Improvement on Alzheimer's Disease and β-Amyloid-Induced Toxicity by Black Raspberry

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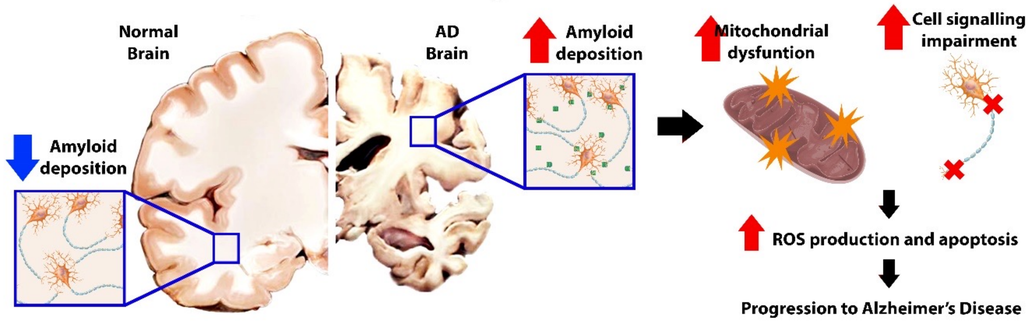
Abstract

Alzheimer's Disease (AD) have become a public health concern due to its high prevalence. The beginning and progression of this disease is still remained unknown and nowadays the medication and treatment for AD only give a minimal effect. According to this problem, another approach is rising to reduce the incidence of AD by supplementation of natural product in daily diet. Black raspberry (BR) is one of the commodities rich in polyphenols which have potential as neuroprotective agent against AD. The aim of this study is to understand the effect of BR to alter the toxicity of Amyloid- β (Aβ) toxicity in HT-22 cell model and improvement of subject with mild cognitive impairment after supplementation with BR. Sample used in this study is BR crude extract, water, ethanol, and acetone fraction. Parameter assessed in the cell study were cytotoxicity assay, neuroprotection against Aβ, apoptosis marker quantification, quantification of ROS production and mitochondrial membrane potential assessment and for pilot study is change in clinical dementia rating (CDR) value, inflammatory marker and antioxidant status of the subject. Result obtained from this study showed that BR supplementation significantly protects the cell from Aβ toxicity, reduce apoptosis and ROS production in HT-22 cell line. Result from human study also shows that BR supplementation significantly reduce CDR value and inflammatory markers and improve the antioxidant status compared to placebo group. In conclusion, BR can reduce the Aβ toxicity and improve cognitive function of subject with mild cognitive impairment.

Keywords: Black raspberry, amyloid-β, mild cognitive impairment.

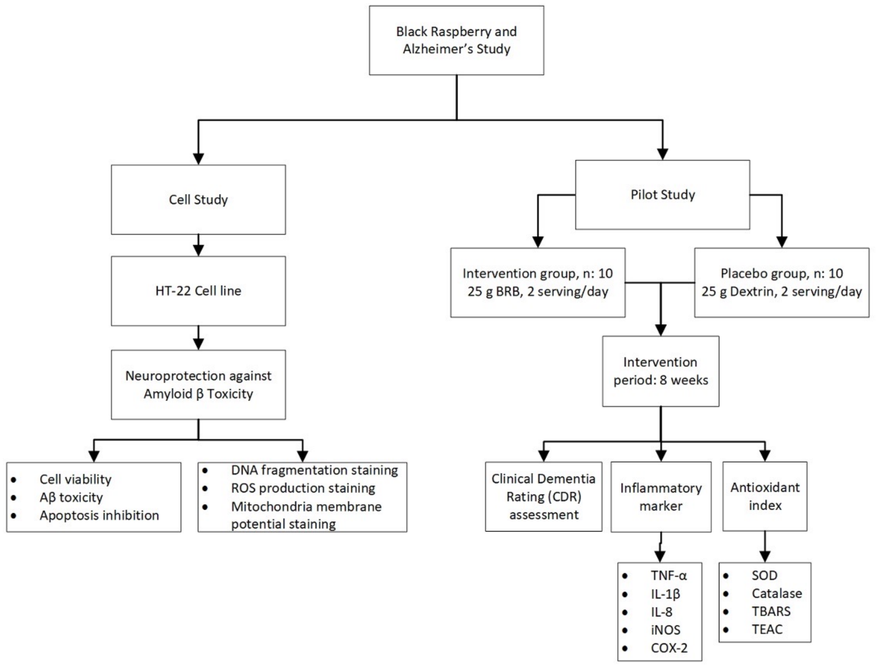
Background



Aim

To assess the effect of black raspberry treatment on β-amyloid-induced toxicity in HT-22 cell line and improvement of CDR value, inflammtory markers and antioxidant indexes of Alzheimer's Disease subject

Study design



Result

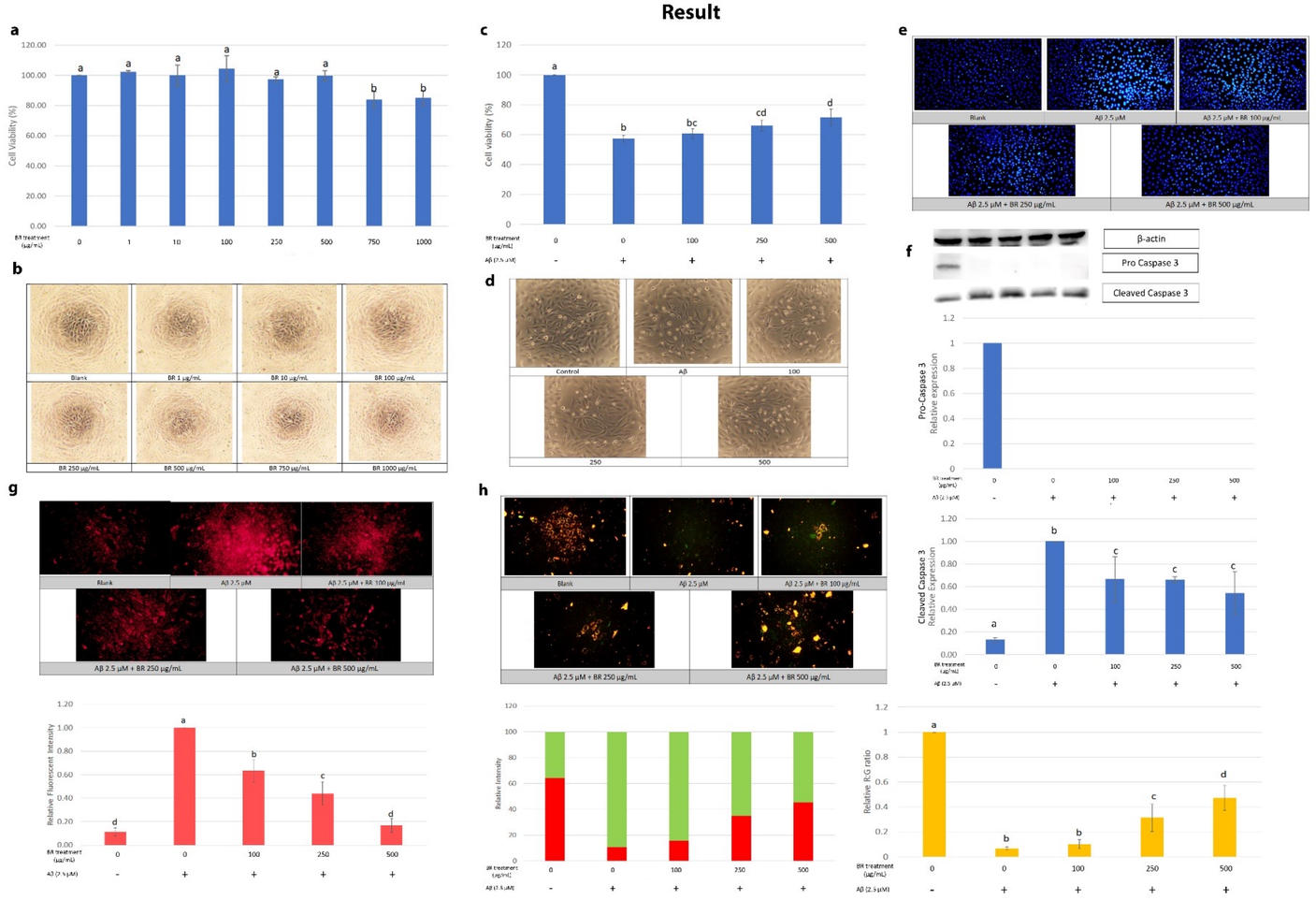


Figure 1. BR Crude Extract Alleviates Aβ Toxicity in HT-22 Cell Line, a & b) Cytotoxicity Assay and Microscopic Observation of HT-22 Cell after BR treatment; c & d) Neuroprotective Effect of BR Crude Extract Against Aβ; e) 4',6-diamidino-2-phenylindole (DAPI) staining for nuclear condensation and fragmentation after treatment; f) Western Blot Analysis for Apoptosis Marker (Cleaved Caspase-3); g) Dihydroethidium (DHE) Staining for Intracellular Superoxide Accumulation; and h) Mitochondrial Membrane Potential Staining using JC-1 Stain. Different superscript letter indicating significant difference ($p<0.05$)

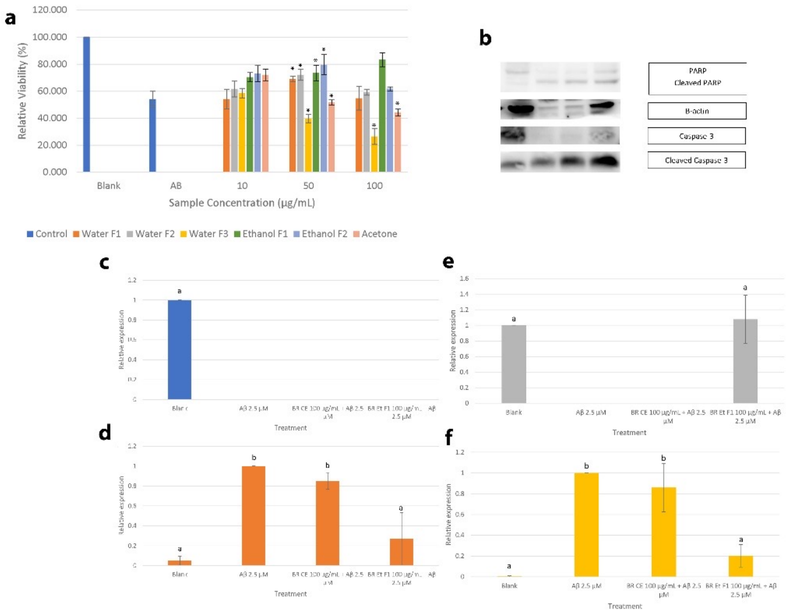


Figure 2. BR Fraction reduce Aβ Toxicity in HT-22 Cell Line , a) Neuroprotective Effect of BR Fraction Against Aβ, b) Western Blot Analysis for WApoptosis Marker (Cleaved Caspase-3 & Cleaved PARP) after treatment with Ethanol F1, c,d,e,f) Relative quantification of apoptosis marker (Pro Caspase-3, Cleaved Caspase-3, PARP, Cleaved PARP respectively)
Different superscript letter indicating significant difference ($p<0.05$), *) significant difference compared with AB treatment ($p<0.05$)

Table 1. Result of Pilot Study after BR intervention for 8 Weeks, a) Changes in CDR value of subject, b)Changes of Different inflammatory Marker, c) improvement of Subject's Oxidative Indexes.

a

# of patients	Improvement (CDR reduce from 0.5 to 0)	No improvement, (CDR remain no change at 0.5)	P value
BRBs	11	0	2.835e-06
Placebo	0	10	

b

	Inflammatory markers		
	Week 0	Week 8	Follow up
TNF-α (pg/mL)			
BRBs	19.76±4.65	6.85±3.27*	7.97±2.17*
Placebo	19.81±2.21	19.59±2.31	19.41±2.39
IL-1β (pg/mL)			
BRBs	0.16±0.07	0.12±0.05*	0.18±0.05*
Placebo	0.19±0.08	0.19±0.05	0.18±0.05
IL-8 (pg/mL)			
BRBs	7.61±5.10	4.63±3.63*	5.94±3.09
Placebo	7.67±4.25	7.86±4.90	7.79±4.23
COX-2 (ng/mL)			
BRBs	1.74±0.71	0.87±0.56*	0.88±0.50*
Placebo	1.68±0.65	1.64±0.72	1.69±0.62
iNOS (ng/mL)			
BRBs	21.15±8.50	20.27±10.28	22.37±11.95
Placebo	21.73±7.44	22.00±7.75	21.21±7.24

c

	Oxidative indexes		
	Week 0	Week 8	Follow up
SOD (U/mL)			
BRBs	696.42±35.30	784.86±46.13*	743.84±55.59*
Placebo	690.72±34.84	695.44±39.65	691.54±41.35
CAT (U/mL)			
BRBs	346.11±14.60	360.84±8.26*	360.21±9.22*
Placebo	352.58±14.16	351.95±11.30	351.14±9.03
TBARS (μmol/L)			
BRBs	4.14±1.20	1.20±0.35*	1.97±0.62*
Placebo	4.20±0.57	4.25±0.74	4.30±0.90
TEAC (μmol Trolox/L)			
BRBs	1319.77±191.90	1840.68±188.73*	1740.09±155.99*
Placebo	1250.90±185.14	1232.00±199.59	1238.40±237.70

*) Significant difference compared to week 0 ($p<0.05$)

Conclusion

BR crude extract and its water and ethanolic fraction can reduce Aβ induced toxicity and imporve mitochondrial function in HT-22 cell. BR powder treatment can improve mild cognitive impairment shown by reduction of CDR value, improvement of inflammatory markers as well as antioxidant status in elderly people