910 **Table 1. Inhibition of Amyloids by Polyphenols**

Types of polyphenols	Types of amyloids	Possible inhibition mechanism	References
EGCG	lysozyme	EGCG dose dependently inhibiting lysozyme fibrillation and modifying the peptide chains with quinonoid moieties under acidic conditions Transforming the preformed lysozyme fibrils to amorphous aggregates through quinopeptide formation Thiol groups as the binding sites for EGCG	8
EGCG	lysozyme	Modulating the pathway towards large, beta-sheet rich amyloid fibril-like aggregates and modifying the preformed fibrils into similar type of large, clustered aggregate assemblies Rendering the surface of aggregates less exposed	46
EGCG	α-synuclein (α-SN)	Producing the off-pathway 'compact' oligomers, but also facilitating the conversion of 'active' oligomers into amyloid fibrils	50
EGCG	α-synuclein (α-SN)	Polyphenolic structure and hydrophobicity serving as the major factors to remodel amyloid fibrils	5
EGCG	α-synuclein (α-SN)	Interactions of α-SN with soluble EGCG increasing the solubility of the peptide, inhibiting amyloid formation	14
EGCG	α-synuclein (α-SN)	Disaggregating amyloid fibrils	57
EGCG	transthyretin (TTR)	EGCG maintained most of the protein in a non-aggregated soluble form EGCG efficiently disaggregating pre-formed TTR amyloid fibrils	22
EGCG	functional amyloid fibrils in P. aeruginosa (Fap)	Inhibiting the ability of Fap to form fibrils and stabilizing protein oligomers Remodeling existing fibrils into non-amyloid aggregates by EGCG	32
EGCG	Aβ, α-synuclein (α-SN)	Converting large, mature α-SN and amyloid-beta fibrils into smaller, nontoxic, amorphous aggregates EGCG directly binding to beta-sheet-rich aggregates and mediates the conformational change without their disassembly into monomers or small diffusible oligomers	33
EGCG	reduced and carboxymethylated K-casein (RCM kappa-CN)	EGCG preventing RCM kappa-CN fibril formation by stabilizing RCM kappa-CN in its native-like state rather than by redirecting its aggregation to the disordered, amorphous aggregation pathway High affinity by strong non-specific hydrophobic associations	38
EGCG	Aβ	Additional non-covalent pi-pi stacking interactions between the polyphenolic and aromatic residues Promoting the formation of off-pathway, highly stable unstructured oligomers	77

EGCG	Aβ	Redirecting Aβ (17-36) from a fibrillar aggregate to an unstructured oligomer The three aromatic groups of the EGCG molecule are in a stereo (nonplanar) configuration, helping it contact the N-terminal, middle, and C-terminal regions of the peptide The inhibition effect of EGCG is specific to the peptide sequence	112
EGCG	Aβ, α-synuclein (α-SN)	Inhibiting the fibrillogenesis of both α-SN and Aβ by directly binding to the natively unfolded polypeptides and preventing their conversion into toxic, on- pathway aggregation intermediates Promoting the formation of unstructured, nontoxic α-SN and amyloid-beta oligomers of a new type instead of beta-sheet-rich amyloid	83
EGCG	adenine, phenylalanine, and tyrosine	Influence on both early and later stages of fibrillation	59
EGCG	phenol soluble modulins	Preventing the assembly of amyloidogenic phenol soluble modulins (PSMs) and disentangling their preformed amyloid fibrils	68
EGCG	the C-terminal region (CTR) of Hfq E. coli protein	Disrupting Hfq-CTR fibrils and inhibiting their formation	78
EGCG	the highly fibrillation-prone protein Fap C	Inhibiting amyloid formation by redirecting the aggregation of Fap C monomers into oligomeric species	105
EGCG	prostatic acid phosphatase (PAP248-286 and PAP85-120) and semenogelins (SEM1 and SEM2)	Remodeling fibrils formed by PAP248-286 termed SEVI (semen derived enhancer of viral infection)	54
gallic acid, green tea extract, EGCG, EGC, EC	Aβ	The inhibitory action on Aβ fibril/oligomer formation	93
gallic acid, and EGCG	bovine serum albumin amyloid fibrils (BSA)	Remodeling or disassembling mature amyloid fibrils High binding affinity and hydrophobic interaction of polyphenols Non-covalent interactions between polyphenols and amyloid fibrils	2
EGCG, EGC,	human calcitonin (hCT)	Vicinal hydroxyl groups on the phenyl ring effectively prevent hCT fibrillization	29

ECG, gallic acid		The oxidation to form a quinone and the subsequent covalent linkage with amino acid residues such as lysine or histidine in hCT	
		Disrupting the crucial electrostatic and aromatic interactions involved in the process of hCT amyloid fibril formation	
		A combination of factors such as covalent linkage formation, aromatic stacking, and hydrogen bonding interactions to inhibit hCT fibril formation by polyphenols	
EGCG, EC	reduced and carboxymethylated K-casein (RCM-kappa-CN)	Flavonoids that had a high degree of hydroxylation and molecular planarity gave good inhibition of RCM-kappa-CN fibril formation	92
EGCG, EGC, ECG	lysozyme	Aromatic interactions, hydrophobic interactions, the radical scavenging activity and autoxidation of polyphenols are likely to be the major reasons for polyphenols being the effective inhibitor	87
A-type EGCG dimer	Aβ	Stronger inhibitory effect on the formation of Aβ (40) amyloid fibrils Possessing more binding sites on Aβ (40) peptide The hydrophobic interaction was the principal driving force to inhibit the formation of Aβ (40) amyloid fibrils by A-type EGCG dimer	63
EGCG and the oxidized EGCG	lysozyme	The oxidized EGCG demonstrates a more potent anti-amyloidogenic capacity than the intact molecule The oxidized EGCG also has a stronger disruptive effect on preformed fibrils than the native form	101
	human stefin B	Inhibiting the phase of nucleation during amyloid fibrils formation	20
	stefin B	Polyphenols with flat aromatic structures can interact with the aggregating protein and inhibit amyloid fibril formation at different stages	28
curcumin	Aβ	The hydrophobic and/or aromatic character of the compounds makes the major contribution to the anti-formation and anti-extension effects on amyloid fibrils, whereas the anti-oxidative potency relates mostly to the promotion of destabilization	80
	Aβ	Redirecting Aβ (17-36) from a fibrillar aggregate to an unstructured oligomer Curcumin binds only to the hydrophobic residues near peptide termini The inhibition effect of curcumin is non-specific in that it stems from strong interference with hydrophobic side-chain association, regardless of the residues' location and peptide sequence	112
	islet amyloid polypeptide (IAPP)	The aggregation inhibition is caused by stabilization of small molecular weight IAPP off-pathway	107

		oligomers by the polyphenols. IAPP-polyphenol hydrogen bonds and pi-pi stacking combined with hydrophobic interactions are responsible for the stabilization of oligomers	
	islet amyloid polypeptide (IAPP)	Inhibiting oligomers on-pathway to fibrils but not fibril formation	114
	transthyretin (TTR)	Strongly suppressing TTR amyloid fibril formation by generating small "off-pathway" oligomers	22
	human lysozyme	Curcumin exerts its inhibitory influence towards human lysozyme fibrillation by interacting with the prefibrillar and fibrillar intermediates resulting in complete suppression of fibrillation	46
	Human stefin B	Influencing the morphology of the mature fibrils	20
	stefin B	Both structural constraints and specific aromatic interactions are important for the inhibition of amyloid fibril formation as they provide proper positioning of the polyphenol inhibitors in the amyloidogenic core.	28
	lysozyme	The inhibitory effects of resveratrol are to prevent hydrophobic interactions between hen egg white lysozyme amyloidogenic prefibrillar species Effectively inhibiting fibrillogenesis and destabilizing preformed fibrils of hen egg white lysozyme in a concentration-dependent manner	34
	Aβ	Effectively and dose-dependently inhibiting Aβ polymerization	52
	Aβ	Resveratrol could suppress Aβ aggregation, but to a much lesser extent	62
resveratrol	Aβ	Inhibitory action on Aβ fibril/oligomer formation Interaction with genes (i.e., SIRT1) and enzymes/proteins located in the plasma membranes, nucleus, and cytoplasm (i.e., secretases, kinases, proteasomes, and PARP) as well as involves their inhibitory action on fibril formation	93
	Aβ	Dose-dependently inhibiting Aβ 42 fibril formation and cytotoxicity but not preventing Aβ 42 oligomerization Directly binding to Aβ 42, interfering in Aβ 42 aggregation, changing the Aβ 42 oligomer conformation and attenuating Aβ 42 oligomeric cytotoxicity	96
	Aβ	Redirecting Aβ (17-36) from a fibrillar aggregate to an unstructured oligomer Resveratrol binds only to the hydrophobic residues near peptide termini The inhibition effect of resveratrol is non-specific in that it stems from strong interference with hydrophobic side-chain association, regardless of the residues' location and peptide sequence	112

	islet amyloid polypeptide (IAPP)	The aggregation inhibition is caused by stabilization of small molecular weight IAPP off-pathway oligomers by the polyphenols IAPP-polyphenol hydrogen bonds and pi-pi stacking combined with hydrophobic interactions are responsible for the stabilization of oligomers	107
	Human cystatin C	Partly inhibiting the amyloid fibril growth	21
	fAβ	Dose-dependently inhibiting formation of fAβ from fresh Aβ (1-40) and Aβ (1-42), as well as their extension. Destabilizing preformed fAβ The effective concentrations (EC50) of quercetin for the formation, extension and destabilization of fAβ were in the order of 0.1-1 micro M	47
	Aβ	The hydrophobic and/or aromatic character of the compounds makes the major contribution to the anti-formation and anti-extension effects on amyloid fibrils, whereas the antioxidative potency relates mostly to the promotion of destabilization	80
	bovine insulin	Dose-dependently inhibiting amyloid formation of insulin Destabilizing the preformed insulin fibrils and transforming the fibrils into amorphous aggregates.	90
	reduced and carboxymethylated K-casein (RCM-kappa-CN)	Flavonoids that had a high degree of hydroxylation and molecular planarity gave good inhibition of RCM-kappa-CN fibril formation	92
	human calcitonin (hCT)	Vicinal hydroxyl groups on the phenyl ring effectively prevent hCT fibrillization The oxidation to form a quinone and the subsequent covalent linkage with amino acid residues such as lysine or histidine in hCT Disrupting the crucial electrostatic and aromatic interactions involved in the process of hCT amyloid fibril formation	29
myricetin		A combination of factors such as covalent linkage formation, aromatic stacking, and hydrogen bonding interactions to inhibit hCT fibril formation by polyphenols	
	fAβ	Dose-dependently inhibiting formation of fAβ from fresh Aβ (1-40) and Aβ (1-42), as well as their extension. Destabilizing preformed fAβ The effective concentrations (EC50) of quercetin for the formation, extension and destabilization of fAβ were in the order of 0.1-1 micro M	47

	Aβ	Binding in a similar hydrophobic region of the amyloid pentamer and exerting the most pronounced inhibition of Aβ (1-42) aggregation	64
	insulin and serum albumin	Promoting disassembly of mature amyloid fibrils Inhibiting amyloid fibril formation of both insulin and serum albumin Substantially suppressing the seed-induced aggregation of both proteins Binding with protein monomers as well as fibrils Strong affinity of myricetin for both the native and partially unfolded conformation of proteins mediated by H-bonds and hydrophobic interactions	73
kaempferol	goat brain cystatin (GBC)	Kaempferol produced a concentration dependent anti-fibrillogenic effects with kaempferol producing more pronounced effect Structural constraints and specific aromatic interactions of polyphenols with β sheets of GBC fibrils	25
rutin	bovine serum albumin amyloid fibrils (BSA)	Remodeling or disassembling mature amyloid fibrils High binding affinity and hydrophobic interaction of polyphenols Non-covalent interactions between polyphenols and amyloid fibrils	2
baicalein	bovine serum albumin amyloid fibrils (BSA)	Remodeling or disassembling mature amyloid fibrils High binding affinity and hydrophobic interaction of polyphenols Non-covalent interactions between polyphenols and amyloid fibrils	2
	bovine serum albumin amyloid fibrils (BSA)	Redirecting the self-assembly of amyloid fibrils into off-pathway hybrid nanostructures Hydrogen bonding and hydrophobic interaction of polyphenols preferentially at crucial amyloidogenic regions can hinder amyloid fibrillation (Phe133, Lys136, Tyr137, Ile141, Tyr160 and Arg185)	3
oleuropein aglycon	Aβ	Oleuropein aglycon is maximally effective when is present at the beginning of the aggregation process Neutralizing any residual toxicity possibly arising from the residual presence of traces of soluble oligomers and other toxic aggregates instead of inducing the release of toxic oligomers	19
	Aβ	Preventing the growth of toxic Aβ (1-42) oligomers and blocking their successive growth into mature fibrils following its interaction with the peptide N terminus	56

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