impact on insulin signaling, long-term BPA exposure appears to exacerbate metabolic dysfunction through mechanisms relevant to both type 2 diabetes mellitus (T2DM) and AD. BPA promotes the aggregation of human islet amyloid polypeptide (hIAPP) and triggers β-cell apoptosis, impairing pancreatic function and systemic glucose regulation. Additionally, its estrogen-mimetic activity may alter hIAPP secretion dynamics, contributing

to insulin resistance and increasing the risk of neurodegenerative outcomes [30]. In hippocampal studies, Wang *et al*. (2022) demonstrated that BPA not only altered neuronal architecture but also disrupted key insulin pathway proteins, including phosphorylated insulin receptor substrate 1 (p-IRS1), protein kinase B (p-AKT), and p-GSK3β [31]. Similarly, Flores *et al*. (2022) identified that BPA-induced overexpression of histone deacetylase 2 (HDAC2) and protein tyrosine phosphatase 1B (PTP1B) contributed to insulin signaling inhibition, leading to intracellular Aβ1-42 and p-tau accumulation in basal forebrain cholinergic neurons [28]. These findings are consistent with the hypothesis that BPA promotes brain insulin resistance via multiple converging pathways, including oxidative stress induction, inflammatory activation, and impaired glucose transport. Evidence from Wang (2017) further links BPA to reduced antioxidant defenses through NRF2 downregulation, reinforcing oxidative stress as a central mediator of its neurotoxic effects [32].

Furthermore, the neurobehavioral implications of BPA exposure are also compelling. Increased ROS generation, synaptic dysfunction, and altered neurotransmitter balance, including norepinephrine, serotonin, dopamine, and glutamate, have been documented. Sarkar *et al*. (2021) found that such neurotransmitter changes are linked to impaired learning, decreased memory retention, and delayed neurodevelopment, emphasizing the risk of cognitive decline [33]. Antioxidant interventions, such as α-lipoic acid (ALA), have shown some capacity to mitigate BPA-induced oxidative damage (Khan *et al*., 2018). Yet, the efficacy of such interventions in preventing or reversing BPA-related neurodegeneration remains to be validated in human populations [34]. Overall, these findings underscore a multi-mechanistic model in which BPA-induced hormonal dysregulation, metabolic disturbances, and oxidative stress converge to promote AD-like pathology.

Despite the strength of preclinical evidence, important methodological limitations must be acknowledged. The majority of studies use rodent or cell culture models, which may not accurately represent human BPA exposure dynamics, metabolism, or susceptibility. Exposure doses in animal studies often exceed environmental levels, limiting direct extrapolation to human risk assessment. Moreover, variability in exposure timing, duration, and administration route complicates cross-study comparisons. Sex-specific effects, particularly relevant given BPA's estrogen-mimicking properties, remain underexplored, and cumulative, lifelong low-dose effects are rarely addressed. Small sample sizes, inconsistent behavioral assessments, and incomplete neuropathological characterization further limit interpretation. Moving forward, thorough longitudinal human cohort studies incorporating exposure biomonitoring, neuroimaging, and molecular biomarker research will be necessary to assess the therapeutic relevance of BPA as a modifiable environmental risk factor for AD.

3.2. Impact of maternal BPA exposure on Alzheimer's disease risk in offspring.

Maternal exposure to BPA during pregnancy or lactation has been increasingly recognized as a critical environmental determinant of offspring neurodevelopment, with strong implications for AD risk later in life. Experimental evidence in Table 3 consistently demonstrates that BPA readily crosses the placental barrier and accumulates in key fetal compartments, including the placenta, amniotic fluid, umbilical cord blood, and fetal serum, thereby exerting direct neurodevelopmental effects during highly sensitive windows of brain formation. Rodent, zebrafish, and non-mammalian vertebrate studies converge in showing that such exposure disrupts neurotransmitter homeostasis, impairs synaptic plasticity, and alters neural network formation. These disruptions are mechanistically linked to AD-like pathologies,

including enhanced amyloid-beta (Aβ) deposition, reduced Aβ clearance, and synaptic protein loss, particularly PSD95, which is vital for synaptic stability and memory consolidation. Notably, microglial activation and pro-inflammatory cytokine release establish a persistent neuroinflammatory state that primes the brain for progressive neurodegeneration, aligning with the chronic inflammatory conditions observed in AD patients [40]. The breadth of evidence highlights the potential for maternal BPA exposure to act as an early-life risk factor that primes the nervous system toward pathological aging and AD-like phenotypes.

Table 3. Summary of findings on how BPA exposure by the mother induced AD in the offspring.

Authors	Type of bisphenol	Sample	Concentration/ Dosage	Exposure window	Duration of treatment	Endpoint / Findings	Remarks
[40]	BPA	Rat pups	5,000 µg/kg· maternal BW	Diluted with corn oil	GD1 until parturition	• Disrupted the transcriptome profiles of genes associated with neuroinflammation and AD in the offspring hippocampus • Maternal BPA exposure increased AD risk in offspring by dysregulating genes associated with AD neuropathology and inflammation	Maternal BPA exposure also disrupted AD-related genes in other tissue types, particularly placental tissues and fetal mammary glands
[41]	BPA	Mice	10 or 100 µM/kg/day	Dissolved in tocopherol-stripped corn oil	9-16 days	• BPA exposure aggravated the insulin resistance produced during pregnancy • Associated with decreased glucose tolerance and increased plasma insulin, triglyceride, and leptin concentrations relative to controls	BPA exposure in adults is associated with a higher risk of type 2 diabetes and heart disease
[42]	BPA	Zebrafish embryo	600 µg/L	Diluted in a petri dish	96 hpf	• C3G abrogates BPA-induced neurobehavioral defects and histological impairment in the zebrafish brain • C3G alleviates cell apoptosis induced by BPA in zebrafish	BPA-induced developmental neurotoxicity through central nerve damage, oxidative stress, and apoptosis in zebrafish, while C3G could rescue the BPA-induced adverse effects
[43]	BPA	Zebrafish	At 1 µM	Dissolved in E3 media	5 dpf	• Prenatal exposure of zebrafish embryos to BPA induced serious oxidative damage and neuronal inflammation, thus leading to reduced cognitive functions	BCA played a beneficial role in reducing or improving neuronal oxidative damage and locomotor behavior caused by BPA
[44]	BPA	Mice	2, 10, 100 µg/kg/d	Via subcutaneous injection	At 3, 6, and 9 months	• Disrupted the equilibrium of kinase and protein phosphatase, essential for p-Tau regulation CDK5/GSK3β/PP2A axis may serve as a potential therapeutic target for BPA-induced neurodegenerative pathological alterations	Recent research has focused on how the brain's PP2A gets changed by different pathways (phosphorylation, methylation, and demethylation) after being exposed to BPA during pregnancy
[45]	BPA	Male mouse brain	50 µg/kg/d	Administered orally	8 weeks	• Perinatal BPA exposure suppressed PSD95 expression in the cerebral cortex and hippocampus of	Pregnancy-related anxiety is linked to lower synaptic density. In the

Authors	Type of bisphenol	Sample	Concentration/ Dosage	Exposure window	Duration of treatment	Endpoint / Findings	Remarks
						postnatal male mice. The absence of PSD95 led to diminished morphological alterations in spines, enhanced spine stability, and inhibited long-term potentiation (LTP) induction, resulting in memory impairment in rodents	brains of male mice after birth, synaptophysin expression and the ratio of excitatory PSD95 to inhibitory gephyrin synaptic protein decrease.
[46]	BPA	Zebrafish	0.5, 1, 2, 4, 8, 16, and 32 mg/L	Diluted in 24-well plates	96 hpf	• Higher levels of total oxysterols at 24 hours post-fertilization indicated a hyper-stimulated BPA-dependent accumulation of cholesterol and/or cholesterol oxidation products	The novel potential application of oxysterols, either individually or even better as a profile, as toxicological biomarkers
[47]	BPA, BPF, BPS	Rat dams and pups	150 µl	Dissolved in corn oil	21 days	• Prenatal bisphenol exposure had a greater impact on gene expression in pups than in dams • Altered genes related to estrogen response, parental care, and epigenetic gene regulation	Bisphenols had a greater effect on pups in terms of the number of differentially expressed genes, and the effects were brain region-specific
[48]	BPA	Zebrafish wild-type AB strain	1, 10, 100, 1000, or 10,000 nM	Diluted in the well plates	5 days	• 10,000 nM BPA also led to skeletal abnormalities associated with the suppression of neuron branching from the spinal cord and abnormal development of the neuromast cell • Short-term BPA exposures altered the greatest number of pathways and diseases	BPA at concentrations equal to or above 100 nM altered locomotive behavior and gene expression patterns that are linked to neurological diseases
[49]	BPA	Adult female Wistar rats and dams	25 µg/L to 2.5 mg/L	Through drinking water	21 days	• Prenatal BPA exposure increased anxiety-like behavior in male offspring • BPA exposure decreased exploratory behavior in both male and female offspring • BDNF and CYP19A1 expression were downregulated in males, whereas upregulated in females	The alteration in the expression of CYP19A1 and DNMT1 suggests that both hormonal and epigenetic dysregulation underlie the long-term BPA-induced effect on anxiety-like behavior in the offspring
[50]	BPA	Female and male ICR mice	35 µg/ml	Dissolved in culture media	2 days	Caffeine and BPA exposure cause harmful effects on the yolk sac placentas, including oxidative stress, apoptosis, hypoxia, and vasculogenic defects	Simultaneous exposure to caffeine and BPA dose-dependently elevated embryonic anomalies and aberrant embryonic cardiac development

Mechanistic studies expand on these findings by highlighting oxidative stress, neuroinflammation, and epigenetic modulation as key drivers of BPA-induced neuropathology. The findings revealed that maternal BPA exposure changed the shape and function of the developing fetus's brain. These alterations included altered neurotransmitter systems, poor synaptic plasticity, and aberrant neural network formation, all of which are important elements in the pathophysiology of AD [41]. It has been discovered that maternal BPA exposure

encourages the build-up of amyloid-beta plaques, a hallmark of AD, in the brains of the offspring. Protective interventions, such as cyanidin-3-O-glucoside (C3G) and Biochanin A (BCA), were shown to partially reverse BPA-induced axonal damage, oxidative injury, and inflammatory cascades, underscoring the potential for targeted antioxidant or anti-inflammatory strategies to mitigate risk. A study focused on the neurodevelopmental toxicity of BPA in zebrafish embryos and the potential protective effects of C3G. The findings revealed that BPA exposure impaired axon development and regeneration in larvae, whereas C3G supplementation mitigated the effects by modulating the transcription of key neurodevelopmental genes [42]. Similarly, research on the neuroprotective effects of BCA against BPA-induced prenatal neurotoxicity in zebrafish indicated that BPA exposure led to significant oxidative stress and neuronal inflammation, resulting in cognitive deficits [43].

Beyond neurodegeneration, maternal BPA exposure has systemic metabolic consequences that may indirectly influence AD susceptibility. Several studies documented impaired glucose tolerance, increased insulin resistance, and altered metabolic homeostasis in both mothers and adult offspring, with some effects persisting into midlife. Research on rat offspring prenatally exposed to BPA showed that it disrupted genes associated with Alzheimer's disease in the hippocampus, increased neuroinflammation, and altered the expression of genes involved in various regulatory networks. These findings suggest that maternal BPA exposure can predispose offspring to neurological disorders through epigenetic and inflammatory pathways [40]. In mice, a study exploring the long-term effects of prenatal BPA exposure found that it caused significant oxidative damage and neuronal inflammation, which persisted into adulthood. This exposure was associated with altered cognitive functions and increased risk of neurodegenerative diseases, such as tauopathies, through mechanisms involving the CDK5/GSK3β/PP2A axis [44]. Finally, studies on mice exposed to BPA during pregnancy indicated that it disrupted glucose homeostasis in both mothers and their adult male offspring. BPA exposure was linked to increased insulin resistance, impaired glucose tolerance, and altered metabolic parameters, highlighting its endocrine-disrupting effectshat can have lasting impacts across generations [41]. These pathways included hormonal changes, oxidative stress, and epigenetic modifications that could irreversibly affect gene expression and brain development and predispose progeny to AD later in life [45]. Overall, the research points to a link between maternal BPA exposure and a higher risk of AD in kids.

Collectively, these findings answer the central research question by providing strong preclinical evidence that maternal BPA exposure can prime offspring for AD-related neuropathology through a combination of direct neurodevelopmental toxicity, sustained inflammatory and oxidative stress responses, and metabolic dysregulation. However, limitations remain, most notably reliance on animal models that may not fully replicate human AD pathophysiology and variability in exposure timing, dose, and duration across studies. To address these gaps, future research should prioritize longitudinal human cohort studies that track maternal BPA exposure and offspring neurocognitive outcomes into adulthood, with rigorous control for confounding factors. Standardization of experimental protocols is essential to improve reproducibility, including harmonized dosing, exposure windows, and biomarker panels. Advanced in vitro models, such as human-induced pluripotent stem cell (hiPSC)-derived neural cultures and brain organoids, offer promising platforms to bridge the translational gap. Additionally, neuroprotective compounds such as cyanidin-3-O-glucoside and biochanin A, which have shown potential in mitigating BPA-induced neurotoxicity in

preclinical models, should be further evaluated in dose–response, pharmacokinetic, and safety studies to assess their feasibility for clinical translation.

3.4. Epidemiological studies of BPA contamination in humans.

Epidemiological evidence, as shown in Table 4, has consistently demonstrated that human exposure to BPA and its analogs is both widespread and persistent, with measurable concentrations detected in multiple biological matrices, including blood, breast milk, placental tissue, urine, and adipose tissue. Such ubiquity underscores BPA's capacity for systemic distribution and bioaccumulation. The primary exposure route in the general population appears to be oral ingestion, particularly via consumption of food and beverages stored in containers fabricated with BPA-containing epoxy resins and polycarbonate plastics. Environmental exposure also constitutes a significant pathway, facilitated by the leaching of BPA into water systems due to inadequate wastewater treatment. Owing to its physicochemical properties, namely, water solubility and pronounced estrogenic activity, BPA poses not only a direct human health risk but also an ecological hazard to aquatic organisms, creating an indirect route for human re-exposure via contaminated water sources [51].

Table 4. Summary of findings from epidemiological studies of BPA contamination in humans.

Authors	Type of bisphenol analogs	Subject	Exposure window	Endpoint / Findings	Remarks
[51]	BPA	100 pregnant women and newborn children	Prenatal exposure and environmental factors	• These metabolites were detectable in the urine of the women from the Generation R study, and compared with other groups, they had relatively high-level exposures to OP pesticides and several phthalates, but similar exposure to BPA	The first report on the biological monitoring of these compounds among the general population in the Netherlands
[52]	BPA	People aged 60 years and older	Environmental exposure	• Positive association between high levels of BPA and low cognitive performance on DRT, especially in males • The third quartile of BPA exposure showed a positive association with low cognition on IRT and global cognition	Association of phenols and parabens with cognitive function may differ between genders
[53]	BPA	Pregnant women between 18 and 40 years	Food and drinks	• Urinary BPA/BPF levels were associated with perturbations in biological pathways closely linked to inflammation, oxidative stress, and endocrine disruption • Chemical identity of 16 metabolites significantly associated with BPA or BPF exposure linked to stress responses, inflammation, neural development, reproduction, and weight regulation	Important to consider the compounding effects of these metabolic changes in mothers and children, in addition to the already disproportionate health burden faced by African American populations
[54]	BPA	146 mother-infant pairs	Prenatal exposure and environmental factors	• Maternal BPA exposure was associated with a global alteration of DNA methylation in the placenta • Maternal BPA exposure was associated with hypermethylation of HLA-DRB6	Interactions between prenatal BPA exposure, DNA methylation patterns in the placenta, and fetal health outcomes
[55]	BPA	Pregnant women have followed their children to 8 years of age	Prenatal exposure and environmental factors	• Most maternal BPA exposure effects on brain volumes were small, with the largest effects observed in the opercular region of the inferior frontal gyrus, superior occipital gyrus, and postcentral gyrus	Associations between prenatal maternal BPA exposure and brain volumes in children had small effect sizes ($\|\rho\|$ <0.3)

Authors	Type of bisphenol analogs	Subject	Exposure window	Endpoint / Findings	Remarks
				Small to medium effects of prenatal BPA exposure on brain volumes in children	

One notable study by Shi *et al*. explored the association between exposure to phenols and parabens, including BPA, and cognitive function in older adults in the United States [52]. The study utilized data from the 2011–2014 National Health and Nutrition Examination Survey (NHANES) involving 961 participants aged 60 or older. The findings indicated that BPA exposure could be linked to cognitive decline, potentially due to alterations in the hippocampus. The study suggested that BPA's lipophilic structure allows it to cross the blood-brain barrier, thereby disrupting the blood-brain and intestinal barriers, which could lead to cognitive impairment by decreasing the expression of memory-related proteins in the hippocampus [52]. Such barrier permeability also extends to the placenta, as evidenced by multiple studies demonstrating prenatal transfer, raising concerns about developmental neurotoxicity. These findings align with emerging mechanistic models suggesting that chronic, low-dose BPA exposure can contribute to neurodegenerative processes through oxidative stress, neuroinflammation, and synaptic disruption.

Furthermore, a study by Tchen *et al*. employed high-resolution metabolomics to assess biological disturbances associated withaternal exposure to BPA and Bisphenol F (BPF) among pregnant African American women [53]. The research highlighted several biological pathways and metabolites associated with BPA and BPF exposure, which are involved in stress responses, inflammation, neural development, reproduction, and weight regulation. Elevated levels of metabolites such as phenylalanine and N-acetyl-L-phenylalanine, which are associated with Alzheimer's disease, were identified, suggesting that dysregulated phenylalanine metabolism could be an important factor in the pathogenesis of such conditions [53]. There is a link between BPA exposure and metabolic diseases like diabetes, insulin resistance, and obesity. It is crucial to remember that additional study is required to identify a precise cause and comprehend the underlying mechanisms.

Besides that, Song *et al*. focused on the epigenetic effects of prenatal BPA exposure on the human placenta [54]. The study found that prenatal exposure to BPA was linked to altered DNA methylation at 282 CpGs mapping to 208 unique genes. Specifically, hypermethylation of the HLA-DRB6 gene was observed, which could influence both immunological and neurological development in offspring. These findings suggest that BPA, as a xenoestrogen, might affect gene expression through epigenetic modifications, potentially leading to long-term health effects [54]. The investigations indicated possible links between BPA exposure and unfavorable health outcomes, though the research is still in its early stages. Among them are conditions that affect reproduction, such as infertility, hormone abnormalities, and unfavorable pregnancy outcomes [53,54]. Clinical investigations have significantly raised public awareness of and prompted regulatory action about BPA. Many nations have imposed restrictions or outright bans on the use of BPA in specific products, especially those intended for newborns and young children [53]. Overall, clinical trial results show that BPA exposure is common and that there may be links between BPA exposure and unfavorable health outcomes. The connections between BPA exposure and metabolic and reproductive issues highlight the need for more study and public health initiatives to reduce BPA exposure and promote safer alternatives.

Collectively, the reviewed studies emphasize that BPA exposure is not only prevalent but also biologically active, exerting measurable effects on metabolic, neurodevelopmental, and epigenetic endpoints across diverse populations. The convergence of data linking BPA to cognitive decline, metabolic dysregulation, and reproductive impairments warrants intensified research efforts. Such investigations should aim to refine biomonitoring approaches, integrate multi-omics data for mechanistic insights, and evaluate intervention strategies. In parallel, public health policies should prioritize exposure reduction, particularly in vulnerable populations such as pregnant women, infants, and socioeconomically disadvantaged groups, to mitigate the potential long-term burden of BPA-associated diseases.

4. Conclusions

In summary, this review emphasizes the substantial and diverse influence of BPA on the development and progression of Alzheimer's disease. According to the synthesis of experimental and clinical evidence, BPA exposure disrupts critical neural pathways, exacerbates oxidative stress, and induces neuroinflammation. These effects contribute to the neuropathological hallmarks of AD, such as amyloid-beta accumulation and tau protein hyperphosphorylation. The results indicate that BPA impairs the insulin signaling pathway, resulting in cognitive deficits and insulin resistance. In addition, the neurodevelopment of offspring is profoundly and enduringly impacted by maternal BPA exposure, which implies a potential intergenerational transmission of the risk of Alzheimer's disease. These disruptions in neural development and function underscore the pervasive and insidious nature of BPA's neurotoxicity. To reduce the long-term risk of neurodegenerative diseases, public health policies should prioritize the reduction of BPA exposure, particularly among vulnerable populations such as pregnant women and young children.

However, despite these advances, important uncertainties remain. The precise molecular cascades by which BPA accelerates AD pathology are incompletely understood, particularly regarding dose–response relationships, low-dose chronic exposure effects, and potential synergistic interactions with other environmental neurotoxicants. Human epidemiological evidence remains limited in scope and is often confounded by mixed exposure sources, making it difficult to accurately quantify individual risk. Moreover, the long-term consequences of maternal exposure across multiple generations have yet to be systematically explored in human cohorts. Future research should prioritize longitudinal human studies with precise exposure assessment, multi-omics profiling to identify early biomarkers of BPA-related neurodegeneration, and mechanistic experiments to clarify critical signaling pathways. Policy and therapeutic implications include promoting BPA-free alternatives in consumer products, implementing stricter exposure limits, and developing early screening guidelines for high-risk populations, particularly pregnant women and young children. Investigating neuroprotective compounds or interventions that counteract BPA-induced oxidative stress and neuroinflammation could offer therapeutic potential. Ultimately, reducing BPA exposure through coordinated regulatory action, public awareness campaigns, and safer material innovations, combined with targeted biomedical research, will be essential to mitigate BPA’s role in AD and safeguard neurological health across generations.

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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