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Targeting Neurotrophin Regulation by Polyphenols: Mechanistic Basis for Cognitive Resilience

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INTRODUCTION

- **Neurotrophins (NTs)** regulate neuronal survival, synaptic plasticity, and cognitive function across the lifespan.
- **Brain-derived neurotrophic factor (BDNF)** dynamically regulates **long-term potentiation (LTP),** dendritic spine growth, and receptor trafficking, particularly via the **N-methyl-D-aspartate** receptors.
- **BDNF** supports function in the adult hippocampal and parahippocampal regions, underlying memory encoding and storage.
- **BDNF** binding to **tropomyosin receptor kinase B (TrkB)** is a central to regulating synaptic and structural plasticity within **the central nervous system** and is strongly associated with broader **cognitive function (CF).**
- Polyphenols may potentiate endogenous **BDNF/TrkB signaling** by acting as receptor antagonists or by enhancing **BDNF/nerve growth factor (NGF)** expression via the gut–brain axis.
- This activiation engages downstream phosphatidylinositol 3-kinase/protein kinase B **(PI3K/Akt),** mitogen-activated protein kinase/extracellular signal-regulated kinase **(MAPK/ERK),** and phospholipase C gamma **(PLCγ)** signalling pathways, which support neurite outgrowth.
- Impaired **BDNF/TrkB** signalling is a common abnormality associated with cognitive decline/dementia onset in normal ageing and age-related diseases (**Figure 1**).

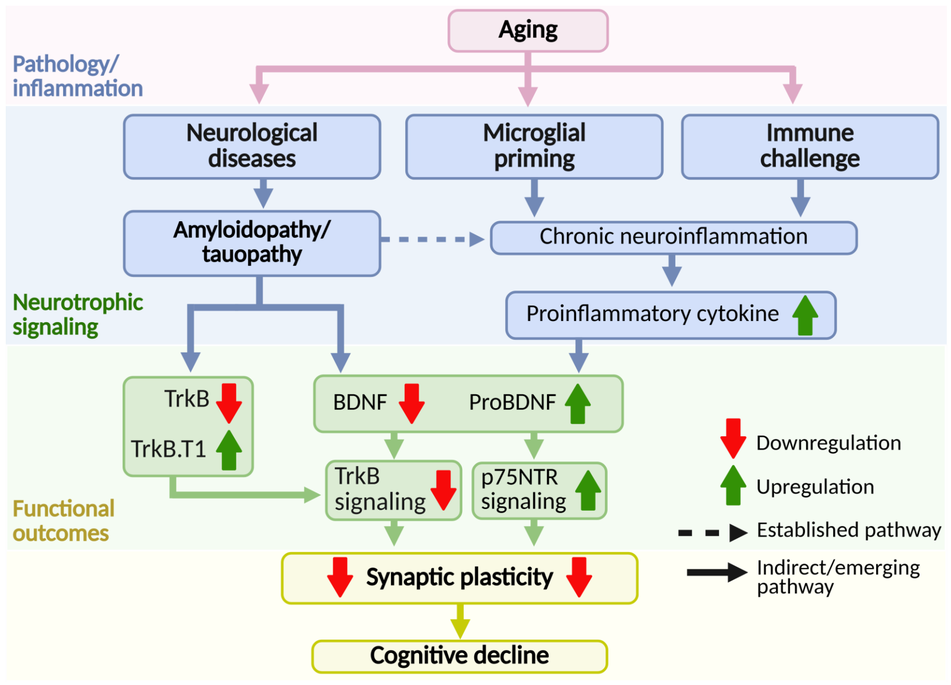

Figure 1: Diagram of the effects on cognitive dysfunction of BDNF signaling disturbance. **Abbreviations:** ProBDNF, precursor brain-derived neurotrophic factor;p75NTR, p75 neurotrophin receptor;TrkB.T1, truncated tropomyosin receptor kinase B isoform;CNS, central nervous system. Created in https://BioRender.com

AIM and METHODOLOGY

- **Design:** Focus on **mechanistic** links between dietary **polyphenols** and **NTs** signaling.
- **Selection criteria:** Preclinical and observational studies reporting reporting molecular, synaptic, or cognitive outcomes.
- **Focus: BDNF**–related pathways, **oxidative stress**, **neuroinflammation**, and **plasticity**.

RESULTS

Research indicates a positive association between **polyphenol-related cognitive performance enhancements** and increased **BDNF** expression and/or protein levels, though causality and mechanistic details remain to be fully elucidated. Polyphenols impact on cerebral flow by:

1) Improving cerebrovascular function;
2) Modulating multidrug-resistant protein-dependent influx and efflux mechanisms;
3) Targeting neuronal and glial activities directly.

Moreover, these natural compounds can support **neurocognitive** health by **upregulating NTs (BDNF** and **NGF)** and stabilizing the inflammatory-redox milieu indispensable for neuroplasticity. Mechanisms include **cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)** and **Trk signaling, nuclear factor erythroid 2-related factor 2 (Nrf2)-driven** antioxidant defenses, **nuclear factor kappa-B (NF-κB)** inhibition**, and epigenetic modulation.**

Animal models and observational human studies suggest significant, though variable, neurocognitive benefits, especially when synergized with exercise and diet patterns. **Optimal doses, lengths of administration, metabolism,** and **targeted polyphenol subclasses for cognitive benefits remain unspecified,** with **suboptimal bioavailability** being a **critical limiting factor. Table 1** compile trials using polyphenols to enhance **CF**. The specific mechanisms underlying the **NT regulation by polyphenols** depend on the specific class of polyphenol **(Figure 2).**

Table 1: Compilation of studies using polyphenols to enhance cognitive function.

Food/ bioactive	Neurotrophic factor	Evidence level	Dosage (mg/day)	Time (wk)	Effect size	Quantitative out-come	Test methods
Resvera-trol	Hippocampal FC (rs-fMRI proxy of BDNF signaling)	*N = 36* obese males, RDBPC	200 + 320 quercetin	26	Medium	AVLT retention ↑, ↑ HC–mPFC FC	AVLT, 3T rs-fMRI
***M. offici-nalis* rich in RA**	Indirect synaptic protection	*N = 23* mild dementia patiens, RDBPC	500	24	Small	NPI-Q improved by 0.5 compared to a 0.7-point decline for placebo	NPI-Q and clinical and neurological as-sessment
Curcumin	Hippocampal BDNF, Wnt/β-catenin ↑	Preclinical (AD mice)	~100	2	Strong	↑ BrdU+/DCX+, ↑ BrdU+/NeuN+, ↑ hippocampal BDNF,	Aβ1–42 i.c.v. mice, IF (BrdU/DCX/NeuN)
GCG	BDNF (hippo-campus, BDNF-TrkB pathway)	Female rats (6-week-old, 140–160g)	200–400	4	Strong	↑ silent synapses (~30% vs ~4%), im-proved spatial memory	Western blot, qPCR, LTP, MWM, serum 17β-Estradiol ELISA assay

Abbreviations: MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; ELISA, enzyme-linked immunosorbent assay; IF, immunofluorescence; qPCR, quantitative polymerase chain reaction; AVLT, Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; NPI-Q, Neuropsychiatric Inventory Questionnaire; HC, hippocampus; mPFC, medial prefrontal cortex; i.c.v., intracerebroventricular; DEXA, dual-energy X-ray absorptiometry; MWM, Morris water maze.

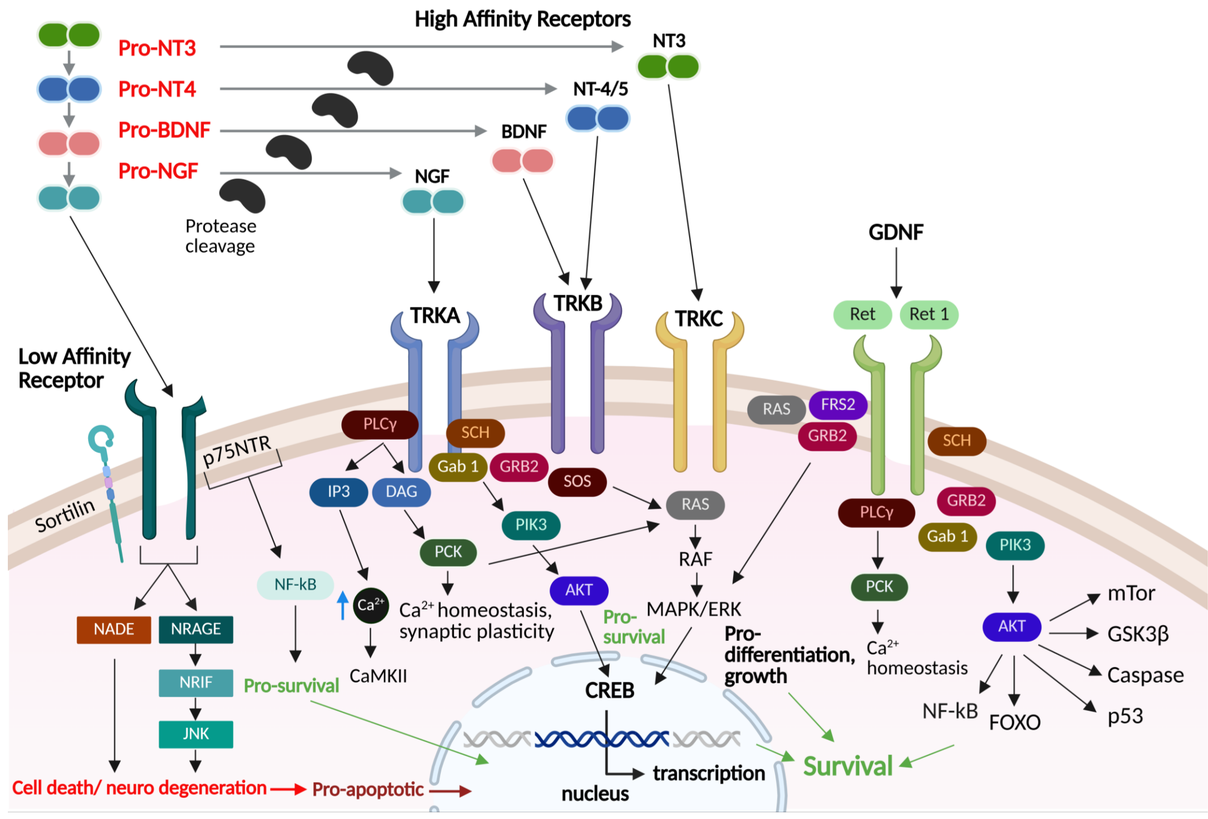

Figure 2: NTs-signaling pathway diagram. **Abbreviations:** TrkA, tropomyosin receptor kinase A; TrkC, tropomyosin receptor kinase C; ProNGF, precursor nerve growth factor; ProNT3, precursor neurotrophin-3; ProNT4, precursor neurotrophin-4; NT3, neurotrophin-3; NT4, neurotrophin-4; GDNF, glial cell line-derived neurotrophic factor; GFRα, GDNF family receptor alpha; Ras, rat sarcoma small GTPase; Raf, rapidly accelerated fibrosarcoma kinase; MEK, MAPK/ERK kinase; mTOR, mechanistic target of rapamycin; GSK3β, glycogen synthase kinase-3 beta; FOXO, forkhead box O transcription factor; BAD, Bcl-2-associated agonist of cell death; Ca^{2+}, calcium ion. Adapted from Witte et al., (2014). Created in https://BioRender.com

Figure 3 consolidates the described pathways and evidence linking dietary polyphenols to **BDNF /TrkB signalling** and **cognitive function.**

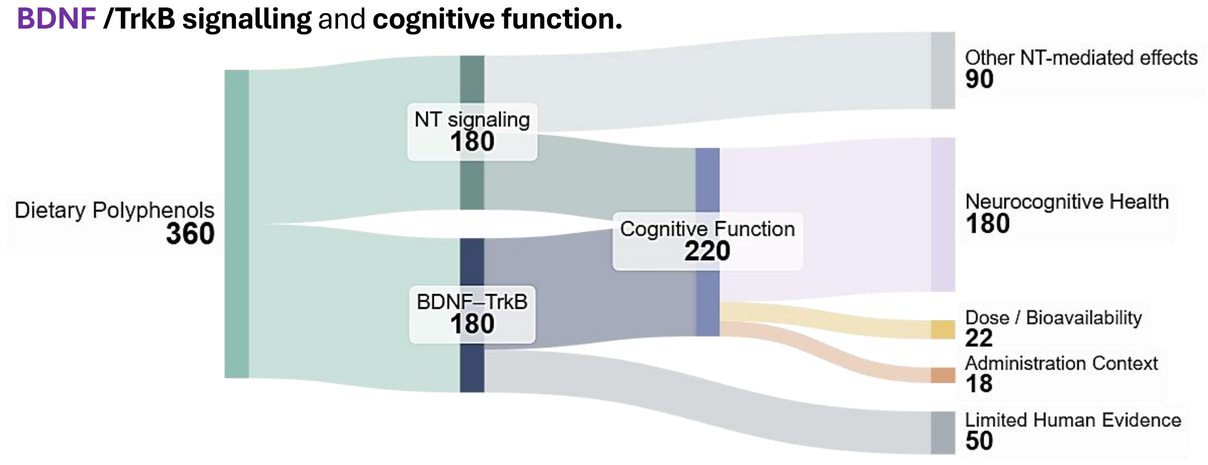

Figure 3: Conceptual framework linking dietary polyphenols, NTs signaling, and neurocognitive health. *Values represent relative conceptual weights and do not correspond to quantitative measurements.* Created with SankeyMATIC: Build a Sankey Diagram

CONCLUSION

Overall, the regular intake of polyphenols has positive effects **on brain plasticity and improves related cognition.** Lack of high-quality human studies and context-dependent effects **(e.g. dosage and bioavailability)** impede translation to **clinical** applications**.**

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