Review

Anti-Inflammatory and Neuroprotective Effects of *Undaria pinnatifida* Fucoidan

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Anti-Inflammatory and Neuroprotective Effects of *Undaria pinnatifida* Fucoidan

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Abstract

Undaria pinnatifida fucoidan (UPF), a sulphated polysaccharide derived from brown seaweed, has attracted increasing scientific interest for its wide-ranging anti-inflammatory and neuroprotective properties. Previous studies have demonstrated that UPF exerts significant anti-inflammatory effects through the downregulation of pro-inflammatory cytokines, inhibition of key signalling pathways such as NF-κB and MAPKs, suppression of oxidative stress, and modulation of immune mediators and gut microbiota. In parallel, emerging evidence highlights UPF's neuroprotective potential, characterised by reduced neuroinflammation, oxidative damage, and amyloid-beta accumulation, alongside enhanced antioxidant defence and neuronal function. Current investigations reinforce these findings, suggesting that UPF may serve as a valuable adjunct in managing inflammation-related disorders and neurodegenerative conditions. This review summarises the current knowledge on UPF's mechanisms of action, with a particular focus on its anti-inflammatory and neuroprotective pathways and implications for brain health, while also identifying gaps for future research and clinical translation.

Keywords: fucoidan; *Undaria pinnatifida*; anti-inflammatory agents; neuroprotective; oxidative stress; immune response

1. Introduction

Fucoidans are a class of highly sulphated polysaccharides which are abundantly present in the cell walls of brown algae, including *Undaria pinnatifida* [1]. These polysaccharides have attracted considerable scientific attention due to their diverse and potent biological activities in the treatment of inflammatory-related diseases [2], metabolic disorders [3], cardiovascular conditions [4], and several cancers [5–7]. The structure of common fucoidans typically consists of a backbone of L-fucose residues linked by α-(1→3) or alternating α-(1→3) and α-(1→4) glycosidic bonds, with varying degrees and patterns of sulfation (mainly at C2, C3, or C4), and may include minor sugars such as galactose, mannose, xylose, and uronic acids, resulting in highly branched and heterogeneous molecules [8]. Their structural diversity, shaped by factors such as seaweed species, degree and position of sulphation, molecular weight, and extraction methods, plays a crucial role in determining their bioactivity [9–12].

Among the various sources of fucoidan, recent research has increasingly focused on *Undaria pinnatifida* fucoidan (UPF), which has shown notable anti-inflammatory [13], antioxidant [14], immunomodulatory [15], antiviral [16], and neuroprotective effects [17] suggesting a significant potential in biomedical applications.

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This review focuses specifically on the anti-inflammatory and neuroprotective activities of UPF, highlighting the molecular mechanisms responsible for these biological effects. It also evaluates the therapeutic potential of UPF in the management of chronic inflammatory conditions and neurodegenerative diseases, offering insights that may guide future research and clinical applications.

2. Anti-inflammatory Activity of UPF

2.1. In Vitro Studies

Several *in vitro* studies have indicated that UPF effectively reduces the expression of key pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), Interleukin - 1 beta (IL-1β), and IL-6, to mitigate diverse inflammation-related responses. A recent investigation has shown that a 4-hour pre-treatment with UPF (10, 50, and 100 μg/ml) significantly suppressed lipopolysaccharide (LPS)-induced upregulation of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, in human macrophages and peripheral blood mononuclear cells (PBMCs) [18]. A low molecular weight UPF (100 μg/ml) also exhibited significant anti-inflammation effects by downregulating the gene expression of these pro-inflammatory cytokines in LPS-induced RAW264.7 cells [19]. Similarly, in a viral challenge model, UPF (200 μg/ml) reduced pro-inflammatory cytokines, including IL-6, IFN-α, interferon gamma (IFN-γ), and TNF-α, in SARS-CoV-2 infected Caco-2-N^{int} cells [16]. These effects are primarily mediated through inhibition of key inflammatory signalling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK), which are known to regulate cytokine gene transcription [20]. For example, treatment with UPF suppresses the nuclear translocation of NF-κB p65 and reduces the phosphorylation of p38 and extracellular signal-regulated kinases (ERK)1/2 MAPKs, leading to a marked decrease in pro-inflammatory cytokine expression [1,19,20]. Vaamonde-García et al. (2021) reported that UPF (5 μg/ml) treatment attenuated IL-1β-induced inflammation in osteoarthritic chondrocytes by blocking nuclear translocation of NF-κB and inhibiting its activation [21]. In addition, UPF inhibited NF-κB signalling and downregulated IL-6 and TNF-α in human colon carcinoma cell line (Caco-2) cells [22].

The suppression of oxidative stress represents a fundamental mechanism by which UPF alleviates inflammation. Oxidative stress, driven by excess reactive oxygen species (ROS), is a key initiator of inflammatory signalling cascades in various cell types [23]. In intestinal epithelial cell line (IEC-6) cells, UPF (100 μg/ml) significantly reduced oxidative damage induced by hydrogen peroxide (H_2O_2), as evidenced by decreased levels of malondialdehyde (MDA) and increased activity of antioxidant enzymes, including catalase (CAT), total superoxide dismutase (T-SOD), and glutathione (GSH) [24]. These changes were associated with protection against apoptosis and inhibition of pro-inflammatory responses, indicating that UPF enhances cellular antioxidant defences to maintain redox balance. Moreover, in RAW264.7 macrophages, low molecular weight UPF (100 μg/ml) inhibited LPS-induced ROS production and suppressed the phosphorylation of key MAPK signalling proteins (p38, ERK1/2, and JNK), leading to a significant reduction in the expression of inflammatory markers such as TNF-α, IL-6, and IL-1β [19]. Phull et al. (2017) found that UPF (15.52–500 μg/ml) exerted significant antioxidant activity in a dose-dependent manner in various *in vitro* antioxidant assays, including iron chelating, hydroxyl, nitric oxide, and DPPH activity, along with a reduction in inflammation responses in rabbit articular chondrocytes [25]. Another *in vitro* study also indicated that *Undaria pinnatifida* water extract (UPE) obtained by ultrasonication (200 and 400 μg/ml) significantly suppressed ROS production and restored H_2O_2-induced viability reduction in monkey kidney (Vero) cells in a dose-dependent manner. [26]. The cell-protective activity of the extract in this study was attributed to its capability to decrease pro-apoptotic protein (Bax) and increase anti-apoptotic protein (Bcl-2) [26].

Interestingly, there are an increasing number of studies correlating the antioxidant properties of UPF with its sulphate content and molecular weight [26–31]. For instance, UPF fractions with higher sulphation levels have been shown to exhibit significantly greater antioxidant activity compared to

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their lower-sulphated counterparts [29]. Moreover, fractionation studies revealed that low molecular weight UPF components possess enhanced antioxidant effects relative to high molecular weight forms, particularly in assays such as DPPH radical scavenging and ferric-reducing antioxidant power (FRAP) tests [30].

UPF inhibits major inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), nitric oxide (NO), and prostaglandin E2 (PGE2) whose overproduction exacerbates inflammatory responses and tissue damage [32,33]. For instance, low molecular weight UPF (100 μg/ml) alleviated LPS-induced inflammation in RAW264.7 cells by suppressing iNOS and COX2 activities [19]. Similarly, Song et al. in 2015 demonstrated that UPF (50 μg/ml) significantly inhibited iNOS and COX-2 expression, as well as attenuated the production of NO and PGE2 in LPS-stimulated RAW264.7 macrophages [34]. Lim et al. (2022) also reported that high molecular weight UPF (500 μg/ml) mitigated MG-11-induced inflammation in Caco-2 cells by suppressing protein expression of COX-2 and iNOS and inhibiting NF-κB activation [22]. Additionally, UPF exerted potent anti-inflammatory effects in rabbit articular chondrocytes, where UPF significantly reduced COX-2 expression in a dose (0–100 μg/ml, 24h) and time (30 μg/ml, 0–48 h) dependent manner [25]. Moreover, Vaamonde-García et al. found that UPF (5 μg/ml) significantly inhibited IL-1β-induced production of NO, PGE2, and IL-6 in osteoarthritic chondrocytes, suggesting an immunomodulatory role of UPF in inflammatory conditions [21].

Recent *in vitro* investigations have suggested that UPF is capable of suppressing chemokine secretion in various inflammatory cells. Chemokines, also known as chemotactic cytokines, are a family of small signalling proteins that significantly contribute to regulating the migration and activation of immune cells during inflammatory responses [1,35]. According to the structure of N-terminal cysteine residues, chemokines are classified into four major subfamilies, including CXXXC (fractalkine), C-X-C (IL-8), C-C (monocyte chemoattractant protein [MCP-1], or monocyte inflammatory protein [MIP-1α], and MIP-1β), and C chemokines (lymphotactin) [35]. Chen et al. (2025) demonstrated that sulphated *Undaria pinnatifida* polysaccharides (50 and 200 μg/ml) significantly reduced MCP-1 production *in vitro* during oxalate crystal-induced inflammation in renal cells [36]. This reduction was linked to decreased cellular inflammation and oxidative stress, indicating the potential role of UPF in modulating chemokine-driven immune cell recruitment [36]. Kim et al. also reported that UPF treatment (100 μg/ml) significantly suppressed MCP-1 expression in 3T3-L1 adipocytes, indicating that UPF inhibits inflammation-associated chemokine signalling during adipocyte differentiation [37]. In addition, Vaamonde-García et al. (2022) indicated that UPF (5 μg/ml) significantly downregulated IL-6 and IL-8 (CXCL8) in IL-1β-induced human chondrocyte cells [38]. Similarly, Wimmer et al. (2025) demonstrated that UPF significantly reduced the secretion of pro-inflammatory chemokines (IL-8 and MCP-1) and increased production of anti-inflammatory cytokines (IL-6 and IL-10) in the Caco-2/THP-1 co-culture system after microbial stimulation [39], indicating that UPF can suppress immune cell recruitment and inflammatory signalling at the gut mucosal level. Moreover, a study on atopic dermatitis found that UPF significantly inhibited the mRNA expression of several key chemokines, including thymus- and activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC), and RANTES (also known as CCL5), in TNF-α or IFN-γ-induced human epidermal keratinocytes [40].

The major outcomes derived from *in vitro* investigations into the anti-inflammatory effects of UPF are listed in **Table 1**.

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Table 1. *In vitro* anti-inflammatory activity of UPF.

Cell Line	Model	Compound	Tested Concentration	Effective Concentration	Activity	Reference
Murine RAW264.7 cells	LPS stimulation	Low molecular weight UPF	1, 10 and 100 μg/ml	1, 10 and 100 μg/ml	Reduced ROS, COX-2 and iNOS; suppressed phosphorylation of p38, ERK1/2, and JNK; and downregulated TNF-α, IL-6, and IL-1β	[19]
		UPF	12.5, 25, and 50 μg/ml	50 μg/ml	Inhibited COX-2 and iNOS, and attenuated production of NO and PGE2	[34]
Human osteoarthritic chondrocytes	IL-1β-induced inflammation	UPF	5, 30, and 100 μg/mL	5 μg/ml	Inhibited NF-κB activation; and reduced production of NO, PGE2, and IL-6	[21]
		UPF	1, 5, and 30 μg/mL	5 μg/ml	Downregulated IL-6 and IL-8 (CXCL8); upregulated Nrf-2, HO-1, and SOD-2.	[38]
THP-1 cells and PBMCs	LPS-induced inflammation	UPF	10, 50, 100, and 200 μg/ml	10, 50, and 100 μg/ml	Reduced expression of TNF-α, IL-1β, and IL-6	[18]
Caco-2-N^{int} cells	SARS-CoV-2 infection	UPF	0–1000 μg/ml	200 μg/ml	Reduced IL-6, IFN-α, IFN-γ, and TNF-α	[16]
Caco-2 cells	MG-H1-induced inflammation	High molecular weight UPF	0–1000 μg/ml	500 μg/ml	Inhibited NF-κB signalling; downregulated IL-6 and TNF-α; and suppressed COX-2 and iNOS expression	[22]

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Table 1. *Cont.*

Cell Line	Model	Compound	Tested Concentration	Effective Concentration	Activity	Reference
IEC-6 cells	H_2O_2-induced oxidative stress	UPF	10, 20, 50, and 100 μg/ml	100 μg/ml	Decreased levels of MDA, and increased CAT, T-SOD, and GSH	[24]
Rabbit articular chondrocytes	Antioxidant assays	UPF	0–500 μg/ml	2.5–100 μg/ml	Reduced COX-2; scavenged DPPH, nitric oxide and hydroxyl radicals; and exhibited iron chelating activity	[25]
Vero cells	H_2O_2-induced viability reduction	Water-ultrasonicated UPE	50, 100, 200, and 400 μg/ml	200 and 400 μg/ml	Suppressed ROS production; decreased Bax; and increased Bcl-2	[26]
Human renal cells	Oxalate crystal-induced inflammation	sulphated *Undaria pinnatifida* polysaccharides	50, 100, 150, 200, and 250 μg/ml	200 μg/ml	Reduced ROS and MCP-1 production; increased SOD content; and decreased secretion of TNF-α and IL-1β	[36]
3T3-L1 adipocytes	Adipogenesis	UPF	1, 10, and 100 μg/ml	100 μg/ml	Reduced production of ROS, SOD, and GPx; and downregulated expression of TNF-α, MCP-1 and PAI-1	[37]
Caco-2/THP-1 coculture	Microbial stimulation	UPF	2.5 g/l	2.5 g/l	Reduced secretion of IL-8 and MCP-1; decreased TNF-α; and increased IL-6 and IL-10	[39]
Human epidermal keratinocyte cell line	TNF-α or IFN-γ-induced inflammation	UPF	400 μg/mL	400 μg/mL	Inhibited expression of TARC, MDC, and RANTES (CCL5)	[40]

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2.2. In Vivo Studies

A substantial body of *in vivo* studies further supports the notion that UPF exerts its anti-inflammatory effects by suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [13,41–43]. Herath et al. (2020) reported that a 7-day oral administration of UPF (400 mg/kg/day) significantly attenuated particulate matter (PM) and ovalbumin (OVA)-induced IL-4, IL-17a, and IL-33 increase in lungs of a murine model of allergic airway inflammation [42]. In a later study, 27 days of UPF supplementation (400 mg/kg/day) significantly reduced TNF-α, IL-6, and IL-1β, and mitigated inflammation responses in the colon of dietary fibre deficiency (FD)-induced mice [24]. Similar effects of UPF were reported by Shi et al. (2024) in a Syrian hamster model of virus infection, where 6 days oral administration of UPF (200 mg/kg/day) alleviated SARS-CoV-2-induced lung and gastrointestinal tract injury by suppressing gene expression of TNF-α and IL-6 [16]. Lim et al. (2022) also indicated that 4 weeks oral administration of high molecular weight UPF (25 mg/kg/day) significantly inhibited MG-H1-caused TNF-α increase in mouse colon tissues [22]. Similarly, a 10-week oral administration of UPF (400 mg/kg/day) suppressed systemic inflammation in a high-fat diet (HFD)-induced obese mouse model [13]. The results of the study showed that UPF significantly reduced the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in skeletal muscle, small intestine, and hypothalamus [13].

The antioxidant properties of UPF have been well demonstrated in animal models of inflammatory-related disorders. In HFD-fed mice, a 10-week oral administration of sulphated polysaccharides from *Undaria pinnatifida* significantly (100, 300, and 500 mg/kg/day) reduced markers of oxidative stress, including MDA and SOD in liver tissues, alongside an inhibition of triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), and TNF-α production, suggesting that the suppression of oxidative stress contributed to hepatic lipid metabolism improvements, and mitigated HFD-induced inflammatory conditions [44]. Similarly, 7 days of UPF oral gavage (100 and 400 mg/kg/day) attenuated MDA in the serum and lungs of PM-induced allergic airway inflammatory mice [42]. Phull et al. (2017) also reported that 25 days UPF administration (150 mg/kg/day) significantly decreased arthritis-induced endogenous antioxidant enzymes such as CAT, peroxidase (POD), and SOD [25]. This reduction was mainly due to UPF capability to scavenge the free radicals, abrogate ROS-induced oxidative stress, and maintain the oxidative flux [25]. In contrast, Kang et al. found that 14 days UPF intraperitoneal administration (100 mg/kg/day) markedly prevented oxidative stress in carbon tetrachloride (CCL_4)-induced rats by increasing antioxidant enzymes (CAT, SOD, and glutathione peroxidase [GPx]), and decreasing markers of oxidative damage (MDA) in liver [45]. These results are in line with the findings of Zheng et al. (2023), where 27 days of UPF treatment (400 mg/kg/day) significantly elevated the levels of CAT and T-SOD, and attenuated myeloperoxidase (MOP) and MDA production in the colon tissues of FD-induced mice [24], suggesting that UPF exerts a protective effect against inflammation-associated oxidative damage by enhancing endogenous antioxidant defences and reducing lipid peroxidation, thereby contributing to the amelioration of oxidative stress in various inflammatory disease models.

Recent studies have also demonstrated that UPF exhibits strong antioxidant activities in an *in vivo* zebrafish model, a vertebrate species with notable biochemical and physiological similarities to mammals [31,46]. The findings suggest that UPF effectively mitigates oxidative stress induced by 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH) and H_2O_2, as evidenced by increased survival rates, reduced cellular apoptosis, decreased heart rate, and lower levels of ROS and lipid peroxidation [31,46].

UPF has been shown to ameliorate inflammatory responses by modulating gut microbiota composition. A bidirectional relationship exists between gut dysbiosis and host inflammation, whereby microbial imbalance promotes inflammatory processes, which in turn further disrupt the gut microbial ecosystem [47–50]. Recent studies have indicated that UPF treatment significantly attenuated intestinal inflammation by restoring microbial balance, notably decreasing *Firmicutes* and increasing *Bacteroidetes* in the gut of HFD-induced obese mice [44,51–54]. Comparable outcomes were

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observed in FD-induced inflammatory mouse models, where 27 days of oral UPF administration (300 and 400 mg/kg/day) led to a marked increase in *Bacteroidetes* and a reduction in *Firmicutes* within colon tissues [24,55]. As the dominant phyla in the gut, *Firmicutes* and *Bacteroidetes* play key roles in maintaining intestinal homeostasis [56], and imbalances in their ratio have been associated with various inflammatory disorders [57–60]. The anti-inflammatory effects of UPF may also derive from its prebiotic properties, as evidenced by reductions in pathogenic taxa (*Faecalibaculum*, *Desulfovibrionales*, *Proteobacteria*, and *Clostridia*) and enrichment of beneficial bacteria (*Akkermania muciniphila*, *Bacteroides*, *Bifidobacterium spp.*, and *Lactobacillus*) [52–54,61]. Additionally, Park et al. (2024) reported that 4 weeks of UPF supplementation (50, 100, and 200 mg/kg/day) significantly increased the abundance of *Papillibacter cinnamivorans*, a butyrate-producing bacterium, in immunosuppressed rats [62]. Butyrate, one of the short-chain fatty acids (SCFAs), mitigates inflammation by interacting with immune cells, promoting anti-inflammatory cytokines, and suppressing pro-inflammatory mediators through G-protein coupled receptors (GPR41/43) and inhibition of histone deacetylases (HDACs) [63,64]. Similarly, Zheng et al. (2023) have suggested that 27 days of UPF supplementation (400 mg/kg/day) significantly restored HFD-induced reduction in colonic SCFAs, including acetate, propionate, and butyrate [24], suggesting that UPF may exert its anti-inflammatory effects, at least in part, by restoring SCFA levels and modulating immune responses through established SCFA-mediated pathways.

UPF has been reported to attenuate immune cell infiltration, including macrophages and T cells, and to ameliorate inflammatory responses in allergic conditions. Herath et al. (2020) indicated that 7 days of UPF oral gavage (400 mg/kg/day) significantly reduced PM-exacerbated infiltration of inflammatory cells, such as $F4/80^+$ macrophages, $CD4^+$ T lymphocytes, $Gr\text{-}1^+$ granulocytes, and eosinophils, in the trachea and lungs of OVA-sensitised mice [42]. The results also showed that UPF decreased serum level of immunoglobulin E (Ige) and suppressed inflammatory provocation-induced increase in goblet cell hyperplasia and mucus secretion [42], suggesting potent therapeutic effects of UPF in allergic airway inflammation. Similarly, Yu et al. (2024) demonstrated that 16 days administration of ethanol-extracted UPE (50, 100, and 200 mg/kg/day) mitigated combined allergic rhinitis and asthma syndrome by inhibiting the accumulation of inflammatory cells, including epithelial cells, eosinophils, neutrophils, lymphocytes, and macrophages, in both nasal and bronchoalveolar lavage fluid, as well as a reduction in Th2 cytokines expression (IL-4, IL-5, and IL-13) [65].

The capability of UPF to re-establish immune homeostasis also plays a significant role in mitigating inflammatory conditions. Several *in vivo* studies have demonstrated that UPF exerts immunomodulatory effects by upregulating the expression of the anti-inflammatory cytokine IL-10 while concurrently downregulating the production of pro-inflammatory cytokines in various animal models of inflammatory intestinal diseases [44,53,55,66].

The main results of in *vivo* evaluations of UPF effects are listed in **Table 2**.

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Table 2. *In vivo* anti-inflammatory activity of UPF.

Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference
HFD-induced obesity	Male and female C57BL/6J mice	UPF	400 mg/kg/day	Oral supplementation for 10 weeks	Skeletal Muscle	Reduced TNF-α, IL-1β, and IL-6	[13]
					Small Intestine	Reduced TNF-α, IL-1β, IL-6, NF-Kb, Tjp1, GPR41, and GPR43	
					Plasma	Reduced IL-1α and IL-6	
	Male and female C57BL/6J mice	UPF	400 mg/kg/day	Oral supplementation for 10 weeks	Faeces	Increased abundance of *Bacteroidetes*, *Bacteroides/Prevotella*, *Akkermansia muciniphila*, and *Lactobacillus*; and reduced F/B ratio	[54]
	Male BALB/c mice	Sulphated polysaccharides from *Undaria pinnatifida*	150 and 300 mg/kg/day	Oral gavage for 10 weeks	Serum	Reduced levels of TC, TG, and LDL-c; increased HDL-c; suppressed FITC and LPS	[53]
					Liver	Increased expression of ABCG8, PPAR-γ, PGC-1α and CAT; reduced content of TC, TG, and MDA; and inhibited LPS production	
					Colon	Increased IL-10 expression; and reduced IL-6	
					Faeces	Increased abundance of *Bacteroidetes*, *Bacteroidaceae*, and *Prevotellaceae*; decreased *Firmicutes*, and *Proteobacteria*; increased levels acetate, propionate, and butyrate; and reduced F/B ratio	

Table 2. *Cont.*

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Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference
HFD-induced obesity	Male BALB/c mice	Sulphated polysaccharides from *Undaria pinnatifida*	100, 300, and 500 mg/kg/day	Oral gavage for 10 weeks	Serum	Reduced levels of TC, TG, LDL-c, LPS, and FITC; and increased HDL-c	[44]
					Liver	Suppressed levels of LDL-c and MDA; and increased SOD	
					Colon	Decreased TNF-α; and increased IL-10	
					Faeces	Increased *Bacteroidetes* abundance; reduced *Firmicutes*, *Desulfovibrionales*, and *Clostridia*; and increased levels acetate, propionate, and butyrate	
	Male C57BL/6J mice	*Undaria pinnatifida* powder	10% (w/w)	Oral supplementation for 10 weeks	Faeces	Increased acetic acid, propionic acid, and butyric acid; increased *Bacteroidetes*, *Bacteroidaceae*, and *Bacteroides*; and reduced *Firmicutes*, *Lachnospiraceae*, *Streptococcaceae*, *Marinifilaceae*	[52]
HFD-induced dyslipidaemia	Male BALB/c mice	UPF	50 and 100 mg/kg/day	Oral gavage for 8 weeks	Serum	Suppressed levels of TC and LDL-c	[51]
					Liver	Attenuated levels of TG and CHO	
					Faeces	Increased *Bacteroidetes*; and reduced *Firmicutes*	
l-NAME-induced hypertension	Male SD rats	UPF	20 and 100 mg/kg/day	Oral gavage for 4 weeks	Thoracic aorta	Increased phosphorylation of eNOS and Akt; and decreased levels of iNOS and NO	[41]
					Serum	Decreased levels of TNF-α and IL-1β	

Table 2. *Cont.*

Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference

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Particulate-matter-induced allergic airway inflammation	Female BALB/c mice	UPF	100 and 400 mg/kg/day	Oral gavage for 7 days	Lung	Suppressed MDA level; attenuated eosinophils, Gr-1+ cells, F4/80+ macrophage, and CD4+ T cell infiltration; and reduced IL-4, IL-17a, and IL-33	[42]
					Trachea	Attenuated eosinophils, Gr-1+ cells, F4/80+ macrophage, and CD4+ T cell infiltration	
					Serum	Inhibited MDA level; attenuated total IgE; and reduced IL-4	
Testosterone-induced BPH	Male SD rats	UPF	40 and 400 mg/kg/day	Oral administration for 4 weeks	Prostate	Reduced levels of testosterone and DHT; increased Bax; and reduced Bcl-2 expression	[43]
					Serum	Decreased levels of IL-1β, TNF-α, testosterone, DHT, and PSA	
Fiber deficiency-induced intestinal inflammation	Male BALB/c mice	UPF	100 and 400 mg/kg/day	Oral supplementation for 4 weeks	Colon	Increased levels of occludin, ZO-1, and claudin-3; reduced expression of TNF-α, IL-6, and IL-1β; increased IL-10; suppressed MDA, MOP, and LPS; promoted CAT and T-SOD; and increased production of acetate, propionate, and butyrate	[24]
	Male BALB/c mice	UPF	300 mg/kg/day	Oral gavage for 4 weeks	Colon	Reduced expression of TNF-α and IL-1β; elevated occludin and IL-10; increased levels of T-SOD and CAT; and decreased COX-2, iNOS, and LPS	[55]
					Faeces	Increased abundance of *Bacteroidetes* and *Bacteroidales*; and decreased *Firmicutes*, *Clostridiales*, and *Ruminococcaceae*	

Table 2. *Cont.*

Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference
		UPF			Lung	Downregulated ACE2, IL-6, and TNF-α	[16]

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SARS-CoV-2 infection	Female Syrian hamsters		100 and 200 mg/kg/day	Oral administration for 6 days	Colon	Reduced levels of ACE2, IL-6, and TNF-α	
					Faeces	Decreased *Firmicutes*, *Limosillactobacter*; increased *Bacteroidota*, *Patescibacteria*, *Allobaculum*, *Candidatus saccharimonas*, and *Ileibacteria*; and increased levels of acetate and propionate	
MG-H1-induced intestinal inflammation	Male ICR mice	High molecular weight UPF	25 and 75 mg/kg/day	Oral administration for 4 weeks	Colon	Inhibited MPO activity; and decreased expression of ZO-1, RAGE, and TNF-α	[22]
Carrageenan induced inflammation	Male SD rats	UPF	50 and 150 mg/kg/day	Oral gavage for 25 days	Serum	Decreased production of CAT, POD, and SOD	[25]
CCL4-induced oxidative stress	Female SD rats	UPF	100 mg/kg/day	Intraperitoneal injection for 2 weeks	Serum	Reduced levels of GOT, GPT, ALP, and LDH	[45]
					Liver	Decreased MDA production; and increased SOD, CAT, and GPx	
Broad-spectrum antibiotics (ABX)-induced tumour model	Male C57BL/6 mice	UPF	400 mg/kg/day	Oral gavage for 3 weeks	Tumour tissue	Reduced levels of $CD31^+$, Bcl2; increased Bax level and $CD8^+$ cells; and decreased $CD4^+$ cells and IDO1 expression	[61]
					Faeces	Increased abundance of *Akkermansia*, *Bifidobacterium*, and *Lactobacillus*	

Table 2. *Cont.*

Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference

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Cyclophosphamide-induced immunosuppression	Male SD rats	High molecular weight UPF	50, 100, and 200 mg/kg/day	Oral administration for 4 weeks	Faeces	Increased abundance of *Papillibacter cinnamivorans* and *Desulfomicrobium orale*; and reduced *Marvinbryantia formatexigens*	[62]
Ovalbumin-induced CARAS	Male BALB/c mice	Ethanol-extracted UPE	50, 100, and 200 mg/kg/day	Oral administration for 16 days	Serum	Attenuated IgE and IgG1 levels; and increased IgG2a	[65]
					Nasal lavage fluid	Increased expression of IFN-γ, SOD, and HO-1; reduced IL-4, IL-5, IL-13, and MDA; and enhanced ZO-1 and occludin	
					Bronchoalveolar lavage fluid	Decreased levels of IL-4, IL-5, IL-13, and MDA; and increased HO-1 and occludin production	
					Lung	Increased expression of occludin and ZO-1	
Salmonella typhimurium-induced inflammation	Male BALB/c mice	UPF	200 and 500 mg/kg/day	Oral administration for 21 days	Colon	Increased expression of occludin and claudin-1; reduced TNF-α, IKBα, p-IKBα, p65, and p-p65; elevated levels of CAT and SOD; and decreased MDA and iNOS	[66]
					Faeces	Reduced abundance of *Proteobacteria*, *Colidextribacter*, and *Oscillibacter*; increased *Parabacteroides*, *Lactobacillus*, *Akkermansia*, *Lachnospiraceae*_NK4A136 group and *Muribaculum*; and enhanced levels of acetate and butyrate	

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2.3. Clinical Trials

A growing body of clinical evidence supports the therapeutic potential of UPF in modulating metabolic, immune, and inflammatory responses in humans. Various human studies have demonstrated that incorporating *Undaria pinnatifida* (4–6 g/day) into diets help improve metabolic parameters, including suppressed postprandial glycaemia, modulated appetite sensations, reduced waist circumference and blood pressure, as well as a decrease in total cholesterol, LDL-cholesterol, and resistin levels [67–70]. *Undaria pinnatifida* also exerts potent immunostimulatory properties to manage Herpes infections by promoting healing and preventing reactivation [71]. Moreover, a clinical trial showed that a single dose of UPF (1 g) modulated microRNA expression related to immune response and inflammation, highlighting its systemic regulatory potential [72]. Additionally, a combination of UPF and *Fucus vesiculosus* fucoidan significantly increased faecal lysozyme levels, a protein known for its antimicrobial and anti-inflammatory functions, suggesting that UPF may promote mucosal barrier integrity and reduce mucosal inflammation [73]. Cox et al. (2023) reported that 3 weeks of UPF supplementation (1 g/day) significantly increased salivary immunoglobulin (Ig) A contents after an intensified training, indicating UPF properties to enhance mucosal immunity and provide protective anti-inflammatory benefits [74,75]. In a double-blind randomised placebo-controlled clinical trial, 2 weeks of UPF administration (1 g/day) significantly suppressed the upregulation of inflammatory cytokines induced by high-intensity exercise [76]. Similarly, UPF combined with green-lipped mussel mitigated joint pain and prediabetes in a randomised, double-blinded clinical setting, demonstrating that UPF elicits antioxidant and anti-inflammatory effects [77].

3. Neuroprotective Effect of UPF

Scientific literature has reported an increasing number of studies highlighting the neuroprotective effects of UPF in promoting brain health and mitigating the progression of neurodegenerative diseases such as Alzheimer's (AD). These effects arise from a multifactorial interplay involving anti-inflammatory [13], anti-apoptotic [78], antiviral [17], and antioxidant activities [79] of UPF. Findings from both *in vitro* and *in vivo* investigations demonstrate that UPF can attenuate neuronal apoptosis, inhibit amyloid-β (Aβ) aggregation, and suppress the activation of microglia and astrocytes by reducing oxidative stress and neuroinflammation across various experimental models of neurodegenerative conditions [13,17].

3.1. In Vitro Studies

Several *in vitro* studies demonstrated that UPF is capable of suppressing inflammation in neurodegenerative conditions, primarily through inhibition of the NF-κB signalling pathway and modulation of the Akt/mTOR and AMPK/mTOR pathways. Notably, Giuliani et al. (2025) reported that UPF (100 μg/ml) significantly attenuated herpes simplex virus type I (HSV-1)-induced AD-like pathology. This included a reduction in amyloid precursor protein (APP) production and Aβ synthesis, alongside inhibiting NF-κB pathway activation and reducing IL-6 expression [17]. Ethanol-extracted UPE (5 μg/ml) also has been suggested to reduce endoplasmic reticulum (ER) stress and increase cell viability in hypothalamic neurons via Akt/mTOR signalling, highlighting its anti-inflammatory and neuroprotective potential [80]. ER stress is closely linked to the activation of inflammatory responses and is increasingly recognised as a contributing factor in the pathogenesis of various neurodegenerative diseases [81]. Additionally, Chen et al. (2025) suggested that low molecular weight UPF (0.125 mg/ml) significantly ameliorated LPS-induced macrophage inflammatory state by promoting its polarisation from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype through the AMPK/mTOR pathway [82]. Literature has indicated that modulating the AMPK/mTOR pathway regulates microglia polarisation and reduces neuroinflammation [83].

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UPF has also been shown to exert neuroprotective effects in various *in vitro* cell models of neurodegeneration by enhancing cell viability and attenuating cytotoxicity, particularly in response to neurotoxic insults such as Aβ and oxidative stress [17,78,79,84–86]. For instance, Wei et al. (2017) demonstrated that pre-treatment with UPF (100, 200, 400 μg/ml) for 24 hours protected PC12 cells from apoptosis induced by $A\beta_{25-35}$ and d-galactose (D-Gal), alongside elevated levels of SOD and GSH [79]. Similar effects were observed in a rat cholinergic basal forebrain neuron model of AD conditions, where treatment of a commercial UPF (1 μM) inhibited cellular and neurotoxic effects of $A\beta_{1-42}$ and suppressed ROS production [84]. In addition, UPF demonstrated strong free radical-scavenging activity, effectively inhibiting DPPH and hydroxyl radicals, and reducing ROS production as well as Aβ synthesis in HSV-1-infected retinal pigment epithelium (RPE) cells [17]. HSV-1 infection and Aβ synthesis have been associated with the development of AD [87]. Mohibbullah et al. (2018) also reported that ethanol-extracted UPE (15 μg/ml) enhanced cell viability and reduced cytotoxicity in hippocampal neurons by decreasing ROS generation, membrane phosphatidylserine exposure, genomic DNA degradation, and restoring hypoxia-induced mitochondrial depolarization [86]. Notably, although both fucoidans reduced $A\beta_{1-42}$-induced oxidative stress and apoptosis levels, UPF exhibited stronger neuroprotective effects than *Fucus vesiculosus* fucoidan, likely due to its distinct structural features such as higher sulphate content and specific molecular weight distribution [78].

The key *in vitro* outcomes regarding the neuroprotective activity of UPF are comprehensively outlined in **Table 3**.

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Table 3. *In vitro* neuroprotective activity of UPF.

Cell Line	Model	Compound	Tested Concentration	Effective Concentration	Activity	Reference
Human RPE cell line	HSV-1-induced Aβ production	HCl-extracted UPF	100 μg/ml	100 μg/ml	Inhibited NF-κB phosphorylation, IL-6 expression, and $A\beta_{42}$ synthesis; and reduced DPPH scavenging and ROS production	[17]
Rat PC-12 cells	Aβ-induced neurotoxicity	UPF	3.125–100 μg/ml	3.125–100 μg/ml	Increased cell viability; reduced $A\beta_{1-42}$ aggregation and cell apoptosis; and enhanced neurite outgrowth	[78]
PC12 cells	Aβ25–35 and d-Gal-induced neurotoxicity	Water-extracted UPF	100, 200, and 400 μg/ml	100, 200, and 400 μg/ml	Improved cell viability; prevented cell apoptosis; reduced levels of cleaved caspase-3, caspase-8, caspase-9, and cytochrome c; increased livin and X-linked apoptosis inhibitor protein expression; and elevated levels of SOD and GSH	[79]
Hypothalamic neurons (GT1-7 cells)	Tunicamycin-induced ER stress	Ethanol-extracted UPE	5–40 μg/ml	5 μg/ml	Increased cell viability; reduced expression of CHOP and ATF-6; decreased levels of cleaved-PARP and cleaved-caspase-3; and modulated AKT/mTOR signalling	[80]
BMDMs	LPS-induced macrophage inflammation	Low molecular weight UPF	0.0625, 0.125, 0.25, 0.5 mg/ml	0.125 mg/ml	Reduced $CD86^+$ proportion; increased $CD206^+$ proportion; regulated AMPK/mTOR pathway	[82]
Rat basal forebrain cholinergic neurons	Aβ-induced neurotoxicity	UPF	50 nM –1 μM	1 μM	Improved neuronal survival; inhibited ROS generation and PKC phosphorylation; and blocked cleavage of caspases 9 and 3	[84]
Rat hippocampal neurons	Hypoxia-mediated oxidative injury	Ethanol-extracted UPE	5, 15, 30 μg/ml	15 μg/ml	Reduced ROS formation; increased cell viability; and decreased cytotoxicity	[86]

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3.2. In Vivo Studies

UPF has emerged as a promising neuroprotective agent due to its ability to attenuate neuroinflammation. For example, 10 weeks of UPF oral administration (400 mg/kg/day) significantly attenuated HFD-induced neuroinflammation in obese mice by downregulating the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IFN-γ) in hypothalamic tissues and suppressing the production of inflammation-related proteins (leucine-rich repeat serine/threonine-protein kinase 2 [Lrrk2], wolframin [Wfs1], and neuroglobin [Ngb]) in the nucleus accumbens [13]. Hu et al. (2014) also reported that a 10-day intrathecal injection of commercial UPF (15, 50, and 100 mg/kg/day) mitigated rat neuropathic pain induced by L5 spinal nerve ligation (SNL). The findings suggested that UPF inhibited microglia and astrocyte activation in the lumbar spinal cord and reduced TNF-α, IL-1β, and IL-6 expression in the spinal dorsal horn [88]. Similarly, Che et al. (2017) demonstrated that intraperitoneal injection of commercial UPF (80 and 160 mg/kg/day) for 7 days significantly ameliorated cerebral ischemia-reperfusion injury (IRI)-caused neurological impairment in rats and significantly decreased the levels of pro-inflammatory cytokines, including IL-1β, IL-6, MPO, and TNF-α [89].

Several *in vivo* studies have highlighted the effects of UPF in neuroprotection and rehabilitation, demonstrating its beneficial properties in inhibiting oxidative stress and attenuation neurotoxic protein aggregation. Specifically, 21 days of oral administration of UPF (50, 100, and 200 mg/kg/day) improved learning and memory impairments in AD-model mice induced by D-Gal, where UPF exhibited potent antioxidant effects, enhancing SOD and GSH activity [79]. The ability of UPF to promote learning and memory in this study is largely attributed to its enhancement of acetylcholine (ACh) content and choline acetyl transferase (ChAT) enzyme activity, along with the inhibition of acetylcholine esterase (AChE) enzyme activity, which are key factors involved in the cognitive dysfunction characteristic of AD [79]. UPF also has been reported to reduce oxidative stress-related proteins (SOD and MDA), suppress pro-apoptotic proteins (p-p53 and Bax), and elevate anti-apoptotic protein (Bcl-2) in IRI-induced rats by inhibiting MAPK pathway [89]. Similarly, Wang et al. (2016) illustrated that intraperitoneal pre-treatment of low molecular weight commercial UPF (50 mg/kg) significantly suppressed neuronal damage and neurological deficits in aged mice after traumatic brain injury (TBI), where UPF exerted these protective effects by inhibiting oxidative stress (reduced MDA, 4-hydroxynonenal [4-HNE], ROS and increased CAT, SOD, GPx) and mitochondrial dysfunction (suppressed cytochrome c release) [90]. In addition, the neuroprotective effects of UPF have been found in an invertebrate model of AD, where UPF (500 ng/ml) alleviated Aβ-induced paralysis by decreasing Aβ deposition and ROS production in transgenic Caenorhabditis elegans [91]. Taken together, these findings suggest that UPF confers neuroprotection across diverse experimental models by modulating oxidative stress, mitochondrial integrity, and apoptosis-related pathways, supporting its potential as a therapeutic agent in the prevention and treatment of neurodegenerative disorders (**Table 4**).

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Table 4. *In vivo* neuroprotective activity of UPF.

Model	Animal	Compound	Dose	Treatment	Tissue	Result	Reference
HFD-induced obesity	Male and female C57BL/6J mice	UPF	400 mg/kg/day	Oral supplementation for 10 weeks	Hypothalamus	Reduced TNF-α, IL-1β, IL-6, and IFN-γ	[13]
					Nucleus accumbens	Suppressed Lrrk2, Wfs1, and Ngb	
SNL-induced neuropathic pain	Male SPF SD rats	UPF	15, 50, and 100 mg/kg/day	Intrathecal injection for 10 days	Lumbar spinal cord	Inhibited microglia and astrocyte activation; and reduced expression of GFAP and mac-1	[88]
					Spinal dorsal horn	Downregulated expression of TNF-α, IL-1β, and IL-6; and attenuated phosphorylation of ERK	
IRI-caused neurological impairment	Male SD rats	UPF	80 and 160 mg/kg/day	Intraperitoneal injection for 7 days	Ischemic brain	Reduced levels of TNF-α, IL-1β, IL-6, MPO, SOD, MDA, p-p53, p-p38, p-ERK, p-JNK, and Bax; and increased Bcl-2	[89]
D-Gal-induced AD model	Male ICR mice	UPF	50, 100, and 200 mg/kg/day	Oral administration for 21 days	Brain	Increased levels of Ach, ChAT, and GSH; reduced AChE activity; and decreased Aβ deposition	[79]
					Serum	Increased levels of SOD and GSH	
Controlled cortical impact-induced TBI	Male C57BL/6 mice	Low molecular weight UPF	10 and 50 mg/kg	Intraperitoneal injection	Brain	Decreased brain edema and cell apoptosis; reduced generation of MDA, 4-HNE, and ROS; increased levels of CAT, SOD, and GPx; suppressed cytochrome c release; and upregulated Sirt3 expression	[90]
Aβ-induced AD model	Caenorhabditis elegans	UPF	50–500 ng/ml	Bath immersion method	Entire organism	Decreased Aβ deposition, aggregation, and fibrillization; increased expression of pbs-2 and pbs-5; and reduced ROS production	[91]

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4. Conclusions

In summary, *Undaria pinnatifida* fucoidan (UPF) exhibits robust anti-inflammatory and neuroprotective properties, as demonstrated by both *in vitro* and *in vivo* studies. UPF exerts its anti-inflammatory effects through the suppression of pro-inflammatory cytokines, inhibition of key signalling pathways (NF-κB, MAPKs), reduction of oxidative stress, and modulation of immune responses, including chemokine expression and gut microbiota composition. Its neuroprotective potential is similarly multifaceted, involving attenuation of neuroinflammation, oxidative damage, and amyloidogenic processes, alongside enhancement of antioxidant defences and neuronal function. Despite these promising findings, the molecular mechanisms underlying UPF's actions remain incompletely understood, and its therapeutic effects in humans have yet to be fully confirmed. Future studies should prioritise detailed mechanistic investigations, standardisation of UPF extraction and characterisation, and the development of targeted delivery systems to enhance its bioavailability. Most critically, well-designed clinical trials are essential to validate UPF's efficacy and safety, and to support its integration into evidence-based therapeutic strategies.

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