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Review article

Polyphenols in dementia: From molecular basis to clinical trials

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ABSTRACT

Dementia is common in the elderly, but there are currently no effective therapies available to prevent or treat this syndrome. In the last decade, polyphenols (particularly curcumin, resveratrol and tea catechins) have been under very close scrutiny as potential therapeutic agents for neurodegenerative diseases, diabetes, inflammatory diseases and aging.

Data were collected from Web of Science (ISI Web of Knowledge), Pubmed and Medline (from 2000 to 2015), by searching for the keywords "dementia" AND "curcumin", "resveratrol", "EGCG", "tea catechins". The same keywords were used to investigate the current state of clinical trials recorded in the NIH clinicaltrials.gov registry.

Starting from the intrinsic properties of the compounds, we explain their specific action in patients with AD and the most common types of dementia. The pharmacological actions of curcumin, resveratrol and tea catechins have mainly been attributed to their antioxidant activity, interaction with cell signaling pathways, anti-inflammatory effect, chelation of metal ions, and neuroprotection. Evidence from *in vitro* and *in vivo* studies on polyphenols have demonstrated that they may play an integral role in preventing and treating diseases associated with neurodegeneration. Furthermore, we critically analyze the clinical trials that we found, which investigate the real pharmacological actions and the possible side effects of these compounds.

This review highlights the potential role of polyphenols in the prevention/treatment of dementia and describes the current limitations of research in this field.

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1. Introduction

Global population aging is having a profound impact on the emergence of the widespread syndrome of dementia, as regards both its extent and global distribution. In the World Alzheimer Report of 2014, dementia is defined as a "syndrome caused by neurodegeneration"; being a primary cause of dependence, disability and mortality [1,2], it has become one of the major health concerns of the twenty-first century [3,4]. Although it mainly affects the elderly, it is estimated that 2-10% of all cases begin before 65 years of age. The frequency then doubles every five years thereafter. The clinical spectrum of dementia varies widely. A distinction is often made between primary degenerative dementias like Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia and dementia with Lewy bodies (Fig. 1), and dementia that is secondary to another disease process, *e.g.* AIDS, Parkinson's disease or Huntington's disease [5,6]. AD, the most common of all cases, has two essential pathological features: neurofibrillary tangles and amyloid plaques [7]. There are also some cases of 'mixed dementia' with pathological hallmarks that can refer to both Alzheimer's and vascular dementia [8]. Alternatively, those who have some cognitive impairment that does not fit the definition of 'dementia' are classified as having 'mild cognitive impairment' (MCI) [9].

Despite the variability of the clinical pictures of dementia, including its rarer forms, there are some common underlying causes. High levels of serum markers of inflammation have mainly been detected in older people with an increased rate of cognitive deterioration. A proinflammatory state has also been found to be related to dementia or cognitive impairment, due to AD and vascular disease [10,11]. Notably, the potential malfunction of amyloid precursor protein (APP), a proinflammatory cytokine, determines a serious neuronal cellular aberration in AD [12]. Inflammation and oxidative stress are responsible for the disruption of the functions of the neurovascular unit, which, in turn, leads to local hypoxia–ischemia, axonal demyelination, and reduced repair potential of the white matter. The consequent damage to the white matter supports the development of AD and VaD [13].

There are some clinically relevant yet expensive possible treatments for AD, such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) [14], but so far none of these have been approved as therapy for dementia. Epidemiological research has provided evidence of specifically modifiable risk and protective factors [15]. Since many risk factors for cognitive decline are likely to be modifiable, individuals' risk of cognitive decline may either increase or decrease depending on environmental factors, including those related to diet and lifestyle [16,17]. Numerous observational studies have suggested that there is a relationship between lifestyle factors, *e.g.* diet and nutrition, and cognition in the elderly [18]. Several studies have suggested that a diet which is high in antioxidant-rich foods, in particular polyphenols, is positively linked with cognitive performance in the elderly, and reduces cognitive decline and the risk of dementia [19]. Polyphenols are a large, abundant group of phytochemicals, recognized as having strong bioactive effects. They mainly occur in fruit, vegetables and beverages, *e.g.* apples, berries, cocoa, herbs, red wine, seeds, onions, and tea [20,21]. The most abundant polyphenols found in the human diet are flavonoids. Polyphenols are also available as dietary supplements. Even though polyphenols were not compounds of interest in the past due to their poor nutritional value, there is now a great deal of attention to their antioxidant and anti-inflammatory potential [22]. As polyphenolic compounds are considered to have strong neuroprotective properties [23], they are currently being studied as a potential treatment for dementia [18].

The present review describes the pharmacological role of the most largely investigated polyphenolic compounds (curcumin, resveratrol and green tea catechins) in preventing and treating dementia, referring to the most recent scientific literature.

2. Chemistry of polyphenols

Polyphenols vary from simple, low molecular weight molecules to large complex tannins and derived polyphenols. The phenolic chemical structure is characterized by one or more aromatic rings, while the hydroxyl groups fixed in ortho or para positions are fundamental for redox reactions. Hence, an increased number of hydroxyl groups in the polyphenol chemical structure is positively correlated with increased redox activity. Phenolic compounds can be categorized into flavonoids (anthocyanidins and anthoxanthins), diferuloylmethanes, stilbenes, and phenolic acids (Fig. 2), and are frequently conjugated to organic acids and sugars. In nature, polyphenols are usually water-soluble compounds but can also be volatile materials [24,25]. Alternatively, polyphenols can be produced by enzymatic and non-enzymatic reactions as secondary metabolites, with a biological relevance. For example, curcuminoids and stilbenes are synthesized by biotransformation that is catalyzed respectively by curcuminoid and stilbene synthase [22].

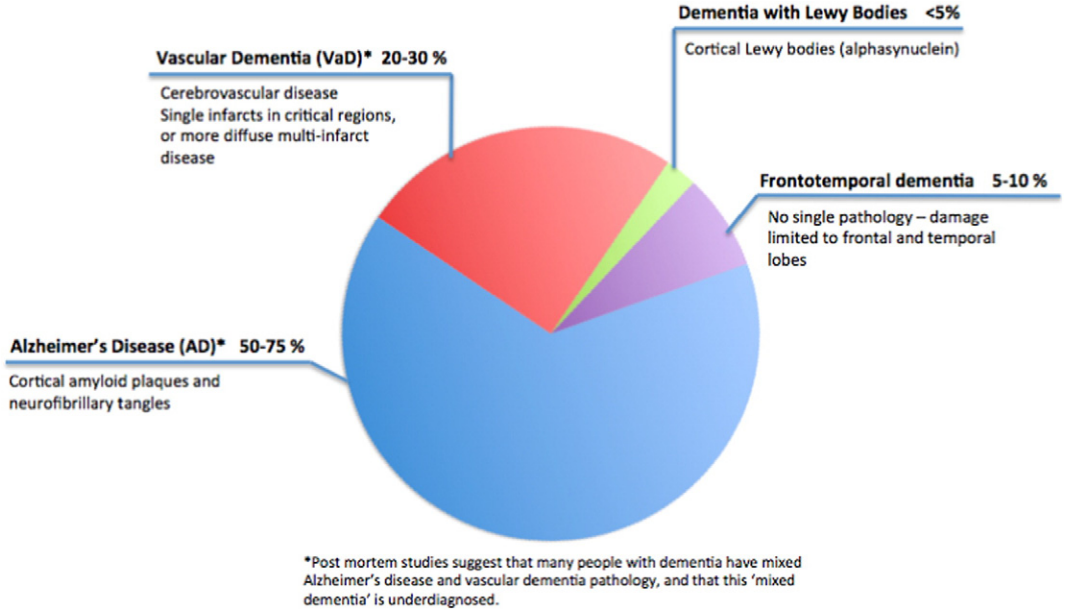

Fig. 1. Characteristics of primary dementia subtypes as classified in the World Alzheimer report 2014 [1].

Curcumin ($C_{21}H_{20}O_6$) (Fig. 3) is the yellow color of turmeric (*Curcuma longa Linn*), and its chemical name is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione. The antioxidant potential of curcumin derives from its capacity to scavenge free radicals due to its unique structure that can donate H-atoms or transfer electrons from two phenolic sites. As this phenolic compound is more soluble in lipophilic conditions, it performs the ROS scavenging activity most effectively within the polar cytoplasm [26].

Resveratrol ($C_{14}H_{12}O_3$) exists in two geometric isomers (Fig. 3). *cis*-Resveratrol is less common and very unstable, while trans-resveratrol is biologically more active than cis-isomer [27]. Resveratrol is well soluble in fat, ethanol and DMSO, but practically insoluble in water. This makes it poorly bioavailable to the human body [27]. Resveratrol demonstrates an unusually strong ability to remove free radicals thanks to the presence of three groups —OH in positions 3, 4 and 5, aromatic rings and a double bond in the molecule. Experimental studies have confirmed that removing hydroxyl groups, or replacing them with —OCH_3 groups, results in a loss of the antioxidant properties of the compound [27].

Flavanols, which are usually called catechins, are different from most flavonoids, because they do not possess a double bond between C2 and C3, and they do not possess C4 carbonyl in ring C. There is a very high content of catechins in green tea, comprising 30–42% of solid green tea extract, and (−)-epigallo-catechin-3-gallate (EGCG) is the most abundant (65% catechin content). Among green tea catechins, EGCG is thought to be the main therapeutic agent of green tea, followed by (−)-epicatechin-3-gallate (ECG), (−)-epicatechin (EC), (−)-epigallocatechin (EGC), and (+)-catechin (C) [28–30].

3. Bioavailability of polyphenols

The bioavailability of polyphenols is largely diversified from one compound to another, due to their chemical structure. Their absorption rate, metabolism, and biological activities are affected by their composition, but also depend on the direct interaction with other dietary components, such as proteins, carbohydrates, fiber, fat and alcohol [31,32]. In order to reach the brain, orally ingested polyphenols must cross two barriers, *i.e.* the enterocytes in the intestine and the blood–brain barrier, and only a few polyphenol aglycones can be absorbed by the small intestine [20,33]. On the contrary, most polyphenolic compounds (*i.e.* esters, polymers and glycosylated forms) are normally highly metabolized or quickly eliminated [20,34]. Thus, these compounds are deglycosylated, dehidroxylated or demethylated by enzymes from the intestine or the colonic microflora [32]. Once absorbed, polyphenolic compounds are released from the enterocytes into the lymph and subsequently into the blood, and undergo substantial biotransformation in the form of methylation, sulfation, glucuronidation, and thiol conjugation reactions [32,35]. These modifications typically alter the chemical properties of polyphenol metabolites, resulting in potentially new biological activities [20]. The dose and nature of the ingested substrates influence the importance of conjugations [32,35]. Besides the gastrointestinal tract, other key sites for the metabolism of dietary polyphenols are the liver, the brain and the skin [31].

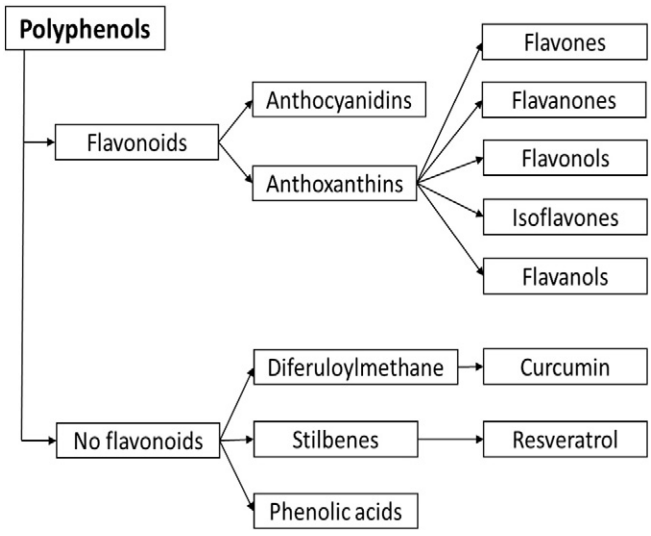

Fig. 2. Classification of polyphenols.

The bioavailability of curcumin is very low, because it is poorly absorbed, and rapidly metabolized and eliminated. Hence, one study on healthy subjects only registered traces of curcumin and its metabolites in the blood and the liver after oral administration [36]. To avoid this problem, adjuvants such as curcumin nanoparticles, phospholipid complex, structural analogues of curcumin and liposomal curcumin are added [37].

As resveratrol has a low oral bioavailability and is rapidly metabolized, metabolites are thought to be responsible for its biological activity, in particular, resveratrol-3-sulfate and resveratrol-3-O-glucuronide [38]. Resveratrol has received considerable attention because its bioavailability and bioactivity in the brain have been demonstrated in animal models [39]; despite this evidence, there have still been no conclusive results in human trials.

In humans, orally administered catechins are absorbed, metabolized and largely excreted within 24 h [40]. Flavonoids are generally absorbed as aglycones; thus, they undergo hydrolysis of the glycosides along the intestinal tract [41]. As with resveratrol, the EC metabolites, epicatechin glucuronide and 30-*O*-methylated epicatechin glucuronide, have been found in the brain [42]. It should also be noted that some green tea catechins possess a strong affinity for blood proteins. For example, the half-life in blood of EGCG could be extended if it is bound to albumin or other blood proteins [32].

4. Pharmacological effects and salubrious benefits of polyphenols

It has been demonstrated that polyphenolic compounds exert a strong antioxidant activity, and therapeutic benefits also derive from their modulatory role in cell signaling and anti-inflammatory activity (Fig. 4). In addition, it is thought that polyphenols may be important in the prevention of multiple diseases, *i.e.* cardiovascular and neurodegenerative diseases, atherosclerosis, type II diabetes, and cancer [43–46].

4.1. Antioxidant activity

The antioxidant power of polyphenolic compounds is given by phenolic groups, which can accept an electron to form relatively stable phenoxyl radicals. Polyphenols thus disrupt chain oxidation reactions in cellular components [47].

Curcumin was first proved to be a potent oxygen free radical scavenger in 1976. Since then, to increase its powerful antioxidant properties, various analogues have been studied, such as synthetic sugar-derivate and 5-chlorocurcumin [48]. Some studies have shown the powerful capability of this compound to scavenge intracellular smaller oxidative molecules such as H_2O_2, HON, ROON [26,49]. Curcumin has also been shown to interact with glutathione S-transferase and reduced glutathione (GSH), leading to lower ROS production [50,51]. More importantly, as curcumin restores the glutathione content and induces the antioxidant enzyme, heme oxygenase-1, it has salubrious effects on the brain, with crucial anti-degenerative functions in AD prevention [52,53].

Similarly, resveratrol has been demonstrated to possess significant free-radical scavenging abilities [54]. However, some authors prefer to ascribe its positive effect to the upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and heme oxygenase [55], and the downregulation of enzymes involved in the production of ROS, such as xanthine oxidase [27].

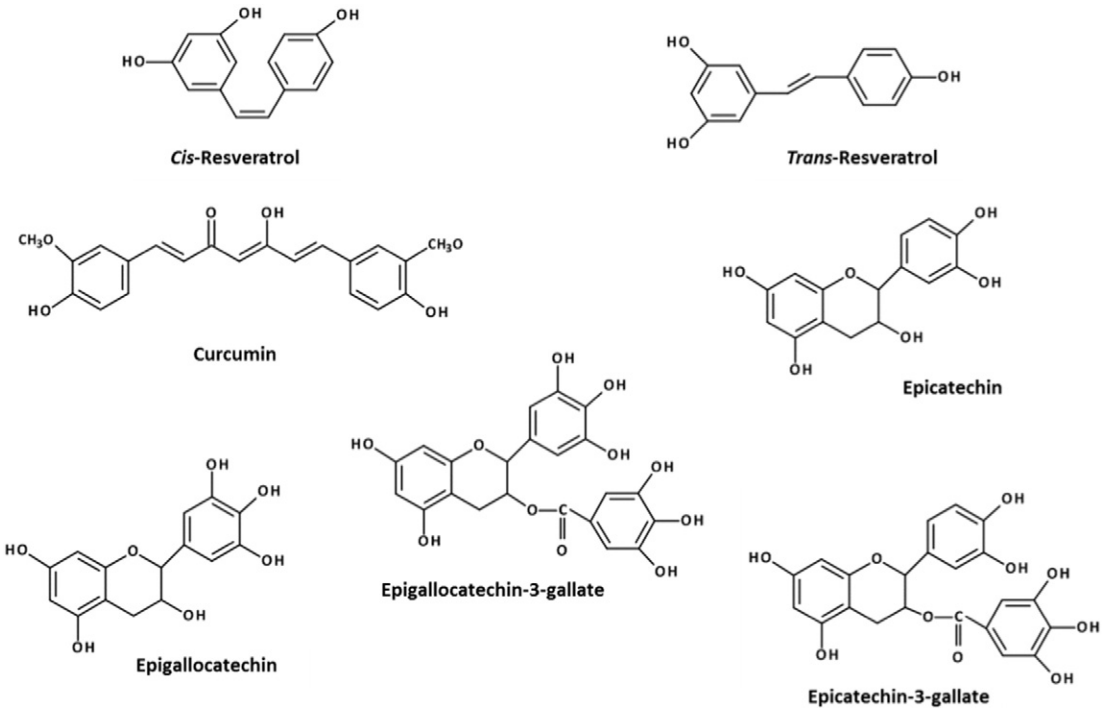

Fig. 3. The chemical structure of some of the polyphenolic compounds described in this review. There are three rings in the flavonoid structure, resulting in the core of flavone. The structure of resveratrol is similar to flavonoid, but curcumin is only vaguely similar.

Catechins are powerful free radical scavengers, in the order ECG > EGCG > EGC > EC > catechin [28,30,56]. EGCG, in different doses, also reduces lipid peroxidation [57]. Indeed, EGCG reduces *in vivo* Aβ (β amyloid)-induced oxidative stress, decreasing hippocampal lipid peroxide in the brains of rats [58]. EGCG also involves the control of antioxidant protective enzymes. A few preclinical studies have highlighted that EGCG increases the levels and the activity of glutathione reductase, GPx, SOD, and CAT [59–63]. Furthermore, in 2005, Choi et al. reported that the compound decreases malondialdehyde levels and caspase activity, in order to protect against apoptosis induced by Aβ [64].

4.2. Cellular signaling modulation: NFκB pathway

Polyphenols do not merely act as free radical scavengers, but may also control signaling processes during inflammation. Indeed, polyphenolic compounds exert their anti-inflammatory effects by modulating pro-inflammatory gene expression like lipoxygenase, cyclooxygenase,

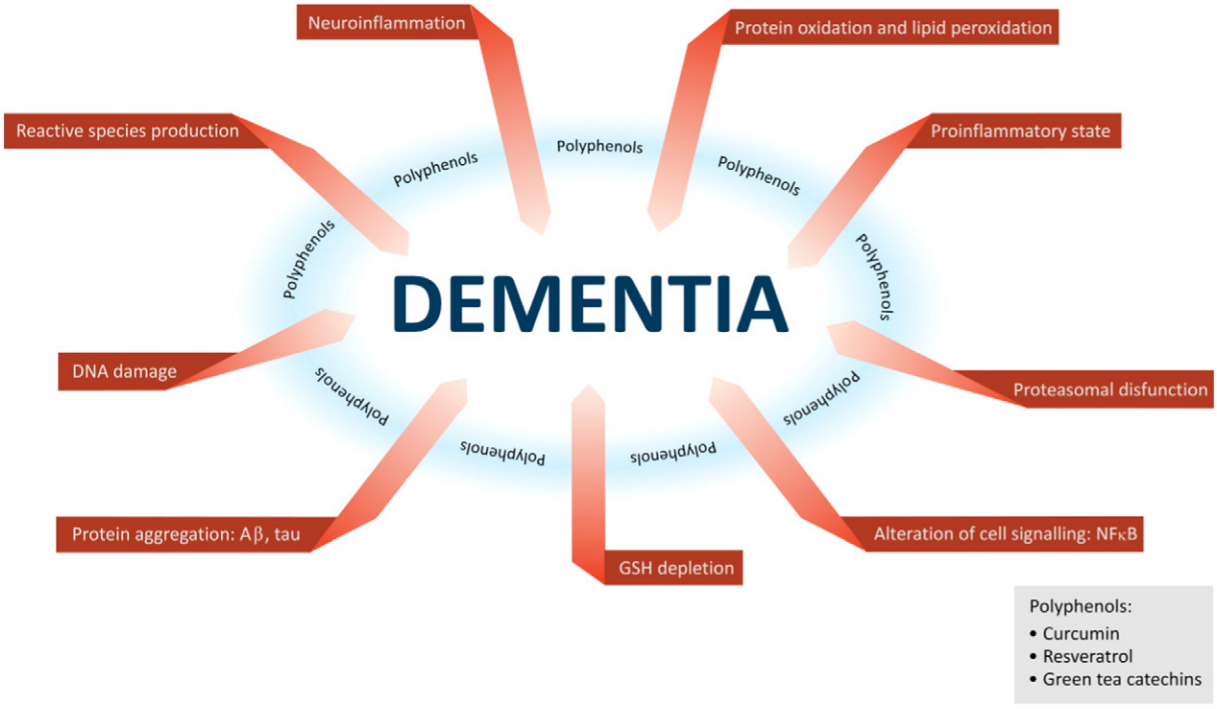

Fig. 4. Common degenerative pathways leading to dementia, and protective effects by polyphenols.

nitric oxide synthases, and some pivotal cytokines, principally *via* Nuclear Factor-kappa B (NFκB) [65]. The transcription factor NFκB is largely expressed in the nervous system, and in neurons it may be found in an inducible or constitutively active form [66].

Curcumin has been found to inhibit NFκB both *in vivo* and *in vitro* [67,68]. Sandur et al. also demonstrated that curcumin suppresses TNF-mediated NFκB activation, thus blocking the production of inducible nitric oxide synthase [69].

Resveratrol inhibits Aβ-induced neural inflammation through a mechanism that involves the downregulation of the NFκB signaling pathway [70].

Relja et al. have recently proved the capacity of green tea polyphenols to inhibit pro-inflammatory changes *via* NFκB regulation [71]. Similarly to resveratrol, catechin hydrate has been demonstrated to protect rat brains against ischemic injury and oxidative damage by inhibiting the expression of NFκB and proinflammatory cytokines such as IL-1β and TNF-α [72]. Analogously, EGCG has been shown to be active in the hippocampus of cultured HT22, reducing glutamate-induced oxidative cytotoxicity *via* inactivation of the NFκB-signaling pathway [73].

4.3. Anti-inflammatory effect

Polyphenols have a well-known anti-inflammatory activity *in vivo* and *in vitro* [41], and can also control chronic diseases characterized by persistent inflammation. Molecular targets can be divided into targets related to the inhibition of: phospholipase A_2, lipoxygenase, and arachidonic acid dependent pathways (*i.e.* cyclooxygenase) [74,75]. Likewise, in humans, polyphenolic compounds have an impact on the production of T helper 1 and 2 cytokine [76,77]. In particular, the immune response in neurodegenerative diseases is modulated through the expression of antiapoptotic factors, the modulation of cell signaling and the control of neuroinflammation [78].

Nemmar et al. demonstrated that curcumin supplementation as oral gavage (45 mg/kg) in male mice significantly reduces systemic inflammation by preventing the release of C-reactive protein and TNF-α [79]. Curcumin modulates the expression of TNF-α [80] by influencing the methylation pattern of TNF-α promoters. This natural compound exerts its anti-inflammatory effects by inhibiting COX-2, TNF-α, cyclinD1, STAT, and NFκB signaling pathways [81].

Resveratrol has been found to inhibit LPS-induced NO and TNF-α production in the N9 mouse microglial cell line [82]. Rahman et al. demonstrated that this molecule acts by blocking the expression of inducible nitric oxide synthase and COX-2, conceivably through the inhibition of NFκB activation [83]. Interestingly, resveratrol exerts beneficial effects on the treatment of ischemia and neurodegenerative diseases thanks to its anti-inflammatory effects [84]. Moreover, Abraham and Johnson demonstrated that resveratrol reduces neuroinflammation, and improves memory along with IL-1β inhibition [85].

There is a plenty of information about the anti-inflammatory properties of tea catechins. Crouvezier et al. suggested that in humans, EC, ECG, EGC, and ECGC have a strong influence on the generation of pro- and anti-inflammatory cytokines [86]. Subsequently, the anti-inflammatory effects of green tea extract polyphenols was proved in different models of acute inflammation [71,87–89]. An *in vivo* study by Chen et al. correlated the powerful anti-inflammatory activity of tea flower polyphenols with the expression of IL-1βmRNA and TNF-α, and the suppression of NO production [90]. *Inter alia*, EGCG inhibits the inflammatory effect of different cytokines [91,92]. Hence, EGCG protects against neuronal injury mediated by inflammation and suppresses microglial activation induced by LPS [93].

4.4. Metal ion chelation

Polyphenols are also well-established metal chelators. Some polyphenolic compounds possess the ability to bind and chelate an exuberance of bivalent metals, such as copper (Cu^{2+}), zinc (Zn^{2+}) and iron (Fe^{2+}) [31,94]. In this way, the rate of Fenton reaction directly diminishes and the oxidation caused by reactive hydroxyls radicals can be prevented [95]. In addition, polyphenols exert an antinutrient function because chelation reduces metal absorption, but they also inhibit digestive enzymes and may precipitate proteins [41]. Some authors argue that there is an apparent link between metal dyshomeostasis and neurodegenerative diseases [94,96]. This apparent link sparked the idea that metal chelation could be used therapeutically. Hence, it has been demonstrated in animal models of neurodegeneration that various iron chelators/antioxidants possess neuroprotective effects [94].

Having observed iron modulation by curcumin in rat-brain homogenates, Dairam et al. justified a curcumin-based therapy in dementia models [97]. Curcumin has also amplified neuroprotection in a rat model of Parkinson's disease through its iron chelating activity and reduced neuron degeneration [98].

There is evidence that green tea catechins are also considerably effective metal chelators [99]. In SH-SY5Y neuroblastoma cells, EGCG has exhibited stronger iron chelation compared to desferrioxamine and increased transferrin receptor protein and mRNA levels [100]. Singh et al. investigated the possibility that EGCG may affect APP processing and proved that a decrease in the free iron pool by EGCG chelation may lead to the suppression of the translation of APP mRNA [101].

4.5. Neuroprotection

A few mechanisms of action for polyphenols have been proposed to investigating their neuroprotective effects; these studies suggest that polyphenolic compounds modulate the activity of intracellular signal transduction molecules and reduce oxidative stress and inflammation [19,102]. *Inter alia*, natural polyphenols have largely been analyzed for their multiple mechanisms of prevention of deposits of amyloidogenic protein formation [78,103,104]. Only a minority of polyphenols, which have shown strong neuroprotective effects in animal or *in vitro* studies, have progressed successfully into active clinical trials in neurodegenerative disorders. One such polyphenol is curcumin [101].

Curcumin shows a strong ability to inhibit oligomer and fibril formation, amyloid aggregation of various amyloidogenic proteins, such as Aβ and α-synuclein [105–107]. Moreover, given its lipophilic nature, curcumin can protect neuronal cells against cytotoxicity caused by the compounds mentioned above. Curcumin prevents the formation of Aβ aggregates by attenuating Aβ precursor protein maturation at endoplasmatic reticulum level [105]. At the same time, it disintegrates preformed aggregates by directly binding to plaques [108].

Resveratrol has a great influence on neuronal cells, reducing cell death and mitigating cerebral damage [109]. It supposedly exhibits an interesting neuroprotective activity, mainly through the activation of sirtuins and counteraction in forming peptide aggregates [27]. Resveratrol and other stilbenes have been shown to inhibit Aβ fibril formation *in vitro* [110], and more generally, Aβ aggregation [111]. In 2015, Ngoungoure et al. reported that this stilbene is a strong inhibitor of transthyretin and APP [112]. Resveratrol also activates the proteasome, whose activity is significantly reduced in the brain of Alzheimer patients [108], leading to an efficient degradation of Aβ [108].

Recent literature has strengthened the hypothesis that the natural compound EGCG may reduce the risk of various neurodegenerative diseases thanks to the different molecular signaling pathways present in its neuroprotective activity. Indeed, EGCG demonstrates neuroprotective actions *via* MAPK, Akt, protein kinase C and α-secretases [113,114]. EGCG also affects the processing of APP through multiple mechanisms, *i.e.* the non-amyloidogenic α-secretase pathway, and also inhibits the β-secretase pathway that leads to the formation of Aβ fibrils [28]. IAPP (Islet Amyloid Polypeptide) amyloid formation is well inhibited by EGCG, and preformed amyloid fibrils are efficaciously disaggregated [115]. Analogously, this catechin can directly transform large, mature Aβ fibrils into minor, non-toxic amorphous amasses of protein [116]. One example is given by the inhibition of the formation of α-synuclein,

converted from large fibrils into smaller non-toxic, amorphous, soluble form. EGCG also efficiently disaggregates preformed transthyretin amyloids fibrils [117,118].

5. Clinical trials

Both *in vivo* and *in vitro* studies of polyphenols have demonstrated that they may play an integral role in preventing and treating dementia. However, it may not be easy to generalize results obtained using animal models to humans. More studies on human subjects are necessary to reach a better awareness of the role of polyphenols on neurodegenerative diseases. The 20 presently listed clinical trials in the NIH clinicaltrials.gov registry (Table 1) highlighted the growing interest in the use of polyphenols. A search using the key words "dementia" AND "curcumin", "resveratrol", "EGCG", and "tea catechins" shows that there are 8 completed studies and 12 ongoing trials, focusing on both primary and secondary dementias. Interestingly, the studies not only investigate the therapeutic action of phenolic compounds, but also the different properties that can prevent the onset of full-blown dementia.

Curcumin and resveratrol are currently the most investigated compounds. Two studies investigated the side effects, drug absorption and biological effects of curcumin in the treatment of AD [119,120]. As no serious adverse events were reported, we can say that generally, curcumin administration is well-tolerated. However, there were insufficient data in both cases to actually prove the efficacy of such treatment. Since the sample size was small and the study duration short, the authors affirmed that curcumin could not have any significant effects on clinical variables. Baum et al., among others, observed that curcumin was likely to delay decline rather than improve cognition [120].

It was impossible to determine the outcomes of the two completed studies about resveratrol supplementation in AD [121,122]. Nevertheless, there are a few ongoing trials investigating the efficacy of resveratrol in MCI and moderate AD, with a different route of administration [123–126].

Table 1
Clinical trials dealing with dementia and polyphenols.

N.	Title	Trial number	Intervention	Condition	First received	Status
1	Efficacy and safety of curcumin formulation in Alzheimer's disease [128]	NCT01001637	Curcumin formulation	Alzheimer's disease	2009	Unknown
2	Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease [120]	NCT00164749	Curcumin	Alzheimer's disease	2004	Completed
3	Short term efficacy and safety of perispinal administration of etanercept in mild to moderate Alzheimer's disease [125]	NCT01716637	Etanercept + curcumin, luteolin, theaflavin, lipoic acid, fishoil, quercetin, resveratrol	Alzheimer's disease	2012	Active, not recruiting
4	Curcumin and yoga therapy for those at risk for Alzheimer's disease [129]	NCT01811381	Curcumin + behavioral treatment: aerobic/anaerobic yoga	Mild cognitive impairment	2013	Recruiting
5	Curcumin in patients with mild to moderate Alzheimer's disease [119]	NCT00099710	Curcumin C3 complex	Alzheimer's disease	2004	Completed
6	18-month study of curcumin [130]	NCT01383161	Curcumin	Age-associated cognitive impairment Mild cognitive impairment	2011	Ongoing, but not recruiting participants
7	Curcumin as a novel treatment to improve cognitive dysfunction in schizophrenia [131]	NCT02104752	Curcumin	Schizophrenia Cognition Psychosis	2014	Recruiting
8	Early intervention in mild cognitive impairment (MCI) with curcumin + bioperine [132]	NCT00595582	Curcumin + bioperine	Mild cognitive impairment	2008	Terminated, has results
9	Targeting inflammation to influence mood following spinal cord injury: a randomized clinical trial [133]	NCT02099890	Omega-3 Vegetation protein powder InflanNox Anti-oxidant Network Chlorella	Neuropathic pain Depression Cognitive impairment Somatic neuropathy Autonomic dysfunction	2014	Completed
10	Telomerase activator and retinal amyloid [134]	NCT02530255	Cycloastragenol	Alzheimer's disease	2015	Recruiting
11	Resveratrol for Alzheimer's disease [121]	NCT01504854	Resveratrol	Alzheimer's disease	2011	Completed
12	Pilot study of the effects of resveratrol supplement in mild-to-moderate Alzheimer's disease [123]	NCT00743743	Longevinex brand resveratrol supplement	Alzheimer's disease	2008	Withdrawn
13	BDPP treatment for mild cognitive impairment (MCI) and prediabetes [124]	NCT02502253	Grape seed polyphenolic extract, resveratrol, concord grape juice	Mild cognitive impairment Alzheimer's disease	2015	Recruiting
14	Randomized trial of a nutritional supplement in Alzheimer's disease [122]	NCT00678431	Resveratrol with glucose, and malate	Alzheimer's disease	2008	Completed
15	Use of resveratrol to decrease acute secondary brain injury following sports-related concussions in boxers (REPAIR) [135]	NCT01321151	Resveratrol	Sports concussion	2011	Completed
16	Resveratrol and Huntington disease (REVHD) [136]	NCT02336633	Resveratrol	Huntington's disease	2015	Recruiting
17	Effects of dietary interventions on the brain in mild cognitive impairment (MCI) [126]	NCT01219244	Caloric restriction Omega-3 Resveratrol	Mild cognitive impairment	2010	Recruiting
18	Green tea consumption affects cognitive dysfunction in the elderly: A pilot study [127]	NCT01594086	Green tea powder	Cognitive impairment	2015	Completed
19	Effects of EGCG (epigallocatechin gallate) in Huntington's disease (ETON-study) [137]	NCT01357681	(2)-Epigallocatechin-3-gallate (EGCG)	Huntington's disease	2011	Completed
20	Sunphenon EGCG (epigallocatechin-gallate) in the early stage of Alzheimer's disease (SUN-AK) [138]	NCT00951834	Epigallocatechin-gallate	Alzheimer's disease	2009	Completed

Ide et al. reported that in the elderly, cognitive function may be improved or at least cognitive dysfunction progression reduced by a daily intake of normal levels of green tea, with relatively low catechin and theanine. Consumption could further reduce the progression of VaD [127]. However, as with curcumin, long-term large-scale controlled studies are needed to further clarify the evidence of the effect of green tea catechins.

6. Conclusions

Even though dementia is a very common disease among aging individuals and also one of the most common causes of impairment and mortality, there are currently no effective therapies available, due to its complex nature and variable forms. One possible way to prevent and/or treat this syndrome is by acting on its modifiable risk factors, among which diet plays an important role. Polyphenols show *in vitro* antioxidant, antinflammatory and antiamyloid activity. These data, together with previous investigations in AD animal models provide a promising basis for further studies in human dementia. However, thus far no evidence has emerged to prove that the reviewed compounds can help to treat dementia. The following explanations may clarify the lack of the expected beneficial outcomes: 1) investigations into the problems of bioavailability of the formulation of curcumin, resveratrol and green tea catechins are needed; 2) more information about absorption, metabolism and how these compounds can pass through the blood-brain barrier to carry out their protective effects are needed; 3) there are differences between human AD and rodent models of amyloidosis as regards both the biology and the metabolism of polyphenols; 4) clinical trials conducted so far have been too short and have included too few patients to demonstrate the benefits of polyphenols on human AD; and 5) there is a long incubation period before the clinical symptoms of the majority of neurodegenerative diseases appear, so epidemiological investigations concerning the consumption of polyphenolic compounds and the progression of diseases should be performed.

In conclusion, we can affirm that polyphenols could be up-and-coming compounds for the conception of new natural therapies for dementia. However, as they may be a novel remedial treatment for dementia, further studies and clinical trials are required.

Abbreviations

AD	Alzheimer's disease
Aβ (β amyloid)	
APP	amyloid precursor protein
CAT	catalase
C	(+)-catechin
COX	cyclooxygenase
DMSO	dimethyl sulfoxide
EC	(−)-epicatechin
ECG	(−)-epicatechin-3-gallate
EGC	(−)-epigallocatechin
EGCG	(−)-epigallo-catechin-3-gallate
GPx	glutathione peroxidase
MCI	mild cognitive impairment
SOD	superoxide dismutase
VaD	vascular dementia

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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