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Dietary Polyphenols as Potential Therapeutics in Alzheimer's Disease: Pleiotropic Effects and Toxicity Prediction Models

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Abstract

Individualized nutritional treatment with polyphenols has been proposed in the early stages of Alzheimer's disease. However, it remains unclear at what doses polyphenols and their metabolites enter the brain tissue and whether they can act at su f cient concentrations. The present review provides useful insights into the multiple modes of actions of selected polyphenols as potential therapeutic tools at the pre-clinical stage of Alzheimer's disease, as well as their ability to cross the blood-brain barrier and their detrimental e fects after high dose consumptions. Several studies proposed f avonoids for their potential value in prevention and treatment of neurodegenerative diseases. The scarcity of clinical data though highlights the need for conducting metabolomics studies and well-designed clinical trials. Prolonged clinical trials with bioinformatics tools are needed to fully elucidate both neuroprotective e fects and possible risks from polyphenol consumption at concentrated high doses.

W , P l he l ; Al hei e ' di ea e; Ne ec i ; C - ici ; C e ; P edic i ; Safe

3 Tg-AD: T i le T ge ic AD M e; AD: Al-hei e ' Di ea e; ABAD: A -B dh g Alc h l Deh d ge a e; AChE: Ace lch h e e a e; ADME: Ab i , Di ib i , Me ab li , d E c e i ; APP: A l id P ec P e ; Ba e1: - ec e a e; BDPP: Bi a ailable P l he lic P e a a i ; BBB: Bl d B a Ba - ie ; BChE: B lch h e e a e; BDNF: B a De ie d Ne hic Fac ; CAT: Ca ala e; CSF: Ce eb al Fl id; DOA: Deca b - e h l Ole e Agl c e; EGCG: E igall ca ech Galla e; ECG: E ica ech Galla e; EPIC: E e P ec i e e iga i Ca ce d N i i ; ER: E d la ic Re ic l ; EVOO: E a Vi - g Oli e Oil; GDNF: Glial-De ie d Ne hic Fac ; GSH: Gl a-hi e; GSK-3: Gl c ge S ha e K a e-3; GSSG: Gl a hi e Di l-hide; GSPE: G a e Seed P h c id E ac ; HMDB: H Me ab l e Da aba e; HT: H d l; IL-1 : e le k -1 ; INOS: d cible Ni ic O ide S ha e; JNK: c-J NH2- e al K a e; MAPK: Mi ge Ac i a ed P e K a e; MDA: Mal dialdeh de; MIND: Medi e e DASH e e i f Ne dege e a i e Dela ; MMP: Ma i Me all e a e; PTP: i ch d ial Pe - abili T i i P e; NGF: Ne e G h Fac ; NF-kB: N clea Fac -ka a B; NO: Ni ic O ide; N f2: E h id 2 ela ed fac 2; OA: Ole e Agl c e; PKC: P e K a e C; PPARGC1 : Pe i- e P life a -Ac i a ed Rece C ac i a 1 Al ha; GalNAc-T : l e ide N-ace l- -galac a l fe a e; QSAR: Q a i- a i e S c e Ac i i Rela i hi ; ROS: Reac i e O ge S ecie ; SMILES: Si li ed M lec la L e B S e ; TET : Te Ele e T l ca i e h l-c e di ge a e ; TNF-a: T Nec i Fac al ha; TTR: T h e ; TEDB: T ic E e Da aba e; T3DB: T d T Ta ge Da aba e

e adi i al Medi e e die d he MIND die , a c bi a i f he Medi e e d he DASH die a egi e , ha e bee e e i el died a e e i e - ha ac l gical l f a eli a g f Al hei e ' di ea e (AD), ed ch g he e e i i hibi g he di ea e g e i . Die a ec e da i f he e e i f AD d he a e a ce f b h heal h cl de a high c i f l he le iched f d ch a f i , ege able , , he b , ice d be e age cl dh g ed e, ea d c ee [1,2].

P l he l a ebi ac i e c d ha a e ead la ba ed d c ch a il , eed , ice , d ied leg e , f i , ege able , c c a d da k ch c la e. M e ha 8000 a e c e l k a e d e ha 4000 ecie ha e bee ide i ed. P l he l ake h he e ge ei he E e P ec ie e iga i Ca ce d N i i (EPIC) d g di e die a a e e e h d [3,4].

A i al die die c l ed h cell h e e ealed a ec i e le f l he l c i diabe e , ca ce , ca di a c la di ea e , e i d e dege e a i e di ea e . F ee adical ca ge g, e ha ch g a i ida defe ce , d0 T 2 09 g

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➢ A h c id : C id , Del h id , Mal id , Pela g id , Pe id

➢ I a e : G i e , Daid e

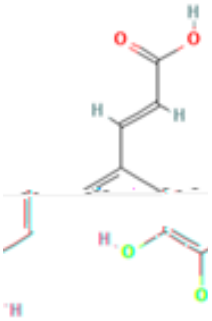
T e b e di i , a able , ad i e d c i , d he e acell la a h a a e e f he ed

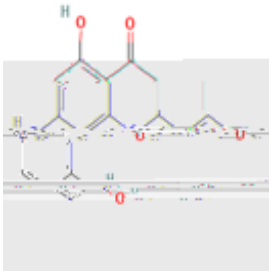
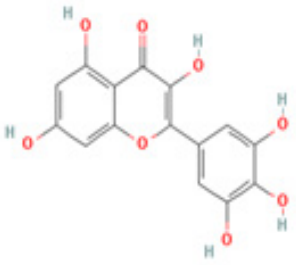
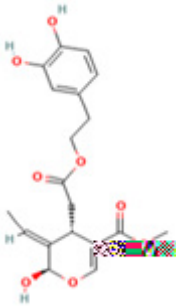
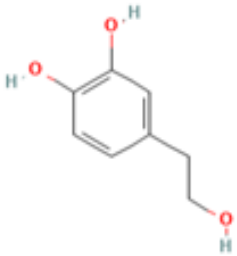
MMP a ec e e d e e- e a e ha a la i le he AD a h g e i d g e i f h b . Le el f MMP2 CSF ha e h a i i ca a cia i i h - a d le el f MMP10 i h a d - a . G e ea ca eh 'e cac hibi g Ma i Me all e a e (MMP)-2, MMP-9 d MMP-12 ac i i ie a a e ed g b a e gel g a h c b ed i h elec h e i ech i e d e ic a a . e ac i i ie f MMP-2 d MMP-9 e e i i ca l e ed b E igall ca ech Galla e (EGCG) d E ica ech Galla e (ECG) [34-36].

Maj bi l gical e ie f e e a l (3, 4′, 5- ih d ilb e) cl de i id , i- a a , e ec i e, ca di ec i e d ica ce echa i . Re e a l (RV) f d ed l g a e k d ed e, h ec i f e deg e a i e di ea e ch a Al hei e' di ea e, h gh i id ac i i d b i la g he e SIRT1 d AMPK lead g A agg ega i clea ce. Si 1 i a NAD+-de de hi e deac la e de a g e ec i aga AD. F he e, H g ' di ea e del, e e a l eg la e he e e i f FOXO e , g e al i al. Re e a l (30 g/kg/da f 8 eek)- d ced Si 1 ac i a i ed ced h h la ed a le el he hi ca egi , a dica ed a a AD del. A e a 52- eek ea i h e e a l, a dec e f a a c k e ch a IL-IR4, IL-12P40, IL-12P70, TNF- d che k e ha be b e ed. F all , e e a l ed ced he ac i i f he Gl c g S ha e K a e-3 (GSK3B), hibi ed E d la ic Re ic l (ER) e he ice hi ca , ed ced APP e e i d l ed he eg la i f a ic la ici , g a ed cell dea h d cell i al [37-40].

L e i a l a id f d cele , cha ile, li e il, ca , ach, eg d e a . L e , d g i e ha ced he ec e i f e hic fac , cl d g Ne e G h Fac (NGF), Glial De i ed Ne hic Fac (GDNF), d B De i ed Ne hic Fac (BDNF) c l ed a a c e . e e e hic fac a e e f e al i al, e g e i d a ic la ici . L e al ed ced al(e a G l-GB57d-2.9 c h(ic)g hibi i b5(eg1. /P K(d2N(a)ecd30-ee 110 a,BaTJETEbiC Bg id-9 (e)13 ( )-9 cJETEM (e)0. fe a13g AD 16DC Galac a l T fe a e (GalNAc-T) i f *in vitro* d cell . e e e i ia e he ce f O-GalNAc gl c la i f APP lead g AD a h g e i [41-43].

M ice (3,5,7,3′,4′,5′-he ah d a l) ha be dica ed a a he a e ic a id di ea e cl d g a a di ea e , a he cle i , ce eb al i che ia, diabe e

Cafeic acid $C_9H_8O_4$ Whole grain four, sunfower seed, Black chokeberry, date, prune juice, dried oregano, thyme, sage, rosemary, spices (Ceylan Cinnamon, cymin, ginger) 		Inhibition of AChE activity and nitrite synthesis; Suppression of oxidative stress; Suppression of infammation		

Naringenin $C_{15}H_{12}O_5$ Orange, Mexican oregano, grapefruit juice 		Suppression of neuroinfammation; Inhibition of AChe activity in a dose-dependent manner	Hepatotoxicity, carcinogenicity, non mutagenicity reported (ToxDP2 Database) Predicted LD50: 2000 mg/kg Predicted Toxicity Class: 4(ProTox-II)	Low
Myricetin $C_{15}H_{10}O_8$ Chinese, bayberry, tea, wine, kale, berries, oranges, tomatoes, honey 		Inhibition of BACE1 activity; Enhancement of BDNF expression	Inhibition of BACE1 activity; Enhancement of BDNF expression	Undefned
Cinnamaldehyde C_9H_8O *Cinnamomum* plant 		Autophagy and αβ amyloid deposition clearance; Destabilization of the whole amyloid fbril	Predicted LD50: 500 mg/kg Predicted Toxicity Class: 4(ProTox-II)	No available data
Oleuropein aglycone (OA) $C_{19}H_{22}O_8$ Extra virgin olive oil, black olives		Autophagy and αβ amyloid deposition clearance; Destabilization of the whole amyloid fbril	Predicted LD_{50}: 500 mg/kg Predicted Toxicity Class: 4(ProTox-II)	No available data
Hydroxytyrosol $C_8H_{10}O_3$ Extra virgin olive oil, olives, wine 		Inhibition of tau aggregation ;		

S a f aj l he lic c d i h hei die a ce , ed e ec i e ac i i ie , ial ici d BBB e ea i . Ada ed f h :// he l-e l e .e /, h ://c f. ii dia. g/ d /, h :// e .cha i e.de/ _II/. LD50, Le hal D e, he a f a che ical hich ca e he dea h f 50% f a la i f e i al *via* al, de al, hala i a ; T DP2 Da aba e, T ici P edic i f Die a P l he l , P T - II, edic i f ici f che ical .

P l he l idi e cell c l e edia d ch g a ge f f ee adical cl dh g O_2 H_2O_2, e i e d i h ial c ic e ec . A i ida age ch a die a l he l ( )-282 (ch)808 T [(c)-16 (1_0/P La g (e -GB)/3DC BT-0.089 T 9 0 59B)/1.9

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