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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.

Contents

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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].

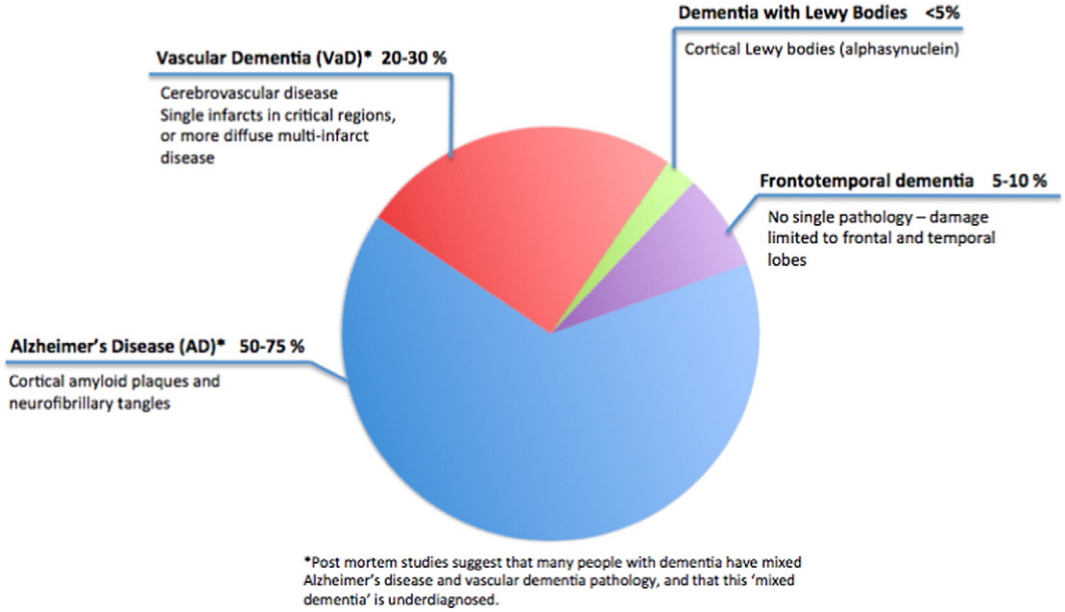

Fig. 1. Characteristics of primary dementia subtypes as classified in the World Alzheimer report 2014 [1].