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Abstract:	The beneficial effects of many different substances have been discovered as a result of regular dietary consumption. This is also the case of curcumin, whose effects have been known for more than 4000 years in eastern countries such as China and India. A curcumin-rich diet was known to combat many different human diseases including cancer and diabetes and reduces inflammation. The effect of Cur treatment of neurological disease has only recently been brought to the attention of researchers and the wider population.In this paper, we summarize the studies on this natural product from its isolation, two centuries ago to its characterization a century later, describe its role in the treatment of neurological diseases, including its cellular and common molecular mechanisms, and report the clinical trials of curcumin with healthy people and patients, commenting on the different approaches adopted by efforts to increase its bioavailability.
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Curcumin and Neurological Diseases.

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Abstract

The beneficial effects of many different substances have been discovered as a result of regular dietary consumption. This is also the case of curcumin, whose effects have been known for more than 4000 years in eastern countries such as China and India. A curcumin-rich diet was known to combat many different human diseases including cancer and diabetes and reduces inflammation. The effect of Cur treatment of neurological disease has only recently been brought to the attention of researchers and the wider population.

In this paper, we summarize the studies on this natural product from its isolation, two centuries ago to its characterization a century later, describe its role in the treatment of neurological diseases, including its cellular and common molecular mechanisms, and report the clinical trials of curcumin with healthy people and patients, commenting on the different approaches adopted by efforts to increase its bioavailability.

Keywords

Curcumin; spinal muscular atrophy; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; multiple sclerosis; epilepsy, neuropathic pain; stroke; spinal cord injury.

Abbreviations in the Text, Tables, and Figure:

Curcumin (Cur); bis-demethoxycurcumin; demethoxycurcumin (DMC); oral (per os); endovenous (EV); intraperitoneal (IP); blood-brain-barrier (BBB); dihydrocurcumin (DHC); tetrahydrocurcumin (THC); dimethoxycurcumin (DiMC); Solid lipid nanoparticles (SLNPs); Liquid crystalline nanocarriers (LCN); Nanostructured lipid carriers (NLC); neurological diseases (NDs); Alzheimer's disease (AD); Parkinson's disease (PD); Multiple Sclerosis (MS); Amyotrophic Lateral Sclerosis (ALS); Spinal Muscular Atrophy (SMA); Spinal Cord Injury (SCI); Apolipoproteina E (APOE); β-amyloid (βA); amyloid precursor protein (APP); Central Nervous System (CNS); acetylcholine (ACh); Food and Drug Administration (FDA); Acetylcholinesterase (AChE); Monoamine oxidases (MAO); *N*-Methyl-D-aspartate receptor (NMDAR); levodopa (L-Dopa); 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Parkin2 (PARK2); α-Synuclein (α-Syn-PARK1/PARK4); Leucine rich repeat kinase2 (LRRK2/PARK8); ubiquitin C-terminal hydrolase like 1 (UCH-L1); PTEN-induced putative kinase 1 (PINK1/PARK6); DJ1 (PARK 7); ATPase type 13A2 (ATP13A2); Catecohol-O-methyl transferase (COMT); ultraviolet

B (UVB); Vitamin (Vit); Hunan Leukocyte antigen (HLA); Major Histocompatibility Complex (MHC); lymphocytes T helper 17 (Th17); Interleukin (IL); Matrix metalloproteinase (MMP); Interferon (IFN); Nitric Oxide Synthase (iNOS); Motor neurons (MNs); Superoxide dismutase (SOD); chromosome 9 open reading frame 72 gene (C9orf72); TAR-DNA-binding protein of 43 kDa (TDP-43); Survival Motor Neuron (SMN); adeno-associated viral (AAV); methylprednisolone sodium succinate (MPSS); recombinant tissue plasminogen activator (rt-PA); γ-aminobutyric acid (GABA); tricyclic anti-depressants (TCAs); selective serotonin (5HT); norepinephrine reuptake inhibitors (SSNRIs); Nuclear respiratory factor 1 (Nrf1); Nuclear erythroid 2-related factor 2 (Nrf2); Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC)1α; Mitochondrial transcription factor A (TFAM); Postsynaptic Density Protein 95 (PSD95); Heat Shock Protein 90 (HSP90); near-infrared fluorescence (NIRF); positron emission tomography (PET); magnetic resonance imaging (MRI); Tumor Necrosis Factor-α (TNFα); intracerebroventricular (ICV); streptozotocin (STZ); Cyclooxygenase 2 (COX2); Nitric oxide (NO); Glial fibrillary acidic protein (GFAP); peroxisome proliferator-activated receptors (PPAR); macrophages and peripheral blood mononuclear cells (PBMCs); Reactive Oxygen Species (ROS); B-cell lymphoma 2 (Bcl2); Bcl2-associated X protein (Bax); Bcl2-associated death promoter (BAD); B-cell lymphoma-extra large (BclXL); Cytochrome (Cyt); Green Fluorescent Protein (GFP); 2,4,5-trihydroxyphenethylamine (6-OHDA); lipopolysaccharide (LPS); insulin-like growth factor (IGF); neurotrophin (NT); autoimmune encephalomyelitis (EAE); Brain-derived neurotrophic factor (BDNF); Nerve growth factor (NGF); Myelin basic protein (MBP); neural stem cells (NSCs); Platelet-derived growth factor receptor α (PDGFRα); retinoic acid-related orphan receptor γ (RORγt); Transforming growth factor beta (TGFβ); uncoupling protein 2 (UCP2); action potentials (APs); heme oxygenase-1 (HO-1); Zonula occludens-1 protein (ZO-1); nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); Monocyte Chemoattractant Protein 1 (MCP1); Chemokine (C-C motif) ligand 5 or RANTES; C-X-C motif chemokine 10 (CXCL10); middle cerebral artery occlusion (MCAO); Toll-like receptor 4 (TLR4); Mitogen-Activated Protein Kinase (MAPK); silent information regulator 1 (Sirt1); stroke-prone spontaneously hypertensive (SHRsp); chronic constriction injury (CCI); opioid-related nociceptin receptor 1 gene (OPRL1); 11β-hydroxysteroid dehydrogenase type I enzyme ($11\beta HSD_1$); metabotropic glutamate receptor 2 (mGlu2); Area under the curve (AUC); maximum concentration value (Cmax); time to reach the maximum concentration value (Tmax); leukotriene-4

(LTB4); leukotriene-5 (LTB5); regulatory T cells; Forkhead Box P3 protein (Foxp3); Relapsing-Remitting Multiple Sclerosis (RRMS); three in week (TIW); isoprostanes (IsoPs); Mini-Mental Status Examination (MMSE); Alzheimer's Disease Assessment Scale-Cognitive test (ADAS-cog); Montreal Cognitive Assessment test (MoCA); ClinicalTrials.gov identifier number (NTC); Turmipure GOLD™ 30% curcuminoids (300 mg) (TG); standard turmeric powder extract 95% curcuminoids (1500 mg) (STE); Novasol® Liquid micellar formulation 6% curcuminoids (1000 mg) (NOV); Meriva® Turmeric Phytosome formulation 20% curcuminoids (1000 mg) (PHYT); Turmeric extract C3 complex® 95% curcuminoids (1500mg) + BioPerine® 95% piperine (15 mg) (TEP); Native turmeric extract (207 mg curcumin) (A); Native turmeric extract with 7-9% volatile turmeric oils (207 mg curcumin) (B); Turmeric extract plus mixture of phytochemicals (207 mg curcumin) (C); Cyclodextrin complex of curcuminoids (207 mg curcumin) (D); Turmeric oleoresin (207 mg curcumin) (E); Liposomal curcumin (207 mg curcumin) (F); Phytosomal curcumin (207 mg curcumin) (G); Micellar turmeric extract (207 mg curcumin) (H);encapsulated curcumin (EC); encapsulated curcumin plus Piperine, Quercetin and Genistein (EC-PQG); free cocoa polyphenols (FCP); encapsulated cocoa polyphenols (ECP).

Introduction

Turmeric, which contains Curcumin (Cur), has been widely used in Indian and Chinese cooking but only relatively recently recognised as a natural protective treatment with proven healing capacity. Cur has been used for the treatment of many different disorders including, but not limited to, neurological disorders (or neurological diseases, NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA), Spinal Cord Injury (SCI), stroke and seizure. The classification of the various etiologies of these disorders is very complex and they affect the Central Nervous System (CNS) in different ways, but they can be categorized, broadly, as follows. Firstly, there are those diseases that cause the loss of cells in particular regions of the brain or specific kinds of neurons, such as AD, PD, MS, ALS and SMA The second group is those diseases in which acute damage causes loss of tissue, such as Stroke and SCI. Finally we have those NDs which involve neither degeneration nor death of cells but in which there is a deficit of cell function, such as seizure disorders[1]. The mechanisms by which Cur treatment plays a role in these diseases are different and range from anti-inflammatory action to the regulation of ion channels and genes.

Curcumin

Cur is a phytopolylphenol pigment (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) obtained from the plant *Curcuma longa* (but also found in Curcuma aromatica, mangga, phaeocaulis, xanthorrhiza, zedoaria, Etlingera elatior, Zingiber cassumunar, and Costus speciosus) and commonly known as turmeric. Turmeric is a perennial herbaceous plant with oblong, palmate roots and tubers that grows spontaneously in southern Asia and Africa, in tropical climate regions with high rainfall and a normal temperature range of between 20 °C to 35 °C [2].

The world's leading country for turmeric production is India with nearly 200,000 hectares and around 900,000 tonnes of production in 2008. Tumeric has been known since the inception of the ancient Indian system of medicine, the Ayurveda, about 4000 years ago; it was first isolated chemically more than 200 years ago and its structure characterized in 1910 [2]. It is Cur that is responsible for turmeric's yellow color and it is used not only for health and as a food preservative but also as a textile dye. The percentage among all the curcuminoids in tumeric of the three major curcuminoids is: Cur (diferuloylmethane)

(about 77%), bisdemethoxycurcumin (BDMC) (about 3%), and demethoxycurcumin (DMC) (about 17%) [3].

Pharmacokinetics of Curcumin

There are three main reasons why little advantage has so far been taken of the therapeutic potential of Cur. The first is its low degree of oral bioavailability, mostly due to its limited absorption, high metabolism, and rapid systemic elimination. Secondly, Cur is poorly soluble in water (about 11 ng/mL) and highly degraded in a basic environment [4]. Thirdly, when Cur is administered per oral administration (per os) most of it is excreted in the feces because it is poorly absorbed: the intestinal tract also because Cur undergoes glucuronidation in the intestinal mucosa inactivating the Cur. Cur then undergoes first pass effect reduction to DHC, THC, and hexahydrocurcumin followed by conjugation to sulfates and glucuronides in the liver [5, 6] and it is eliminated through the urine [4]. Many pharmacokinetic studies performed in humans and rodents have shown that the greatest plasma concentrations reached after oral administration were 0.051 mg/mL from 12 g Cur in human, 0.22 mg/mL from 1 g/kg in the mouse and 1.35 mg/mL from 2 g/kg in the rat [7]. It was determined that the bioavailability of Cur orally was only 1% [8, 9], much less than is achieved endovenously (EV) and intraperitoneally (IP) [8, 9].

Cur appears in the plasma 15 minutes after IP administration; 45 minutes later it is detectable in the liver, spleen, intestines, and kidneys but only traces appear in the brain despite the fact that Cur efficiently passes the blood-brain-barrier (BBB).

In a rodent model the presence of l-piperoylpiperidine (piperine)—an alkaloid produced from black pepper fruits (Piper nigrum and other plants from the family Piperaceae), an inhibitor of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase)—increases the bioavailability of oral Cur by up to 154% [8] and leads to the presence of Cur in the brain being detectable up to 96 hours after administration [9].

The bioavailability of Cur can be increased by administering its derivatives which display enhanced biological activity and improved pharmacokinetics: one example is dimethoxycurcumin (DiMC), which has higher levels of metabolic stability and pro-oxidant and anticancer activity [10].

Nanocarriers for Curcumin Delivery

In clinical trials, when administered together with food in doses between 1 and 4 g/per day, as capsules or as powder, Cur did not produce improvements in AD patients [11].

Since the efficacy of Cur has been demonstrated in cell models, the main issues for human trials are protection from its fast metabolism and, more broadly, increasing its bioavailability, so manufacturers have responded by producing lipid-based nanoparticles [12]. Among them, solid lipid nanoparticles (SLNPs) underwent an intensive development because they combine the benefit of carrier systems like liposomes (being composed of biocompatible lipids and fatty acids), with the benefits of polymeric solid particles, which efficiently protect the loaded drug (either lipophilic and hydrophilic) against chemical degradation in the harsh environment of the gastrointestinal tract.

Many different strategies have so far been used for Cur delivery *in vivo*, such as Longvida® (Verdure Sciences Inc.), an SLNP-formulation which can achieve from 0.1 to 0.2 μM (0.037 to 0,074 μg/ml) levels of Cur in the plasma and 1–2 μM (0.37-0.74 μg/ml) in the brain [13]. Nanostructured lipid carriers (NLC), developed as an evolution of SLNP, are also widely used since they can contain larger quantities of drugs [12]. Liposome-encapsulated Cur has been demonstrated to be a safe formulation where Cur is delivered into the cells via membrane endocytosis or fusion, as seen in animals models [14].

Pharmacodynamics of Curcumin

Many molecular targets are affected by Cur, either by physical interaction or by modulation of enzyme activity, or transcription factors. In a gene expression analysis in tumor cells, Cur has been found capable of up-regulating 202 mRNAs and down-regulating 505 mRNAs [15]. Many transcription factors (and their gene targets) involved in tumorigenesis, cell proliferation, cell survival, inflammation, invasion, and angiogenesis, are thus modified negatively or positively; Cur can also regulate the expression of growth factors, their receptors, and some downstream signaling pathways [16].

Curcumin Trials on Healthy Patients

Many different trials (observational or phase 1-3) have been performed on healthy adults, testing the effects of Cur. Most of them aimed to determine its pharmacokinetics by using one or other of its various formulations in order to identify a safe and effective method of delivery (Supplementary material).

Some trials, for instance, compared the different formulations of Cur administration: pow-

der, nanoparticle and proprietary NCT01925287, NCT01982734, NCT01330810, NCT01403545, NCT02474953, NCT03085680, NCT03746158, NCT03530436, NCT03621865, NCT03289507, NCT00181662, and NCT01288859. Most of these analyses investigated the age and sex-related pharmacokinetics profile safety of Cur formulations, and dosage [17-21]. Others, however, tested the impact of oral Cur on heme oxygenase-1 (HO-1) NCT00895167 (Phase 1 trial) or its effect in iron metabolism NCT01489592 (Phase 2 trial).

In observational clinical trials, on the other hand, analyses were conducted of the overall effects of various substances coadministered with Cur, including green and black teas, polygonum cuspidatum extract, soybean extract, resveratrol, sesamin, acetyl-L-carnitine, lipoic acid, quercetin, pomegranate and cinnamon bark; changes in oxidative stress and inflammation in the blood were studied in trials NCT00768118, NCT01752868, and NCT02815475 (Supplementary material).

Neurological Diseases

Alzheimer's Disease (AD)

Dementia is a neuropsychiatric disorder distinguished by a mix of functional disability and progressive psychological, behavioral and cognitive deterioration (WHO 2012).

In 2015 it was estimated that about 46.8 million people were affected by dementia worldwide, almost 30% more (9.9 million new cases) than the 2010 estimate [22]. It is anticipated that 74.7 million people will be affected by 2030 and 131.5 million by 2050.

There are two broad categories of dementia: irreversible—in forms such as AD, frontotemporal dementia, vascular dementia and Lewy body dementia—and reversible, such as cases caused by HIV, hypercalcemia, abnormalities in vitamin (Vit) B12 and folic acid, and changes in thyroid hormone levels [22].

Annually, more than 35 million people contract AD, which is the most widespread neurodegenerative disease, responsible for 60 to 80% of dementia cases [23].

The onset of AD onset is marked in most cases by deficits in one or more cognitive fields, including but not limited to memory, language, orientation, and executive function; behavioral disturbances occur in the later stages [22]. Although dementia is not a typical characteristic of aging [24], older age is one of the consistent and unvarying risk factors, the others being Apolipoprotein E (APOE) genotype e4 allele and family history. Other risk factors—such as education and occupational achievements, cardiovascular risk (e.g. hyper-

tension), diabetes, smoking, obesity, psychosocial factors (e.g., depression and alcohol consumption), and lifestyle factors such as physical activity—are modifiable by the patient [23].

Atrophic hippocampus and cerebral cortex are the macroscopic landmarks present in AD patients [25]; at the cellular and subcellular level AD patients show the presence of amyloid (A) or plaques consisting of βA protein and the accumulation of hyperphosphorylated Tau protein, which indicate the formation of neurofibrillary tangles, and, consequently, extensive neuronal death [26, 27]. Furthermore, APOE mechanisms [27, 28], genetic imprint factors [29], and oxidation processes [30] are also involved in the neurodegeneration of AD patients. The irregular folding and aggregation of A peptides into senile plaques is implicated in the initial phases of AD neurodegeneration. Various isoforms of A peptides, the most common being 40 and 42 amino acids long, are produced from sequential proteolysis of the amyloid precursor protein (APP), a transmembrane glycoprotein of approximately 770 amino acids expressed by several cells, including the neurons of the CNS. The cleavage of APP takes place through the enzymes α-, β- and ɣ-secretase. The amyloid pathway starts when APP is cleaved by β-secretase, thereby forming insoluble peptides with 39 to 43 fragments which easily aggregate into oligomers around cells and have a crucial role in pathogenic events [22]. The βAPP fragments, especially the βA-42 isoform, have pronounced cytotoxic properties related to the process of neurodegeneration caused by the facilitation of the formation of oxyradicals and the deregulation of calcium homeostasis, due to lipid dysregulation of the cell membrane. Moreover, these fragments form the insoluble structures that characterize AD histopathologically (senile plaques) and this process ultimately leads to neuronal death [22]. The Tau protein promotes a kind of assembly of tubulin, providing microtubule stability [22].

To date, the therapeutic approaches for AD are merely symptomatic and can improve memory and cognitive functions. The therapies in use are directed to improving cholinergic transmission via the inhibition of acetylcholine (ACh); indeed, the only drugs approved for AD treatment by the U.S. Food and Drug Administration (FDA) are palliatives: Acetylcholinesterase (AChE) enzyme inhibitors (galantamine, donepezil, and rivastigmine), and inhibitors of monoamine oxidase (MAO) B, which is highly expressed in the astrocytes and pyramidal neurons of AD patients [33], and interacts with γ-secretase enzyme. Both MAO and AChE inhibitors can assist memory and cognitive functions, and diminish the AD-related symptoms. In Europe memantine, a drug that mainly blocks *N*-

Methyl-D-aspartate receptor (NMDAR) but also serotonergic, cholinergic, and dopaminergic receptors, is also approved for AD treatment.

Curcumin treatment of Alzheimer's Disease

Since Cur contains two phenols connected by a linear β-diketone linker, it exhibits peculiar photophysical and photochemical properties [31]. In particular, Cur binds to βA plaques with the emission of a highly fluorescent signal, which makes it an important diagnostic tool for AD [32] including in the use of two-photon microscopy, near-infrared fluorescence (NIRF), positron emission tomography (PET), and magnetic resonance imaging (MRI) [33].

Cur inhibits βA levels, deposits and aggregation, by reducing the degree to which it self-assembles and inducing the disaggregation of fibrillar Aβ40 [32, 34, 35]. It also inhibits the formation of fibrillar βA and destabilizes fibrillar Aβ40 and Aβ42 *in vitro,* showing a protective effect to βA toxicity [36, 37]. Cur also helps in protecting mitochondria from the toxic effects of βA: for instance it reduces oxidative stress in PC12 caused by βA [38] and reduces brain IL1β and oxidized proteins in APP mice [39].

Cur pretreatment prevents βA-induced toxicity in human neuroblastoma cells (SH-SY5Y), increasing the levels of mRNA and proteins for mitochondria biogenesis genes such as Nuclear respiratory factor 1 (Nrf1), Nuclear erythroid 2-related factor 2 (Nrf2), Peroxisome proliferator-activated receptor gamma coactivator (PGC)1α, Mitochondrial transcription factor A (TFAM) and synaptophysin and Postsynaptic Density Protein 95 (PSD95) [40]. Cur is also able to inhibit Glycogen synthase kinase-3 (GSK-3), which regulates the phosphorylation of tau [41], and protects cells from tau-induced neurotoxicity [42].

No NDs (AD included) exist without microglia activation [43]; indeed it was demonstrated that βA reroutes microglia from their neuroprotective phenotype to their neurotoxic phenotype [44]. Since during βA accumulation the microglia and the inflammatory mediators are activated, further βA accumulation and neuroinflammation are induced. Cur blocks extracellular signal-regulated kinase 2 (ERK1/2) and p38 kinase signaling in βA-activated microglia *in vitro*, reducing the synthesis of IL1β, Tumor Necrosis Factor-α (TNFα), IL6 mRNAs, and proteins (Fig. 1) [45].

Interestingly, Cur has an inhibitory effect on acetylcholinesterase like many drugs used in AD therapy, however, up to date, no studies on Cur inhibition of acetylcholinesterase has been performed in the context of AD cell or animal models [46].

In vivo studies have confirmed the protective effect of Cur in AD. It was demonstrated in a rat model of AD induced by intracerebroventricular injection of streptozotocin (ICV-STZ) that Cur is able to reduce the deficits in the Object Recognition Test by decreasing neuroinflammation and increasing adult neurogenesis [47].

Moreover, in a mouse model of AD, Cur treatment caused suppression of the neuroinflammatory response, decreasing the levels of inflammatory molecules such as IL1β, TNFα, Cyclooxygenase (COX)2, and Nitric oxide (NO), and decreasing the number of Glial fibrillary acidic protein (GFAP)- and Iba-1-positive cells, probably because of the promotion of peroxisome proliferator-activated receptor (PPAR)γ activity (Fig. 1) [48].

Many clinical trials studying the effects of Cur in AD are ongoing (Supplementary material).

One of the first trials to assess the effects of Cur on AD-affected patients was started in 2004 (NCT00164749); it was a pilot study (Phase 1) which tested the effects of Cur in the better-absorbed formulations of powder or capsule [49]. Since the study was conducted for only a short period of time, and the placebo-treated patients did not show any cognitive decline, the effect of Cur on cognition was not clear, although βA aggregation was counteracted [11].

NCT03085680 is a Phase 2-3 trial aimed at understanding whether taking Cur as a dietary supplement (1000 mg/day) could maintain or improve physical and cognitive activity in aged individuals; molecular inflammatory biomarkers were analyzed. NCT01982734 is a Phase 1 trial in which, because native Cur has poor bioavailability, different formulations of Cur were administered, together with other phytochemicals, to healthy individuals in order to analyze their pharmacokinetics. The administration of native curcuminoids with different phytochemicals increased the bioavailability of Cur only slightly, but the micellar solubilization of Cur increased the area under the curve (AUC) 88 times more than produced native Cur [19]. In an early Phase 1 trial (NCT01925287), the same authors had previously studied the differences of pharmacokinetics between the sexes, demonstrating that males and females have different responses to the administration of micellar Cur [18].

Because the oral administration of solid-lipid curcumin particles (SLCP or Longvida) induced a significant amelioration of memory deficit in rodent models of AD, a Phase 2

clinical trial (NCT01001637) analyzed the potential efficacy and safety of SLCP as a dietary supplement in order to assess whether it could induce improvements in mental capacity in AD patients and βA concentration in the blood changed after this treatment. Although the estimated date for the completion of this trial was November 2010, no results are yet available.

It was shown recently that Cur is able to moderate or reverse memory impairment with no placebo effect in an animal model of AD [50], which has stimulated the continuation of studies on humans. Although Cur may correct immune defects of cells, such as macrophages and peripheral blood mononuclear cells (PBMCs), in AD patients [51], a recent meta-analysis has shown that clinical trials, while showing tolerability, have produced contradictory results on the efficacy of chronically administered Cur, [52, 53].

Parkinson's Disease (PD)

PD was first reported in 5000 BC [1], in India, and named Kampavata. In the modern age, the first medical description, as a "shaking palsy", was by the British doctor James Parkinson, in the early 19th century. It was also in India that the first PD treatment was found because the people there used (probably without knowing the real reasons), seeds containing therapeutic levels of levodopa (L-Dopa), which is nowadays the most important symptomatic approach [54].

PD, which is induced by the massive death of dopaminergic neurons of the *substantia nigra,* is the most recurrent movement disorder distinguished by progressive muscle control loss. Bradykinesia, rigidity and rest tremor are highlighted as pivotal signs of the disease and cause impaired balance; mental symptoms of the disease have also been recorded [55, 56].

The prevalence of the disease usually ranges from 100 to 200 per 100,000 people and it is somewhat more frequent in men than in women. Most commonly the onset of PD is between 65 and 70 years of age, although it can rarely—in less than 5% of cases—be present in younger patients; in most cases of onset before the age of 40 the cause is genetic alterations [55].

For most of the 20th century the medical view was that sporadic PD was correlated with environmental contaminants but this changed, on the basis that there are no compelling data indicating that any particular toxin is responsible for sporadic PD. Chronic contact with rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been shown to

have a low probability of causing PD [57], although a recent meta-analysis showed that the risk of PD increases by 5% after 5 years of pesticide exposure and by 11% after 10 years [58].

Genetic forms of PD constitute only 5–10% of all cases [59]. The major genes identified and proved to be causal in PD are Parkin (PARK) 2, α-synuclein (α-Syn-PARK1/PARK4), Leucine-rich repeat kinase2 (LRRK2/PARK8), ubiquitin C-terminal hydrolase-like 1 (UCH-L1), PTEN-induced putative kinase 1 (PINK1/PARK6), DJ1 (PARK 7), and ATP-ase type 13A2 (ATP13A2) [60].

The treatments of PD are directed to the maintenance of dopamine receptor stimulation. This is achieved in a range of ways: by administering a precursor of dopamine, by using agonists of the dopamine receptor, by reducing the metabolism of dopamine, and by balancing the ratio between dopamine and ACh.

L-Dopa has been the most widely used treatment; it can pass the BBB (while dopamine cannot) and is metabolized into dopamine by the enzyme dopa decarboxylase in the dopaminergic neurons of the *substantia nigra*. The absence of non-physiological pulsatile striatal dopamine receptor stimulation is probably the cause of various maladaptive neuronal responses [61]. Other approaches involve the use of dopamine receptor agonists such as ergoline derivatives—although these raise some cardiac and pulmonary safety concerns—and other, non-ergolitic, dopamine receptors agonists [62], which also induce a less pulsatile level of dopamine receptor stimulation than L-Dopa. Finally, other approaches have included MAOB inhibitors such as rasagiline and selegiline, which are irreversible and prompt a rise in the synaptic dopamine level, and safinamide, which is a reversible MAOB inhibitor with antiglutaminergic properties [63].

The preparations of L-Dopa contain carbidopa or benserazide to impede the peripheral metabolism of dopamine. This therapeutical approach reduces L-Dopa's peripheral metabolism to a secondary pathway that involves Catechol-O-methyltransferase (COMT), and the inhibition of the COMT pathway increases the bioavailability of L-Dopa [63].

Curcumin treatment of Parkinson's Disease

As the second most common neurological disease, PD has been the subject of many studies, including a number on the use of Cur. A range of approaches have been adopted in both cell and animal models.

In SH-SY5Y dopaminergic cells, the level of Heat Shock Protein 90 (HSP90) was increased by MPTP treatment, and Cur reversed this effect. The effect induced by Cur was significantly reduced by silencing HSP90; on the other hand, its overexpression increased the influence of Cur on PD, most likely via up-regulation of HSP90 [64]. In an analogous experiment using DMC and rotenone-treated SH-SY5Y cells, DMC could protect against (100 nM, 3.9 mg/ml) rotenone-induced cytotoxicity, increasing cell viability by 86 ± 3.97% more than the control in the presence of 50 nM (1.7 mg/ml) of DMC; this effect was likely due to a reduction in Reactive Oxygen Species (ROS) (Fig. 1). DMC also decreased apoptosis in rotenone-pretreated SH-SY5Y cells, decreasing the expression of B-cell lymphoma 2 (Bcl2), Bcl2-associated X protein (Bax), Bcl2-associated death promoter (BAD), B-cell lymphoma-extra large (BclXL), caspase-3, 6, 8, and 9, and Cytochrome (Cyt)-c in mitochondria and cytosol (Fig. 1) [65]. In the rotenone PD rat model, Cur restored motor deficits and increased the antioxidant enzyme activities underlying its antioxidant potential *in vivo*, most likely playing a neuroprotective effect [66]; it also protected or reversed synaptic alteration in the hippocampus [67].

Cur can bind α-Syn, the main component of Lewis Bodies and hamper its accumulation in the DA neurons [68].

In transgenic mice over-expressing human Green Fluorescent Protein (GFP)-tagged wild-type α-synuclein (Syn-GFP), chronic and acute Cur treatment induced an improvement in motor behavior which was correlated with an increase in phosphorylated α-synuclein protein to the levels found in the cortical presynaptic terminals [69].

In another rat PD model (2,4,5-trihydroxyphenethylamine (6-OHDA)-induced), Cur reversed the deficits generated by 6-OHDA [70], improved rotational behaviour [71], reduced the death of DA neurons in the *substantia nigra* [71, 72], and inhibited the activation of astrocytes, most likely through the Wnt/ β-Catenin signaling pathway [71].

Multiple Sclerosis (MS)

About 0.1% of the population of North America and Europe is hit by this devastating autoimmune disorder [73]. First described by Carswell in 1838, and named by Charcot [74], MS is a disease that primarily attacks the myelinated CNS. As far as is known to date, the genetic involvement in the disease is limited to a modest increase of disease susceptibility, but many well-defined environmental factors are considered risk factors, such as ultraviolet B light (UVB), Epstein-Barr virus infection, smoking, Vitamin D (Vit D), and obesity

[75]. Initially, MS was grouped as an organ-specific T-cell mediated autoimmune disease, but more recently the accepted view has changed to also include B-cells [76].

All over the world, in both developed and developing countries, the incidence of MS is greater the further north we go, most likely because UVB increases the production of skin Vit D [77]. Currently, the sex ratio is close to 3:1 (F:M) in most developed countries, but this ratio has been increasing, from 1:1, since the beginning of the last century [78].

Over 150 loci (mostly single nucleotide polymorphisms) [79] have been linked with sensitivity to MS, one of which is the Human Leukocyte Antigen (HLA) gene cluster, which accounts for up to 10.5% of the genetic variance [80]. Although intense molecular analysis of the HLA region in MS has been undertaken, more research is required in order to build integrated models that can rationalize the role of the Major Histocompatibility Complex (MHC) in MS pathogenesis. It is believed that lymphocytes T helper 17 (Th17) cells, a unique proinflammatory lineage of effector/memory, are implicated in the pathogenesis of MS, but we also know that many interleukins and cytokines are altered in MS, such as Interleukin (IL)6, Matrix metalloproteinase (MMP)9 enzyme activity, Interferon (IFN)γ, IL17 and IL12 family cytokines, and inducible Nitric Oxide Synthase (iNOS) [81].

The main treatments for MS are the immunosuppressant natalizumab, ocrelizumab, fingolimod, or immunomodulators, typically IFNβ, teriflunomide, and glatiramer acetate. Another approach is immune reconstitution therapy by means of cladribine and alemtuzumab[76]. Symptomatic therapies comprise anticholinergics for bladder dysfunction and medication for neuropathic pain such as gabapentin and derivatives, or tricyclic antidepressants [76].

<u>Curcumin treatment of Multiple Sclerosis</u>

In a cellular model of MS in which human astrocyte cell lines (U373-MG) were treated with lipopolysaccharide (LPS), it was shown that Cur reduced both the release of IL6 and MMP9 activity, although it affected neither mRNA levels of insulin-like growth factor (IGF)-1 nor neurotrophin (NT)-3. These results indicate that Cur can cause an anti-inflammatory response by acting on astrocytes in the CNS [82].

Analogous studies were also performed in mouse models using the autoimmune encephalomyelitis (EAE) model for MS. Cur inhibits IFNγ, IL17 and IL12 family cytokines expression in the CNS [81]. These results agree with those obtained in a similar rat model where the level of myelination was increased in Cur treated animals, most likely by the

restoration of iNOS mRNA levels and by potentiating the Nrf2 cellular defense pathway against oxidative stress [83]. Moreover, in this model Cur enhanced all of the following: Brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF), the level of Myelin basic protein (MBP), Nestin (a neural stem cells (NSCs) marker, Olig2, Platelet-derived growth factor receptor α (PDGFR α), and oligodendrocyte progenitors markers [83].

In a clinical study, it was demonstrated that Cur (nano micelle formulation), was able to reduce the fraction of Th17 cells in the peripheral circulation (after 6 months, 80 mg/day) [84]. Since increasing numbers of Th17 cells were linked in MS patients to raised levels of IL23 and IL17A, and increased expression of retinoic acid-related orphan receptor γ (RORγt), these authors also evaluated the effect of Cur treatments on these factors. They observed significantly lower levels of RORγt mRNA and reduced IL17 secretion, while the expression levels and concentration of IL23 mRNA were not influenced [84].

NCT03150966 is a Phase 2 trial (Supplementary material) which aims to understand the impact of oral nanocurcumin on the levels of expression in MS of different microRNAs (such as miRNA-106b, miRNA-25, and miRNA-326), transcription factors (Foxp3 and RORγt), cytokines (such as Transforming growth factor β (TGFβ) and IL17) and T regulatory and Th17 cells. In another Phase 2 trial (NCT01514370) the safety and efficacy of dietary supplements of Cur were tested in patients with active relapsing MS already under IFN1β treatment. For both trials, the results are not yet available.

Amyotrophic Lateral Sclerosis (ALS)

Another devastating neurological disease is ALS, in which MNs (upper and lower) are dramatically affected, causing death from respiratory failure. Worldwide, there are five new cases per year per 100,000 of population, and, due to the short average survival time, the incidence is 1.7 per 100,000. Defects in RNA processing and protein clearance might be involved in the mechanisms of the pathogenesis. Since its description by Charcot in 1874, much knowledge has been accumulated [85] and, to date, ALS can be divided into sporadic (s) and familial (f). The first gene found to be involved in the disease was the superoxide dismutase (SOD) 1, but since its discovery more than other 20 genes have been found to be involved [86], which between them explain more than 50 % of the fALS. These genes can be characterized as either causative or related to susceptibility (such as

ataxin 2) [85]. Some reports have indicated that SOD1 pathological inclusions present in ALS share similarities with amyloid fibrils produced *in vitro* [87].

The most commonly responsible for ALS is the repeat expansions in the chromosome 9 open reading frame 72 gene (C9orf72), with 40% of patients having a family history and about 10% with no family history. Many laboratories have, in cases of fALS, found mutations of TAR-DNA-binding protein of 43 kDa (TDP-43). This is a ubiquitously and constitutively expressed DNA–RNA-binding protein, involved in gene transcription repression, regulation of exon splicing, and nuclear body functions. Mutated TDP-43 is abnormally cleaved, ubiquitinated and phosphorylated; it aggregates and is mislocalized in the neuritis or cytoplasm [88]. TDP 43 aggregates of this protein in the affected nerve cells were noticed in most sporadic ALS cases, indicating their pivotal role in ALS [89, 90].

Many environmental conditions have been implicated in the epidemiology of ALS pathogenesis, including smoking, pesticide contamination, alcohol, lead, viral and fungal infections, electromagnetic radiation, and physical exercise [85].

To date, two drugs with moderate effects have been approved by the FDA for ALS treatment: riluzole, a glutamate receptor antagonist, and the free radical scavenger edaravone. Many other encouraging treatment strategies are being explored, among them Vit E, Ginkgo biloba, melatonin, folic acid, α-lipoic acid, and regular exercise of low and moderate intensity [91].

Curcumin treatment of Amyotrophic Lateral Sclerosis

The role of Cur treatment in recovering the impairment induced by overexpression of TDP-43 has been analyzed using NSC-34 cells transfected with TDP-43 as an ALS cellular model. DMC has a protective effect on mitochondrial membrane potential, decreasing the levels of uncoupling protein (UCP) 2 [92]. These protective effects of Cur also involve the initiation and propagation of action potentials (APs), which are enhanced by the overexpression of TDP-43 [93].

Cur regulates the early aggregation phases of reduced SOD1, allowing the production of non-fibrillar smaller and less toxic aggregates. It also binds these products strongly, most likely in aggregation-prone regions of intermediates, blocking the exposed aggregation site on these molecules, and inhibiting the production of toxic species in the aggregation pathway [94]. A clinical trial using nanocurcumin as an add-on therapy to riluzole found a

significantly increased survival rate in patients with ALS after 12 months of treatment [95].

Spinal Muscular Atrophy (SMA)

SMA is a recessive autosomal disorder with a worldwide incidence of 1 in 6,000-10,000 live births [96-98]. One person in 40 is a healthy carrier (heterozygote for this condition). Although this is a matter of debate, the beginning of the disease and the age of death are still used as criteria in the categorization of SMA patients, and about 25% of patients elude a precise classification. SMA can be classified in order of severity as Werdnig-Hoffmann disease (SMA1), SMA Intermediate (SMA2), SMA mild or Kugelberg-Welander disease (SMA3) and the adult form (SMA4) [99].

The reduced expression of Survival Motor Neuron (*SMN)* is responsible for SMA, and all patients harbor inactivating mutations of the telomeric *SMN1* gene. A centromeric *SMN2* gene, a partially functional paralog, can, however, partially compensate for the lack of *SMN1,* depending on its copy number [100].

Currently, two hypotheses are offered as explanations of the molecular mechanisms of the SMA. The first is that changes in the level of SMN protein, a 38 kDa protein important for RNA splicing [101, 102], alters the transduction of some genes critical in the physiology of the MNs. The second is that SMN protein has other particular functions in the MNs.

Many therapeutical approaches have been tested in order to find an effective treatment for SMA, and it was only recently that a splicing modifier called nursinersen was found to be clinically effective and received FDA approval. Nursinersen increases the level of exon 7 inclusion in SMN protein derived from the *SMN2* gene and so reduces the degeneration of MNs. Several trials have established that nusinersen is effective in SMA, with few adverse effects [103]. Intrathecal administration every 4 months (after a loading period) were able to reach the motor landmarks and growth parameters without fatalities and without ventilation being required. This treatment was also extended recently to older patients (who had already presented the symptoms and signs of the disease) in the hope that they would benefit from the drug.

Gene therapy is another potentially resolutive approach, in which the correct *SMN1* gene is inserted in the genome by means of a viral vehicle (adeno-associated viral (AAV) vectors). A single intravenous injection can ensure a systemic distribution of the gene. In the first AveXis trial, the treated patients reached (to date) 20 months of age, with a survival

rate of 100%, as against the 8% historically found in the untreated cohort [103]. Other therapeutical approaches for SMA involve the enhancement of muscle responses [104].

Curcumin treatment of Spinal Muscular Atrophy

Many studies on SMA are done on fibroblasts since these cells are easily obtained from patients and unaffected relatives. For instance, primary fibroblasts from (Type I) SMA patient which have two intact SMN2 genes were administered with Cur for 24 h, then SMN expression analysis was performed by RT-PCR (using fibroblasts from the healthy carrier as a control). The *SMN1*/*SMN2* mRNA ratio was ≈2:1 in control fibroblasts and ≈1:2 in patient fibroblasts. In these cells, Cur induces exon 7 inclusion and brings the *SMN1*/*SMN2* mRNA ratio to 2:1 depending on the Cur concentration [105]. SMN protein and the number of gems (Gemini of Cajal bodies) also increase after Cur treatment [105]. This is also true in fibroblasts from SMA 2 patients with three copies of SMN2 [106]. Since fibroblasts are not the most affected cells in SMA an *in vitro* approach using neuron-like cells (PC12) was performed by Bora-Tatar et al [107]. In this work, PC12 cells were stably transfected with a gene that knocks down *SMN1*. Cur was not able to change the SMN protein level and the neurite length in the SMN knockdown PC12 cells [107].

Spinal Cord Injury (SCI)

The overall incidence of SCI is 10.5 cases per 100,000 in the world population [108]. In SCI, the force applied during an accident—at work, on a bike, in a car, or in sport—causes deformation or/and breakage of the bone, which can damage the nervous tissue, inducing so-called ‘primary damage’ which is related to the amount of energy transferred to the nervous tissue. The other pivotal aspect of this disease is the ‘secondary damage’ caused by the patient’s immune system response, which attempts to fix the damage but instead causes an exacerbation of the impairment [1].

The variability of degree and type of injury in human patients makes finding a single strategy for the treatment of SCI a complex matter. The therapeutic scheme of intervention comprises early surgery to decompress the spinal cord and stabilize the spine, followed by transfer to a specialist rehabilitation center. Unfortunately, there is so far no treatment that can completely repair the spinal cord tissue. The current standard therapy includes the administration of methylprednisolone sodium succinate (MPSS) in order to decrease lipid peroxidation and free radical production and to prevent edemas, and thus to reduce SCI

damage. Other approaches have been hypothesized, based to date on preclinical work, cellular intervention with either substitutive or simply paracrine action, used in animal models by our group [1, 109-113] and by others with and without biomaterials (see [114] for a comprehensive review of the literature).

Curcumin treatment of Spinal Cord Injury

Most of the analyses of the effects of Cur on SCI have been conducted on rodent models of SCI with different types of damage: contusion and hemisection (at thoracic level 8 or 9), ischemia-reperfusion injury, and compression by clips or balloon.

In a model of clip compression, it was found that protein expression of HO-1, which exerts a significant protective role against oxidative injury [115], was increased after Cur treatment (of the lesioned animals) significantly more than in sham or lesioned not Cur treated animals. In addition, Cur caused a higher expression of Zonula occludens-1 protein (ZO-1), thus limiting the SCI-induced disruption of tight junctions and maintaining blood-spinal cord barrier integrity [115]. Moreover, Cur plays an anti-inflammatory effect by attenuating the increase of both TNFα and NFκB, the nuclear factor kappa-light-chain-enhancer of activated B cells [115].

Another important peculiarity of SCI (in the clip compression model) is the formation of glial scar due to astrocytes, which induces a severe obstacle to neural regeneration. Cur inhibits glial scar formation [116], most likely by suppressing NFκB activity since both Cur and p65-NFκB siRNA silencing reduce astrocyte activation, limiting GFAP (a marker of cell activation) and the overexpression of α-smooth muscle actin (α-sma a marker of fibrosis). Moreover, Cur induces the down-regulation of chemokines released (possibly through the induction of Nrf2) by astrocytes [117] such as Monocyte Chemoattractant Protein 1 (MCP1), Chemokine (C-C motif) ligand 5 or RANTES and C-X-C motif chemokine 10 (CXCL10) [118], which are important factors for macrophage and T-cell infiltration. All these effects contribute to reductions in glial scar inflammation.

Using a balloon compression method, it was found that the administration of Cur ameliorated behavioral performance in the first week after SCI, by improving locomotor and sensory performance [119]. It also reduced glial scar development by lowering the levels of RANTES and macrophage inflammatory proteins, reducing IL2, curtailing inflammatory cell invasion and decreasing NFκB activity (Fig. 1) [119].

In a hemisection model of SCI in rat, Cur was able to inhibit neuron loss and apoptosis, blocking astrocyte activation, and reducing the neurological deficit by down-regulating GFAP expression [120].

In an ischemia-reperfusion injury in rat, confirmation was found of the anti-inflammatory effect of Cur in reducing the elevation of NO, TNFα, and the levels of IL1β levels tissue protein, and Cur significantly reduced the increase in caspase-3 levels after injury (Fig. 1) [121]. Analogous results were obtained in a contusive mouse model, indicating the robustness and replicability of Cur action [122].

Cur and other substances with anti-inflammatory effects were tested in a Phase 3 open-label study which aimed to describe the effects of diet on chronic inflammation in SCI (NCT02099890, Supplementary material). The trial showed that these treatments, including Cur, induced a reduction of inflammatory molecules and neuroactive compounds such as prostaglandins PGE2 and (PGE3) and leukotrienes LTB5 and LTB5 [123].

Stroke

Reduction of the blood supply in some brain areas can result in a sudden loss of brain function. Stroke is the second most common cause of death worldwide after cardio-circulatory diseases; its incidence is contingent on race and age. A recent meta-analysis demonstrated that, worldwide, more than 36% of patients suffering a hemorrhagic stroke died in the first month and more than 50% died within the first year [124].

The main factor responsible for the disease is the occlusion of arteries, small or large. The main aim of the conventional therapeutical approach is to decrease the size of the thrombus and to prevent the formation of clots by the use of recombinant tissue plasminogen activator (rt-PA), the only FDA approved drug [124, 125].

Curcumin treatment of Stroke

By using a middle cerebral artery occlusion (MCAO) in a rat model it was observed that Cur treatment reduces infarct volume [126-129] and brain edema at 24 h [127, 130] and achieved better neurological scores than a vehicle-treated group [126, 127, 131, 132]. These effects are likely due to the attenuation of oxidative stress (in terms of lipid peroxidation). Cur also reduced neuronal apoptosis by augmenting the antiapoptotic Bcl2 protein at mitochondrial levels (Fig. 1), reduced the cytosolic translocation of Cyt- c [126, 129] and reduced the mitochondrial membrane potential [130]. Another important effect exert-

ed by Cur, during the reperfusion phase, is the reduction of adherent neutrophils at the vascular endothelium level and the reduction of vascular endothelium activation due to the lowering of TNFα NFκB-mediated expression [127]. In the same model Cur treatment reduced inflammation by means of Toll-like receptor 4 TLR4/p38/Mitogen-Activated Protein Kinase (MAPK) or by the activation of silent information regulator 1 (Sirt1) pathways, inducing a reduction in the expression of IL6, TNFα (Fig. 1) [128, 130, 132], and iNOS, and a reduction of autophagy via PI3K/Akt/mTOR [132].

Cur also has a protective effect in a rat model stroke-prone spontaneously hypertensive (SHRsp), delaying the onset of stroke and increasing the probability of survival. These effects are most likely due to an increase in the presence of proteins of the mitochondrial anion carrier family and a Cur-induced physiological regulation of mitochondrial ROS generation [133]. These results were also confirmed in a cellular model with HUVECs, using H_2O_2 to simulate oxidative stress *in vitro* which was attenuated by Cur treatment [133]. Results analogous to those described for rat were also obtained in a mouse model of MCAO where Cur treatment reduced cerebral infarction and neuronal apoptosis *in vivo* and *in vitro* on N2a cells, most likely reducing mitochondrial dysfunction [134].

Epilepsy

A seizure results from a deficit of cell function—without cell degeneration and death—and it is considered epilepsy if two episodes occur with no known cause. The global prevalence of epilepsy is 7.6 per 1,000 and increases with age; the incidence is 61.4 per 100,000 person-years [135]. Seizures are due to uncontrolled discharges in the brain that cause muscle contractions and unconsciousness [1].

Seizures can be classified as generalized (absence, tonic-clonic, myoclonic and atonic), partial (simple and complex) and status epilepticus [136]. Only 30% of epilepsy cases are related to traumas such as lack of oxygen during labor, head injuries altering the fragile electrical system in the brain, lead poisoning, meningitis, encephalitis [1] and gene alterations [137].

The therapeutical approach is usually symptomatic; anti-epileptic drugs have three main sites of intervention: membrane stabilization, reduction of excitatory neurotransmitter release and increase of γ-aminobutyric acid (GABA)-mediated inhibition. Between 20 and 30 % of epilepsy patients, however, are resistant to these interventions and so need a surgical approach [138].

Curcumin treatment of Epilepsy

In induced status epilepticus (by electrical stimulation) in rats, Cur treatment did not reduce seizure, most likely because it did not at appropriate level into the brain [139]. In a kainic acid-induced epilepsy model, however, Cur was able to attenuate cognition deficits, inflammation and neuronal death, suppressing inflammation protein expression such as IL1, and cleaved caspase-1 in the hippocampus [140]. And in an iron-induced epilepsy model, Cur was able to reduce the overexpression of Na_v 1.1 and Na_v 1.6 sodium channels [141].

Neuropathic Pain

The main cause of neuropathic pain is the dysregulation of the somatosensory nervous system. Elevated levels of response to pain stimuli (hyperalgesia), abnormal, unpleasant sensations (dysesthesia), and pain in response to stimuli that should not be felt as pain (allodynia) are usually the hallmarks of this disease. Peripheral neuropathic pain may derive from injuries to the peripheral nerves—motor, sensory, or autonomic—or from diseases such as cancer, diabetes, AIDS, herpes, , SCI, MS, and from trauma such as mastectomy and stroke [142]. On the other hand, central neuropathic pain can be a consequence of brain injury and SCI, stroke and MS [142]. The prevalence of neuropathic pain in the general population has been estimated at 6.9–10.0% [143]. The main pharmacological approach to this disease involves opioids, but this is problematic: they have little clinical efficacy, they bring the danger of abuse and patients develop tolerance. Other treatments include anti-depressants such as tricyclic anti-depressants (TCAs), selective serotonin (5HT) and norepinephrine reuptake inhibitors (SSNRIs) [142].

Curcumin treatment of Neuropathic Pain

Chronic constriction injury (CCI) in mouse by means of sciatic nerve ligature has been shown to respond to chronic, but not acute, Cur administration through a reduction in thermal hyperalgesia and mechanical allodynia. These effects were mediated by noradrenaline and 5HT descending pathway depletion; indeed, $5HT_{1A}R$ and spinal β2 adrenergic blocking receptors abolish the effect of Cur [144]. Moreover, acute inhibition of *δ*-opioid receptors and μ-opioid receptors abolishes the analgesic effects of Cur on thermal hyper-

algesia and mechanical allodynia [144]. This result was also supported by cellular analysis using neuroglia cells, where it was found that the expression of the opioid-related nociceptin receptor 1 gene (OPRL1) was also down-regulated [145]. In an analogous model, the effect of chronic treatment with Cur was to block the expression of 11β-hydroxysteroid dehydrogenase type I enzyme ($11\beta HSD_1$) and to reduce thermal hyperalgesia and mechanical allodynia [146].

Mouse neuropathic pain model induced by formalin showed a response to Cur treatment inducing a noticeable hypoacetylation of histones H3 and H4 in dorsal root ganglia and down-regulation of the metabotropic glutamate receptor 2 (mGlu2) receptor in the spinal cord [147].

Comprehensive Curcumin Mechanisms in Neurological Diseases

We can identify common pathways by which Cur, regardless of the motivation for its use, can exert its effects.

Inflammation is a common factor in many neurological diseases. Although the diseases described above have many differences, one common factor is increased levels of IL2 and 6, TNFα, COX2, and MMP9 activity (Fig. 1) [148, 149]. In most cases, NFκB plays a pivotal role in this inflammatory response by inducing the production of TNFα, which also mediates ROS activation. Since Cur has an inhibitory effect on NFκB, its use in treatment can induce a reduction of the inflammation (Fig. 1) [148]. These effects can be also mediated by the MAPK pathway that leads to the production of TNFα, and, indeed, Cur has been proven capable of inhibiting this pathway (Fig. 1). Moreover, in AD, PD, MS, and SCI neuronal death in distinct regions of the CNS is also mediated by ROS, and oxidative stress in AD seems to be due to TNFα-mediated NFκb activation (Fig. 1) [148].

Cur is also able to modulate apoptosis in PD, SCI and Stroke, most likely by enhancing NFκB-reduced expression of Bcl2 and BclXL and by reducing the NFκB-induced expression of Bax, BAD and caspases (Fig. 1) [16]. Another interesting mechanism that can be modulated by Cur is monocyte chemotaxis and T-lymphocyte differentiation. Inflammatory diseases such as MS, SCI, and AD are characterized by the phlogosis invasion of various areas [84, 118, 119, 150]. MCP1 is the pivotal controller of monocyte recruitment and activation of T-lymphocyte via the binding of the CCR2 receptor. This chemokine is modulated by various pathways including AP1, JNK, NFκb, and MAPK that could be negatively regulated by Cur (Fig. 1) [149, 151].

Conclusions

Mens sana in corpore sano relates not only to physical exercise [152, 153] but also to other lifestyle factors such as healthy rest and good diet, which nowadays includes a wide range of "old" supplements that have arrived from eastern cultures, one of which is Cur. Our increased understanding of its proven protective capacity against many different diseases, including the neurological ones, and of its molecular actions, have encouraged researchers to find ways of making it work more efficiently. The recently developed formulations represent new pathways for the treatment of many neurological diseases, some of which previously had no effective treatment.

AUTHOR CONTRIBUTIONS

DB wrote the paper. RA prepared the tables and the graphical abstract. DB prepared Fig. 1. RA and DB revised and discussed the text figures and tables.

CONFLICT OF INTEREST

The Authors declare no conflicts of interests.

Figure Legend

Effects of Cur on common pathways involved in different neurological diseases.

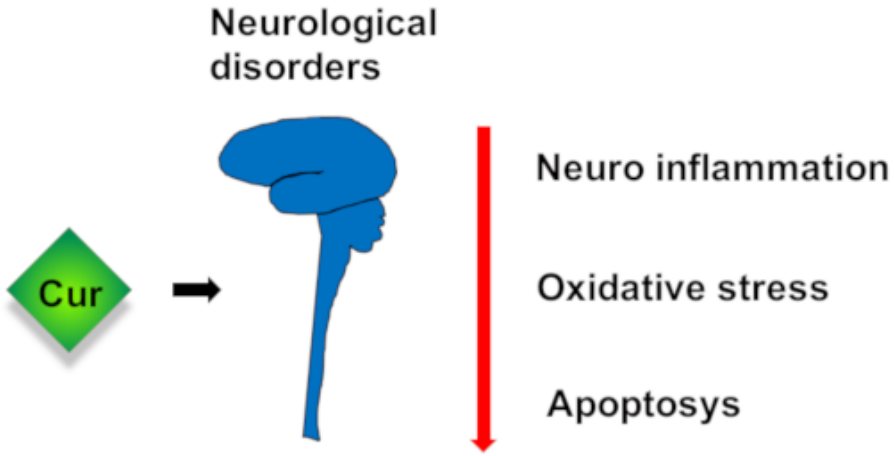
Cur induces a suppressive activity on different pathways, reducing the recruitment of monocytes, apoptosis, and inflammation.

Blue: pathways affected by NDs; red: pathways affected by cellular activation; orange: pathways affected by apoptosis; pink: pathways affected by inflammation.

➡ indicate positive effects, ⊥ indicate negative effects.

Abbreviations as in the abbreviation list.

Graphical abstract



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Abstract

The beneficial effects of many different substances have been discovered as a result of regular dietary consumption. This is also the case of curcumin, whose effects have been known for more than 4000 years in eastern countries such as China and India. A curcumin-rich diet was known to combat many different human diseases including cancer and diabetes and reduces inflammation. The effect of Cur treatment of neurological disease has only recently been brought to the attention of researchers and the wider population.

In this paper, we summarize the studies on this natural product from its isolation, two centuries ago to its characterization a century later, describe its role in the treatment of neurological diseases, including its cellular and common molecular mechanisms, and report the clinical trials of curcumin with healthy people and patients, commenting on the different approaches adopted by efforts to increase its bioavailability.

Keywords

Curcumin; spinal muscular atrophy; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; multiple sclerosis; epilepsy, neuropathic pain; stroke; spinal cord injury.

Abbreviations in the Text, Tables, and Figure:

Curcumin (Cur); bis-demethoxycurcumin; demethoxycurcumin (DMC); oral (per os); endovenous (EV); intraperitoneal (IP); blood-brain-barrier (BBB); dihydrocurcumin (DHC); tetrahydrocurcumin (THC); dimethoxycurcumin (DiMC); Solid lipid nanoparticles (SLNPs); Liquid crystalline nanocarriers (LCN); Nanostructured lipid carriers (NLC); neurological diseases (NDs); Alzheimer's disease (AD); Parkinson's disease (PD); Multiple Sclerosis (MS); Amyotrophic Lateral Sclerosis (ALS); Spinal Muscular Atrophy (SMA); Spinal Cord Injury (SCI); Apolipoproteina E (APOE); β-amyloid (βA); amyloid precursor protein (APP); Central Nervous System (CNS); acetylcholine (ACh); Food and Drug Administration (FDA); Acetylcholinesterase (AChE); Monoamine oxidases (MAO); *N*-Methyl-D-aspartate receptor (NMDAR); levodopa (L-Dopa); 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Parkin2 (PARK2); α-Synuclein (α-Syn-PARK1/PARK4); Leucine rich repeat kinase2 (LRRK2/PARK8); ubiquitin C-terminal hydrolase like 1 (UCH-L1); PTEN-induced putative kinase 1 (PINK1/PARK6); DJ1 (PARK 7); ATPase type 13A2 (ATP13A2); Catecohol-O-methyl transferase (COMT); ultraviolet

B (UVB); Vitamin (Vit); Hunan Leukocyte antigen (HLA); Major Histocompatibility Complex (MHC); lymphocytes T helper 17 (Th17); Interleukin (IL); Matrix metalloproteinase (MMP); Interferon (IFN); Nitric Oxide Synthase (iNOS); Motor neurons (MNs); Superoxide dismutase (SOD); chromosome 9 open reading frame 72 gene (C9orf72); TAR-DNA-binding protein of 43 kDa (TDP-43); Survival Motor Neuron (SMN); adeno-associated viral (AAV); methylprednisolone sodium succinate (MPSS); recombinant tissue plasminogen activator (rt-PA); γ-aminobutyric acid (GABA); tricyclic anti-depressants (TCAs); selective serotonin (5HT); norepinephrine reuptake inhibitors (SSNRIs); Nuclear respiratory factor 1 (Nrf1); Nuclear erythroid 2-related factor 2 (Nrf2); Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC)1α; Mitochondrial transcription factor A (TFAM); Postsynaptic Density Protein 95 (PSD95); Heat Shock Protein 90 (HSP90); near-infrared fluorescence (NIRF); positron emission tomography (PET); magnetic resonance imaging (MRI); Tumor Necrosis Factor-α (TNFα); intracerebroventricular (ICV); streptozotocin (STZ); Cyclooxygenase 2 (COX2); Nitric oxide (NO); Glial fibrillary acidic protein (GFAP); peroxisome proliferator-activated receptors (PPAR); macrophages and peripheral blood mononuclear cells (PBMCs); Reactive Oxygen Species (ROS); B-cell lymphoma 2 (Bcl2); Bcl2-associated X protein (Bax); Bcl2-associated death promoter (BAD); B-cell lymphoma-extra large (BclXL); Cytochrome (Cyt); Green Fluorescent Protein (GFP); 2,4,5-trihydroxyphenethylamine (6-OHDA); lipopolysaccharide (LPS); insulin-like growth factor (IGF); neurotrophin (NT); autoimmune encephalomyelitis (EAE); Brain-derived neurotrophic factor (BDNF); Nerve growth factor (NGF); Myelin basic protein (MBP); neural stem cells (NSCs); Platelet-derived growth factor receptor α (PDGFRα); retinoic acid-related orphan receptor γ (RORγt); Transforming growth factor beta (TGFβ); uncoupling protein 2 (UCP2); action potentials (APs); heme oxygenase-1 (HO-1); Zonula occludens-1 protein (ZO-1); nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); Monocyte Chemoattractant Protein 1 (MCP1); Chemokine (C-C motif) ligand 5 or RANTES; C-X-C motif chemokine 10 (CXCL10); middle cerebral artery occlusion (MCAO); Toll-like receptor 4 (TLR4); Mitogen-Activated Protein Kinase (MAPK); silent information regulator 1 (Sirt1); stroke-prone spontaneously hypertensive (SHRsp); chronic constriction injury (CCI); opioid-related nociceptin receptor 1 gene (OPRL1); 11β-hydroxysteroid dehydrogenase type I enzyme ($11\beta HSD_1$); metabotropic glutamate receptor 2 (mGlu2); Area under the curve (AUC); maximum concentration value (Cmax); time to reach the maximum concentration value (Tmax); leukotriene-4

(LTB4); leukotriene-5 (LTB5); regulatory T cells; Forkhead Box P3 protein (Foxp3); Relapsing-Remitting Multiple Sclerosis (RRMS); three in week (TIW); isoprostanes (IsoPs); Mini-Mental Status Examination (MMSE); Alzheimer's Disease Assessment Scale-Cognitive test (ADAS-cog); Montreal Cognitive Assessment test (MoCA); ClinicalTrials.gov identifier number (NTC); Turmipure GOLD™ 30% curcuminoids (300 mg) (TG); standard turmeric powder extract 95% curcuminoids (1500 mg) (STE); Novasol® Liquid micellar formulation 6% curcuminoids (1000 mg) (NOV); Meriva® Turmeric Phytosome formulation 20% curcuminoids (1000 mg) (PHYT); Turmeric extract C3 complex® 95% curcuminoids (1500mg) + BioPerine® 95% piperine (15 mg) (TEP); Native turmeric extract (207 mg curcumin) (A); Native turmeric extract with 7-9% volatile turmeric oils (207 mg curcumin) (B); Turmeric extract plus mixture of phytochemicals (207 mg curcumin) (C); Cyclodextrin complex of curcuminoids (207 mg curcumin) (D); Turmeric oleoresin (207 mg curcumin) (E); Liposomal curcumin (207 mg curcumin) (F); Phytosomal curcumin (207 mg curcumin) (G); Micellar turmeric extract (207 mg curcumin) (H);encapsulated curcumin (EC); encapsulated curcumin plus Piperine, Quercetin and Genistein (EC-PQG); free cocoa polyphenols (FCP); encapsulated cocoa polyphenols (ECP).

Introduction

Turmeric, which contains Curcumin (Cur), has been widely used in Indian and Chinese cooking but only relatively recently recognised as a natural protective treatment with proven healing capacity. Cur has been used for the treatment of many different disorders including, but not limited to, neurological disorders (or neurological diseases, NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA), Spinal Cord Injury (SCI), stroke and seizure. The classification of the various etiologies of these disorders is very complex and they affect the Central Nervous System (CNS) in different ways, but they can be categorized, broadly, as follows. Firstly, there are those diseases that cause the loss of cells in particular regions of the brain or specific kinds of neurons, such as AD, PD, MS, ALS and SMA The second group is those diseases in which acute damage causes loss of tissue, such as Stroke and SCI. Finally we have those NDs which involve neither degeneration nor death of cells but in which there is a deficit of cell function, such as seizure disorders[1]. The mechanisms by which Cur treatment plays a role in these diseases are different and range from anti-inflammatory action to the regulation of ion channels and genes.

Curcumin

Cur is a phytopolylphenol pigment (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) obtained from the plant *Curcuma longa* (but also found in Curcuma aromatica, mangga, phaeocaulis, xanthorrhiza, zedoaria, Etlingera elatior, Zingiber cassumunar, and Costus speciosus) and commonly known as turmeric. Turmeric is a perennial herbaceous plant with oblong, palmate roots and tubers that grows spontaneously in southern Asia and Africa, in tropical climate regions with high rainfall and a normal temperature range of between 20 °C to 35 °C [2].

The world's leading country for turmeric production is India with nearly 200,000 hectares and around 900,000 tonnes of production in 2008. Tumeric has been known since the inception of the ancient Indian system of medicine, the Ayurveda, about 4000 years ago; it was first isolated chemically more than 200 years ago and its structure characterized in 1910 [2]. It is Cur that is responsible for turmeric's yellow color and it is used not only for health and as a food preservative but also as a textile dye. The percentage among all the curcuminoids in tumeric of the three major curcuminoids is: Cur (diferuloylmethane)

(about 77%), bisdemethoxycurcumin (BDMC) (about 3%), and demethoxycurcumin (DMC) (about 17%) [3].

Pharmacokinetics of Curcumin

There are three main reasons why little advantage has so far been taken of the therapeutic potential of Cur. The first is its low degree of oral bioavailability, mostly due to its limited absorption, high metabolism, and rapid systemic elimination. Secondly, Cur is poorly soluble in water (about 11 ng/mL) and highly degraded in a basic environment [4]. Thirdly, when Cur is administered per oral administration (per os) most of it is excreted in the feces because it is poorly absorbed: the intestinal tract also because Cur undergoes glucuronidation in the intestinal mucosa inactivating the Cur. Cur then undergoes first pass effect reduction to DHC, THC, and hexahydrocurcumin followed by conjugation to sulfates and glucuronides in the liver [5, 6] and it is eliminated through the urine [4]. Many pharmacokinetic studies performed in humans and rodents have shown that the greatest plasma concentrations reached after oral administration were 0.051 mg/mL from 12 g Cur in human, 0.22 mg/mL from 1 g/kg in the mouse and 1.35 mg/mL from 2 g/kg in the rat [7]. It was determined that the bioavailability of Cur orally was only 1% [8, 9], much less than is achieved endovenously (EV) and intraperitoneally (IP) [8, 9].

Cur appears in the plasma 15 minutes after IP administration; 45 minutes later it is detectable in the liver, spleen, intestines, and kidneys but only traces appear in the brain despite the fact that Cur efficiently passes the blood-brain-barrier (BBB).

In a rodent model the presence of l-piperoylpiperidine (piperine)—an alkaloid produced from black pepper fruits (Piper nigrum and other plants from the family Piperaceae), an inhibitor of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase)—increases the bioavailability of oral Cur by up to 154% [8] and leads to the presence of Cur in the brain being detectable up to 96 hours after administration [9].

The bioavailability of Cur can be increased by administering its derivatives which display enhanced biological activity and improved pharmacokinetics: one example is dimethoxycurcumin (DiMC), which has higher levels of metabolic stability and pro-oxidant and anticancer activity [10].

Nanocarriers for Curcumin Delivery

In clinical trials, when administered together with food in doses between 1 and 4 g/per day, as capsules or as powder, Cur did not produce improvements in AD patients [11].

Since the efficacy of Cur has been demonstrated in cell models, the main issues for human trials are protection from its fast metabolism and, more broadly, increasing its bioavailability, so manufacturers have responded by producing lipid-based nanoparticles [12]. Among them, solid lipid nanoparticles (SLNPs) underwent an intensive development because they combine the benefit of carrier systems like liposomes (being composed of biocompatible lipids and fatty acids), with the benefits of polymeric solid particles, which efficiently protect the loaded drug (either lipophilic and hydrophilic) against chemical degradation in the harsh environment of the gastrointestinal tract.

Many different strategies have so far been used for Cur delivery *in vivo*, such as Longvida® (Verdure Sciences Inc.), an SLNP-formulation which can achieve from 0.1 to 0.2 μM (0.037 to 0,074 μg/ml) levels of Cur in the plasma and 1–2 μM (0.37-0.74 μg/ml) in the brain [13]. Nanostructured lipid carriers (NLC), developed as an evolution of SLNP, are also widely used since they can contain larger quantities of drugs [12]. Liposome-encapsulated Cur has been demonstrated to be a safe formulation where Cur is delivered into the cells via membrane endocytosis or fusion, as seen in animals models [14].

Pharmacodynamics of Curcumin

Many molecular targets are affected by Cur, either by physical interaction or by modulation of enzyme activity, or transcription factors. In a gene expression analysis in tumor cells, Cur has been found capable of up-regulating 202 mRNAs and down-regulating 505 mRNAs [15]. Many transcription factors (and their gene targets) involved in tumorigenesis, cell proliferation, cell survival, inflammation, invasion, and angiogenesis, are thus modified negatively or positively; Cur can also regulate the expression of growth factors, their receptors, and some downstream signaling pathways [16].

Curcumin Trials on Healthy Patients

Many different trials (observational or phase 1-3) have been performed on healthy adults, testing the effects of Cur. Most of them aimed to determine its pharmacokinetics by using one or other of its various formulations in order to identify a safe and effective method of delivery (Supplementary material).

Some trials, for instance, compared the different formulations of Cur administration: pow-

der, nanoparticle and proprietary NCT01925287, NCT01982734, NCT01330810, NCT01403545, NCT02474953, NCT03085680, NCT03746158, NCT03530436, NCT03621865, NCT03289507, NCT00181662, and NCT01288859. Most of these analyses investigated the age and sex-related pharmacokinetics profile safety of Cur formulations, and dosage [17-21]. Others, however, tested the impact of oral Cur on heme oxygenase-1 (HO-1) NCT00895167 (Phase 1 trial) or its effect in iron metabolism NCT01489592 (Phase 2 trial).

In observational clinical trials, on the other hand, analyses were conducted of the overall effects of various substances coadministered with Cur, including green and black teas, polygonum cuspidatum extract, soybean extract, resveratrol, sesamin, acetyl-L-carnitine, lipoic acid, quercetin, pomegranate and cinnamon bark; changes in oxidative stress and inflammation in the blood were studied in trials NCT00768118, NCT01752868, and NCT02815475 (Supplementary material).

Neurological Diseases

Alzheimer's Disease (AD)

Dementia is a neuropsychiatric disorder distinguished by a mix of functional disability and progressive psychological, behavioral and cognitive deterioration (WHO 2012).

In 2015 it was estimated that about 46.8 million people were affected by dementia worldwide, almost 30% more (9.9 million new cases) than the 2010 estimate [22]. It is anticipated that 74.7 million people will be affected by 2030 and 131.5 million by 2050.

There are two broad categories of dementia: irreversible—in forms such as AD, frontotemporal dementia, vascular dementia and Lewy body dementia—and reversible, such as cases caused by HIV, hypercalcemia, abnormalities in vitamin (Vit) B12 and folic acid, and changes in thyroid hormone levels [22].

Annually, more than 35 million people contract AD, which is the most widespread neurodegenerative disease, responsible for 60 to 80% of dementia cases [23].

The onset of AD onset is marked in most cases by deficits in one or more cognitive fields, including but not limited to memory, language, orientation, and executive function; behavioral disturbances occur in the later stages [22]. Although dementia is not a typical characteristic of aging [24], older age is one of the consistent and unvarying risk factors, the others being Apolipoprotein E (APOE) genotype e4 allele and family history. Other risk factors—such as education and occupational achievements, cardiovascular risk (e.g. hyper-

tension), diabetes, smoking, obesity, psychosocial factors (e.g., depression and alcohol consumption), and lifestyle factors such as physical activity—are modifiable by the patient [23].

Atrophic hippocampus and cerebral cortex are the macroscopic landmarks present in AD patients [25]; at the cellular and subcellular level AD patients show the presence of amyloid (A) or plaques consisting of βA protein and the accumulation of hyperphosphorylated Tau protein, which indicate the formation of neurofibrillary tangles, and, consequently, extensive neuronal death [26, 27]. Furthermore, APOE mechanisms [27, 28], genetic imprint factors [29], and oxidation processes [30] are also involved in the neurodegeneration of AD patients. The irregular folding and aggregation of A peptides into senile plaques is implicated in the initial phases of AD neurodegeneration. Various isoforms of A peptides, the most common being 40 and 42 amino acids long, are produced from sequential proteolysis of the amyloid precursor protein (APP), a transmembrane glycoprotein of approximately 770 amino acids expressed by several cells, including the neurons of the CNS. The cleavage of APP takes place through the enzymes α-, β- and ɣ-secretase. The amyloid pathway starts when APP is cleaved by β-secretase, thereby forming insoluble peptides with 39 to 43 fragments which easily aggregate into oligomers around cells and have a crucial role in pathogenic events [22]. The βAPP fragments, especially the βA-42 isoform, have pronounced cytotoxic properties related to the process of neurodegeneration caused by the facilitation of the formation of oxyradicals and the deregulation of calcium homeostasis, due to lipid dysregulation of the cell membrane. Moreover, these fragments form the insoluble structures that characterize AD histopathologically (senile plaques) and this process ultimately leads to neuronal death [22]. The Tau protein promotes a kind of assembly of tubulin, providing microtubule stability [22].

To date, the therapeutic approaches for AD are merely symptomatic and can improve memory and cognitive functions. The therapies in use are directed to improving cholinergic transmission via the inhibition of acetylcholine (ACh); indeed, the only drugs approved for AD treatment by the U.S. Food and Drug Administration (FDA) are palliatives: Acetylcholinesterase (AChE) enzyme inhibitors (galantamine, donepezil, and rivastigmine), and inhibitors of monoamine oxidase (MAO) B, which is highly expressed in the astrocytes and pyramidal neurons of AD patients [33], and interacts with γ-secretase enzyme. Both MAO and AChE inhibitors can assist memory and cognitive functions, and diminish the AD-related symptoms. In Europe memantine, a drug that mainly blocks *N*-

Methyl-D-aspartate receptor (NMDAR) but also serotonergic, cholinergic, and dopaminergic receptors, is also approved for AD treatment.

Curcumin treatment of Alzheimer's Disease

Since Cur contains two phenols connected by a linear β-diketone linker, it exhibits peculiar photophysical and photochemical properties [31]. In particular, Cur binds to βA plaques with the emission of a highly fluorescent signal, which makes it an important diagnostic tool for AD [32] including in the use of two-photon microscopy, near-infrared fluorescence (NIRF), positron emission tomography (PET), and magnetic resonance imaging (MRI) [33].

Cur inhibits βA levels, deposits and aggregation, by reducing the degree to which it self-assembles and inducing the disaggregation of fibrillar Aβ40 [32, 34, 35]. It also inhibits the formation of fibrillar βA and destabilizes fibrillar Aβ40 and Aβ42 *in vitro,* showing a protective effect to βA toxicity [36, 37]. Cur also helps in protecting mitochondria from the toxic effects of βA: for instance it reduces oxidative stress in PC12 caused by βA [38] and reduces brain IL1β and oxidized proteins in APP mice [39].

Cur pretreatment prevents βA-induced toxicity in human neuroblastoma cells (SH-SY5Y), increasing the levels of mRNA and proteins for mitochondria biogenesis genes such as Nuclear respiratory factor 1 (Nrf1), Nuclear erythroid 2-related factor 2 (Nrf2), Peroxisome proliferator-activated receptor gamma coactivator (PGC)1α, Mitochondrial transcription factor A (TFAM) and synaptophysin and Postsynaptic Density Protein 95 (PSD95) [40]. Cur is also able to inhibit Glycogen synthase kinase-3 (GSK-3), which regulates the phosphorylation of tau [41], and protects cells from tau-induced neurotoxicity [42].

No NDs (AD included) exist without microglia activation [43]; indeed it was demonstrated that βA reroutes microglia from their neuroprotective phenotype to their neurotoxic phenotype [44]. Since during βA accumulation the microglia and the inflammatory mediators are activated, further βA accumulation and neuroinflammation are induced. Cur blocks extracellular signal-regulated kinase 2 (ERK1/2) and p38 kinase signaling in βA-activated microglia *in vitro*, reducing the synthesis of IL1β, Tumor Necrosis Factor-α (TNFα), IL6 mRNAs, and proteins (Fig. 1) [45].

Interestingly, Cur has an inhibitory effect on acetylcholinesterase like many drugs used in AD therapy, however, up to date, no studies on Cur inhibition of acetylcholinesterase has been performed in the context of AD cell or animal models [46].

In vivo studies have confirmed the protective effect of Cur in AD. It was demonstrated in a rat model of AD induced by intracerebroventricular injection of streptozotocin (ICV-STZ) that Cur is able to reduce the deficits in the Object Recognition Test by decreasing neuroinflammation and increasing adult neurogenesis [47].

Moreover, in a mouse model of AD, Cur treatment caused suppression of the neuroinflammatory response, decreasing the levels of inflammatory molecules such as IL1β, TNFα, Cyclooxygenase (COX)2, and Nitric oxide (NO), and decreasing the number of Glial fibrillary acidic protein (GFAP)- and Iba-1-positive cells, probably because of the promotion of peroxisome proliferator-activated receptor (PPAR)γ activity (Fig. 1) [48].

Many clinical trials studying the effects of Cur in AD are ongoing (Supplementary material).

One of the first trials to assess the effects of Cur on AD-affected patients was started in 2004 (NCT00164749); it was a pilot study (Phase 1) which tested the effects of Cur in the better-absorbed formulations of powder or capsule [49]. Since the study was conducted for only a short period of time, and the placebo-treated patients did not show any cognitive decline, the effect of Cur on cognition was not clear, although βA aggregation was counteracted [11].

NCT03085680 is a Phase 2-3 trial aimed at understanding whether taking Cur as a dietary supplement (1000 mg/day) could maintain or improve physical and cognitive activity in aged individuals; molecular inflammatory biomarkers were analyzed. NCT01982734 is a Phase 1 trial in which, because native Cur has poor bioavailability, different formulations of Cur were administered, together with other phytochemicals, to healthy individuals in order to analyze their pharmacokinetics. The administration of native curcuminoids with different phytochemicals increased the bioavailability of Cur only slightly, but the micellar solubilization of Cur increased the area under the curve (AUC) 88 times more than produced native Cur [19]. In an early Phase 1 trial (NCT01925287), the same authors had previously studied the differences of pharmacokinetics between the sexes, demonstrating that males and females have different responses to the administration of micellar Cur [18].

Because the oral administration of solid-lipid curcumin particles (SLCP or Longvida) induced a significant amelioration of memory deficit in rodent models of AD, a Phase 2

clinical trial (NCT01001637) analyzed the potential efficacy and safety of SLCP as a dietary supplement in order to assess whether it could induce improvements in mental capacity in AD patients and βA concentration in the blood changed after this treatment. Although the estimated date for the completion of this trial was November 2010, no results are yet available.

It was shown recently that Cur is able to moderate or reverse memory impairment with no placebo effect in an animal model of AD [50], which has stimulated the continuation of studies on humans. Although Cur may correct immune defects of cells, such as macrophages and peripheral blood mononuclear cells (PBMCs), in AD patients [51], a recent meta-analysis has shown that clinical trials, while showing tolerability, have produced contradictory results on the efficacy of chronically administered Cur, [52, 53].

Parkinson's Disease (PD)

PD was first reported in 5000 BC [1], in India, and named Kampavata. In the modern age, the first medical description, as a "shaking palsy", was by the British doctor James Parkinson, in the early 19th century. It was also in India that the first PD treatment was found because the people there used (probably without knowing the real reasons), seeds containing therapeutic levels of levodopa (L-Dopa), which is nowadays the most important symptomatic approach [54].

PD, which is induced by the massive death of dopaminergic neurons of the *substantia nigra,* is the most recurrent movement disorder distinguished by progressive muscle control loss. Bradykinesia, rigidity and rest tremor are highlighted as pivotal signs of the disease and cause impaired balance; mental symptoms of the disease have also been recorded [55, 56].

The prevalence of the disease usually ranges from 100 to 200 per 100,000 people and it is somewhat more frequent in men than in women. Most commonly the onset of PD is between 65 and 70 years of age, although it can rarely—in less than 5% of cases—be present in younger patients; in most cases of onset before the age of 40 the cause is genetic alterations [55].

For most of the 20th century the medical view was that sporadic PD was correlated with environmental contaminants but this changed, on the basis that there are no compelling data indicating that any particular toxin is responsible for sporadic PD. Chronic contact with rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been shown to

have a low probability of causing PD [57], although a recent meta-analysis showed that the risk of PD increases by 5% after 5 years of pesticide exposure and by 11% after 10 years [58].

Genetic forms of PD constitute only 5–10% of all cases [59]. The major genes identified and proved to be causal in PD are Parkin (PARK) 2, α-synuclein (α-Syn-PARK1/PARK4), Leucine-rich repeat kinase2 (LRRK2/PARK8), ubiquitin C-terminal hydrolase-like 1 (UCH-L1), PTEN-induced putative kinase 1 (PINK1/PARK6), DJ1 (PARK 7), and ATP-ase type 13A2 (ATP13A2) [60].

The treatments of PD are directed to the maintenance of dopamine receptor stimulation. This is achieved in a range of ways: by administering a precursor of dopamine, by using agonists of the dopamine receptor, by reducing the metabolism of dopamine, and by balancing the ratio between dopamine and ACh.

L-Dopa has been the most widely used treatment; it can pass the BBB (while dopamine cannot) and is metabolized into dopamine by the enzyme dopa decarboxylase in the dopaminergic neurons of the *substantia nigra*. The absence of non-physiological pulsatile striatal dopamine receptor stimulation is probably the cause of various maladaptive neuronal responses [61]. Other approaches involve the use of dopamine receptor agonists such as ergoline derivatives—although these raise some cardiac and pulmonary safety concerns—and other, non-ergolitic, dopamine receptors agonists [62], which also induce a less pulsatile level of dopamine receptor stimulation than L-Dopa. Finally, other approaches have included MAOB inhibitors such as rasagiline and selegiline, which are irreversible and prompt a rise in the synaptic dopamine level, and safinamide, which is a reversible MAOB inhibitor with antiglutaminergic properties [63].

The preparations of L-Dopa contain carbidopa or benserazide to impede the peripheral metabolism of dopamine. This therapeutical approach reduces L-Dopa's peripheral metabolism to a secondary pathway that involves Catechol-O-methyltransferase (COMT), and the inhibition of the COMT pathway increases the bioavailability of L-Dopa [63].

Curcumin treatment of Parkinson's Disease

As the second most common neurological disease, PD has been the subject of many studies, including a number on the use of Cur. A range of approaches have been adopted in both cell and animal models.

In SH-SY5Y dopaminergic cells, the level of Heat Shock Protein 90 (HSP90) was increased by MPTP treatment, and Cur reversed this effect. The effect induced by Cur was significantly reduced by silencing HSP90; on the other hand, its overexpression increased the influence of Cur on PD, most likely via up-regulation of HSP90 [64]. In an analogous experiment using DMC and rotenone-treated SH-SY5Y cells, DMC could protect against (100 nM, 3.9 mg/ml) rotenone-induced cytotoxicity, increasing cell viability by 86 ± 3.97% more than the control in the presence of 50 nM (1.7 mg/ml) of DMC; this effect was likely due to a reduction in Reactive Oxygen Species (ROS) (Fig. 1). DMC also decreased apoptosis in rotenone-pretreated SH-SY5Y cells, decreasing the expression of B-cell lymphoma 2 (Bcl2), Bcl2-associated X protein (Bax), Bcl2-associated death promoter (BAD), B-cell lymphoma-extra large (BclXL), caspase-3, 6, 8, and 9, and Cytochrome (Cyt)-c in mitochondria and cytosol (Fig. 1) [65]. In the rotenone PD rat model, Cur restored motor deficits and increased the antioxidant enzyme activities underlying its antioxidant potential *in vivo*, most likely playing a neuroprotective effect [66]; it also protected or reversed synaptic alteration in the hippocampus [67].

Cur can bind α-Syn, the main component of Lewis Bodies and hamper its accumulation in the DA neurons [68].

In transgenic mice over-expressing human Green Fluorescent Protein (GFP)-tagged wild-type α-synuclein (Syn-GFP), chronic and acute Cur treatment induced an improvement in motor behavior which was correlated with an increase in phosphorylated α-synuclein protein to the levels found in the cortical presynaptic terminals [69].

In another rat PD model (2,4,5-trihydroxyphenethylamine (6-OHDA)-induced), Cur reversed the deficits generated by 6-OHDA [70], improved rotational behaviour [71], reduced the death of DA neurons in the *substantia nigra* [71, 72], and inhibited the activation of astrocytes, most likely through the Wnt/ β-Catenin signaling pathway [71].

Multiple Sclerosis (MS)

About 0.1% of the population of North America and Europe is hit by this devastating autoimmune disorder [73]. First described by Carswell in 1838, and named by Charcot [74], MS is a disease that primarily attacks the myelinated CNS. As far as is known to date, the genetic involvement in the disease is limited to a modest increase of disease susceptibility, but many well-defined environmental factors are considered risk factors, such as ultraviolet B light (UVB), Epstein-Barr virus infection, smoking, Vitamin D (Vit D), and obesity

[75]. Initially, MS was grouped as an organ-specific T-cell mediated autoimmune disease, but more recently the accepted view has changed to also include B-cells [76].

All over the world, in both developed and developing countries, the incidence of MS is greater the further north we go, most likely because UVB increases the production of skin Vit D [77]. Currently, the sex ratio is close to 3:1 (F:M) in most developed countries, but this ratio has been increasing, from 1:1, since the beginning of the last century [78].

Over 150 loci (mostly single nucleotide polymorphisms) [79] have been linked with sensitivity to MS, one of which is the Human Leukocyte Antigen (HLA) gene cluster, which accounts for up to 10.5% of the genetic variance [80]. Although intense molecular analysis of the HLA region in MS has been undertaken, more research is required in order to build integrated models that can rationalize the role of the Major Histocompatibility Complex (MHC) in MS pathogenesis. It is believed that lymphocytes T helper 17 (Th17) cells, a unique proinflammatory lineage of effector/memory, are implicated in the pathogenesis of MS, but we also know that many interleukins and cytokines are altered in MS, such as Interleukin (IL)6, Matrix metalloproteinase (MMP)9 enzyme activity, Interferon (IFN)γ, IL17 and IL12 family cytokines, and inducible Nitric Oxide Synthase (iNOS) [81].

The main treatments for MS are the immunosuppressant natalizumab, ocrelizumab, fingolimod, or immunomodulators, typically IFNβ, teriflunomide, and glatiramer acetate. Another approach is immune reconstitution therapy by means of cladribine and alemtuzumab[76]. Symptomatic therapies comprise anticholinergics for bladder dysfunction and medication for neuropathic pain such as gabapentin and derivatives, or tricyclic antidepressants [76].

<u>Curcumin treatment of Multiple Sclerosis</u>

In a cellular model of MS in which human astrocyte cell lines (U373-MG) were treated with lipopolysaccharide (LPS), it was shown that Cur reduced both the release of IL6 and MMP9 activity, although it affected neither mRNA levels of insulin-like growth factor (IGF)-1 nor neurotrophin (NT)-3. These results indicate that Cur can cause an anti-inflammatory response by acting on astrocytes in the CNS [82].

Analogous studies were also performed in mouse models using the autoimmune encephalomyelitis (EAE) model for MS. Cur inhibits IFNγ, IL17 and IL12 family cytokines expression in the CNS [81]. These results agree with those obtained in a similar rat model where the level of myelination was increased in Cur treated animals, most likely by the

restoration of iNOS mRNA levels and by potentiating the Nrf2 cellular defense pathway against oxidative stress [83]. Moreover, in this model Cur enhanced all of the following: Brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF), the level of Myelin basic protein (MBP), Nestin (a neural stem cells (NSCs) marker, Olig2, Platelet-derived growth factor receptor α (PDGFR α), and oligodendrocyte progenitors markers [83].

In a clinical study, it was demonstrated that Cur (nano micelle formulation), was able to reduce the fraction of Th17 cells in the peripheral circulation (after 6 months, 80 mg/day) [84]. Since increasing numbers of Th17 cells were linked in MS patients to raised levels of IL23 and IL17A, and increased expression of retinoic acid-related orphan receptor γ (RORγt), these authors also evaluated the effect of Cur treatments on these factors. They observed significantly lower levels of RORγt mRNA and reduced IL17 secretion, while the expression levels and concentration of IL23 mRNA were not influenced [84].

NCT03150966 is a Phase 2 trial (Supplementary material) which aims to understand the impact of oral nanocurcumin on the levels of expression in MS of different microRNAs (such as miRNA-106b, miRNA-25, and miRNA-326), transcription factors (Foxp3 and RORγt), cytokines (such as Transforming growth factor β (TGFβ) and IL17) and T regulatory and Th17 cells. In another Phase 2 trial (NCT01514370) the safety and efficacy of dietary supplements of Cur were tested in patients with active relapsing MS already under IFN1β treatment. For both trials, the results are not yet available.

Amyotrophic Lateral Sclerosis (ALS)

Another devastating neurological disease is ALS, in which MNs (upper and lower) are dramatically affected, causing death from respiratory failure. Worldwide, there are five new cases per year per 100,000 of population, and, due to the short average survival time, the incidence is 1.7 per 100,000. Defects in RNA processing and protein clearance might be involved in the mechanisms of the pathogenesis. Since its description by Charcot in 1874, much knowledge has been accumulated [85] and, to date, ALS can be divided into sporadic (s) and familial (f). The first gene found to be involved in the disease was the superoxide dismutase (SOD) 1, but since its discovery more than other 20 genes have been found to be involved [86], which between them explain more than 50 % of the fALS. These genes can be characterized as either causative or related to susceptibility (such as

ataxin 2) [85]. Some reports have indicated that SOD1 pathological inclusions present in ALS share similarities with amyloid fibrils produced *in vitro* [87].

The most commonly responsible for ALS is the repeat expansions in the chromosome 9 open reading frame 72 gene (C9orf72), with 40% of patients having a family history and about 10% with no family history. Many laboratories have, in cases of fALS, found mutations of TAR-DNA-binding protein of 43 kDa (TDP-43). This is a ubiquitously and constitutively expressed DNA–RNA-binding protein, involved in gene transcription repression, regulation of exon splicing, and nuclear body functions. Mutated TDP-43 is abnormally cleaved, ubiquitinated and phosphorylated; it aggregates and is mislocalized in the neuritis or cytoplasm [88]. TDP 43 aggregates of this protein in the affected nerve cells were noticed in most sporadic ALS cases, indicating their pivotal role in ALS [89, 90].

Many environmental conditions have been implicated in the epidemiology of ALS pathogenesis, including smoking, pesticide contamination, alcohol, lead, viral and fungal infections, electromagnetic radiation, and physical exercise [85].

To date, two drugs with moderate effects have been approved by the FDA for ALS treatment: riluzole, a glutamate receptor antagonist, and the free radical scavenger edaravone. Many other encouraging treatment strategies are being explored, among them Vit E, Ginkgo biloba, melatonin, folic acid, α-lipoic acid, and regular exercise of low and moderate intensity [91].

Curcumin treatment of Amyotrophic Lateral Sclerosis

The role of Cur treatment in recovering the impairment induced by overexpression of TDP-43 has been analyzed using NSC-34 cells transfected with TDP-43 as an ALS cellular model. DMC has a protective effect on mitochondrial membrane potential, decreasing the levels of uncoupling protein (UCP) 2 [92]. These protective effects of Cur also involve the initiation and propagation of action potentials (APs), which are enhanced by the overexpression of TDP-43 [93].

Cur regulates the early aggregation phases of reduced SOD1, allowing the production of non-fibrillar smaller and less toxic aggregates. It also binds these products strongly, most likely in aggregation-prone regions of intermediates, blocking the exposed aggregation site on these molecules, and inhibiting the production of toxic species in the aggregation pathway [94]. A clinical trial using nanocurcumin as an add-on therapy to riluzole found a

significantly increased survival rate in patients with ALS after 12 months of treatment [95].

Spinal Muscular Atrophy (SMA)

SMA is a recessive autosomal disorder with a worldwide incidence of 1 in 6,000-10,000 live births [96-98]. One person in 40 is a healthy carrier (heterozygote for this condition). Although this is a matter of debate, the beginning of the disease and the age of death are still used as criteria in the categorization of SMA patients, and about 25% of patients elude a precise classification. SMA can be classified in order of severity as Werdnig-Hoffmann disease (SMA1), SMA Intermediate (SMA2), SMA mild or Kugelberg-Welander disease (SMA3) and the adult form (SMA4) [99].

The reduced expression of Survival Motor Neuron (*SMN)* is responsible for SMA, and all patients harbor inactivating mutations of the telomeric *SMN1* gene. A centromeric *SMN2* gene, a partially functional paralog, can, however, partially compensate for the lack of *SMN1,* depending on its copy number [100].

Currently, two hypotheses are offered as explanations of the molecular mechanisms of the SMA. The first is that changes in the level of SMN protein, a 38 kDa protein important for RNA splicing [101, 102], alters the transduction of some genes critical in the physiology of the MNs. The second is that SMN protein has other particular functions in the MNs.

Many therapeutical approaches have been tested in order to find an effective treatment for SMA, and it was only recently that a splicing modifier called nursinersen was found to be clinically effective and received FDA approval. Nursinersen increases the level of exon 7 inclusion in SMN protein derived from the *SMN2* gene and so reduces the degeneration of MNs. Several trials have established that nusinersen is effective in SMA, with few adverse effects [103]. Intrathecal administration every 4 months (after a loading period) were able to reach the motor landmarks and growth parameters without fatalities and without ventilation being required. This treatment was also extended recently to older patients (who had already presented the symptoms and signs of the disease) in the hope that they would benefit from the drug.

Gene therapy is another potentially resolutive approach, in which the correct *SMN1* gene is inserted in the genome by means of a viral vehicle (adeno-associated viral (AAV) vectors). A single intravenous injection can ensure a systemic distribution of the gene. In the first AveXis trial, the treated patients reached (to date) 20 months of age, with a survival

rate of 100%, as against the 8% historically found in the untreated cohort [103]. Other therapeutical approaches for SMA involve the enhancement of muscle responses [104].

Curcumin treatment of Spinal Muscular Atrophy

Many studies on SMA are done on fibroblasts since these cells are easily obtained from patients and unaffected relatives. For instance, primary fibroblasts from (Type I) SMA patient which have two intact SMN2 genes were administered with Cur for 24 h, then SMN expression analysis was performed by RT-PCR (using fibroblasts from the healthy carrier as a control). The *SMN1*/*SMN2* mRNA ratio was ≈2:1 in control fibroblasts and ≈1:2 in patient fibroblasts. In these cells, Cur induces exon 7 inclusion and brings the *SMN1*/*SMN2* mRNA ratio to 2:1 depending on the Cur concentration [105]. SMN protein and the number of gems (Gemini of Cajal bodies) also increase after Cur treatment [105]. This is also true in fibroblasts from SMA 2 patients with three copies of SMN2 [106]. Since fibroblasts are not the most affected cells in SMA an *in vitro* approach using neuron-like cells (PC12) was performed by Bora-Tatar et al [107]. In this work, PC12 cells were stably transfected with a gene that knocks down *SMN1*. Cur was not able to change the SMN protein level and the neurite length in the SMN knockdown PC12 cells [107].

Spinal Cord Injury (SCI)

The overall incidence of SCI is 10.5 cases per 100,000 in the world population [108]. In SCI, the force applied during an accident—at work, on a bike, in a car, or in sport—causes deformation or/and breakage of the bone, which can damage the nervous tissue, inducing so-called ‘primary damage’ which is related to the amount of energy transferred to the nervous tissue. The other pivotal aspect of this disease is the ‘secondary damage’ caused by the patient’s immune system response, which attempts to fix the damage but instead causes an exacerbation of the impairment [1].

The variability of degree and type of injury in human patients makes finding a single strategy for the treatment of SCI a complex matter. The therapeutic scheme of intervention comprises early surgery to decompress the spinal cord and stabilize the spine, followed by transfer to a specialist rehabilitation center. Unfortunately, there is so far no treatment that can completely repair the spinal cord tissue. The current standard therapy includes the administration of methylprednisolone sodium succinate (MPSS) in order to decrease lipid peroxidation and free radical production and to prevent edemas, and thus to reduce SCI

damage. Other approaches have been hypothesized, based to date on preclinical work, cellular intervention with either substitutive or simply paracrine action, used in animal models by our group [1, 109-113] and by others with and without biomaterials (see [114] for a comprehensive review of the literature).

Curcumin treatment of Spinal Cord Injury

Most of the analyses of the effects of Cur on SCI have been conducted on rodent models of SCI with different types of damage: contusion and hemisection (at thoracic level 8 or 9), ischemia-reperfusion injury, and compression by clips or balloon.

In a model of clip compression, it was found that protein expression of HO-1, which exerts a significant protective role against oxidative injury [115], was increased after Cur treatment (of the lesioned animals) significantly more than in sham or lesioned not Cur treated animals. In addition, Cur caused a higher expression of Zonula occludens-1 protein (ZO-1), thus limiting the SCI-induced disruption of tight junctions and maintaining blood-spinal cord barrier integrity [115]. Moreover, Cur plays an anti-inflammatory effect by attenuating the increase of both TNFα and NFκB, the nuclear factor kappa-light-chain-enhancer of activated B cells [115].

Another important peculiarity of SCI (in the clip compression model) is the formation of glial scar due to astrocytes, which induces a severe obstacle to neural regeneration. Cur inhibits glial scar formation [116], most likely by suppressing NFκB activity since both Cur and p65-NFκB siRNA silencing reduce astrocyte activation, limiting GFAP (a marker of cell activation) and the overexpression of α-smooth muscle actin (α-sma a marker of fibrosis). Moreover, Cur induces the down-regulation of chemokines released (possibly through the induction of Nrf2) by astrocytes [117] such as Monocyte Chemoattractant Protein 1 (MCP1), Chemokine (C-C motif) ligand 5 or RANTES and C-X-C motif chemokine 10 (CXCL10) [118], which are important factors for macrophage and T-cell infiltration. All these effects contribute to reductions in glial scar inflammation.

Using a balloon compression method, it was found that the administration of Cur ameliorated behavioral performance in the first week after SCI, by improving locomotor and sensory performance [119]. It also reduced glial scar development by lowering the levels of RANTES and macrophage inflammatory proteins, reducing IL2, curtailing inflammatory cell invasion and decreasing NFκB activity (Fig. 1) [119].

In a hemisection model of SCI in rat, Cur was able to inhibit neuron loss and apoptosis, blocking astrocyte activation, and reducing the neurological deficit by down-regulating GFAP expression [120].

In an ischemia-reperfusion injury in rat, confirmation was found of the anti-inflammatory effect of Cur in reducing the elevation of NO, TNFα, and the levels of IL1β levels tissue protein, and Cur significantly reduced the increase in caspase-3 levels after injury (Fig. 1) [121]. Analogous results were obtained in a contusive mouse model, indicating the robustness and replicability of Cur action [122].

Cur and other substances with anti-inflammatory effects were tested in a Phase 3 open-label study which aimed to describe the effects of diet on chronic inflammation in SCI (NCT02099890, Supplementary material). The trial showed that these treatments, including Cur, induced a reduction of inflammatory molecules and neuroactive compounds such as prostaglandins PGE2 and (PGE3) and leukotrienes LTB5 and LTB5 [123].

Stroke

Reduction of the blood supply in some brain areas can result in a sudden loss of brain function. Stroke is the second most common cause of death worldwide after cardio-circulatory diseases; its incidence is contingent on race and age. A recent meta-analysis demonstrated that, worldwide, more than 36% of patients suffering a hemorrhagic stroke died in the first month and more than 50% died within the first year [124].

The main factor responsible for the disease is the occlusion of arteries, small or large. The main aim of the conventional therapeutical approach is to decrease the size of the thrombus and to prevent the formation of clots by the use of recombinant tissue plasminogen activator (rt-PA), the only FDA approved drug [124, 125].

Curcumin treatment of Stroke

By using a middle cerebral artery occlusion (MCAO) in a rat model it was observed that Cur treatment reduces infarct volume [126-129] and brain edema at 24 h [127, 130] and achieved better neurological scores than a vehicle-treated group [126, 127, 131, 132]. These effects are likely due to the attenuation of oxidative stress (in terms of lipid peroxidation). Cur also reduced neuronal apoptosis by augmenting the antiapoptotic Bcl2 protein at mitochondrial levels (Fig. 1), reduced the cytosolic translocation of Cyt- c [126, 129] and reduced the mitochondrial membrane potential [130]. Another important effect exert-

ed by Cur, during the reperfusion phase, is the reduction of adherent neutrophils at the vascular endothelium level and the reduction of vascular endothelium activation due to the lowering of TNFα NFκB-mediated expression [127]. In the same model Cur treatment reduced inflammation by means of Toll-like receptor 4 TLR4/p38/Mitogen-Activated Protein Kinase (MAPK) or by the activation of silent information regulator 1 (Sirt1) pathways, inducing a reduction in the expression of IL6, TNFα (Fig. 1) [128, 130, 132], and iNOS, and a reduction of autophagy via PI3K/Akt/mTOR [132].

Cur also has a protective effect in a rat model stroke-prone spontaneously hypertensive (SHRsp), delaying the onset of stroke and increasing the probability of survival. These effects are most likely due to an increase in the presence of proteins of the mitochondrial anion carrier family and a Cur-induced physiological regulation of mitochondrial ROS generation [133]. These results were also confirmed in a cellular model with HUVECs, using H_2O_2 to simulate oxidative stress *in vitro* which was attenuated by Cur treatment [133]. Results analogous to those described for rat were also obtained in a mouse model of MCAO where Cur treatment reduced cerebral infarction and neuronal apoptosis *in vivo* and *in vitro* on N2a cells, most likely reducing mitochondrial dysfunction [134].

Epilepsy

A seizure results from a deficit of cell function—without cell degeneration and death—and it is considered epilepsy if two episodes occur with no known cause. The global prevalence of epilepsy is 7.6 per 1,000 and increases with age; the incidence is 61.4 per 100,000 person-years [135]. Seizures are due to uncontrolled discharges in the brain that cause muscle contractions and unconsciousness [1].

Seizures can be classified as generalized (absence, tonic-clonic, myoclonic and atonic), partial (simple and complex) and status epilepticus [136]. Only 30% of epilepsy cases are related to traumas such as lack of oxygen during labor, head injuries altering the fragile electrical system in the brain, lead poisoning, meningitis, encephalitis [1] and gene alterations [137].

The therapeutical approach is usually symptomatic; anti-epileptic drugs have three main sites of intervention: membrane stabilization, reduction of excitatory neurotransmitter release and increase of γ-aminobutyric acid (GABA)-mediated inhibition. Between 20 and 30 % of epilepsy patients, however, are resistant to these interventions and so need a surgical approach [138].

Curcumin treatment of Epilepsy

In induced status epilepticus (by electrical stimulation) in rats, Cur treatment did not reduce seizure, most likely because it did not at appropriate level into the brain [139]. In a kainic acid-induced epilepsy model, however, Cur was able to attenuate cognition deficits, inflammation and neuronal death, suppressing inflammation protein expression such as IL1, and cleaved caspase-1 in the hippocampus [140]. And in an iron-induced epilepsy model, Cur was able to reduce the overexpression of Na_v 1.1 and Na_v 1.6 sodium channels [141].

Neuropathic Pain

The main cause of neuropathic pain is the dysregulation of the somatosensory nervous system. Elevated levels of response to pain stimuli (hyperalgesia), abnormal, unpleasant sensations (dysesthesia), and pain in response to stimuli that should not be felt as pain (allodynia) are usually the hallmarks of this disease. Peripheral neuropathic pain may derive from injuries to the peripheral nerves—motor, sensory, or autonomic—or from diseases such as cancer, diabetes, AIDS, herpes, , SCI, MS, and from trauma such as mastectomy and stroke [142]. On the other hand, central neuropathic pain can be a consequence of brain injury and SCI, stroke and MS [142]. The prevalence of neuropathic pain in the general population has been estimated at 6.9–10.0% [143]. The main pharmacological approach to this disease involves opioids, but this is problematic: they have little clinical efficacy, they bring the danger of abuse and patients develop tolerance. Other treatments include anti-depressants such as tricyclic anti-depressants (TCAs), selective serotonin (5HT) and norepinephrine reuptake inhibitors (SSNRIs) [142].

Curcumin treatment of Neuropathic Pain

Chronic constriction injury (CCI) in mouse by means of sciatic nerve ligature has been shown to respond to chronic, but not acute, Cur administration through a reduction in thermal hyperalgesia and mechanical allodynia. These effects were mediated by noradrenaline and 5HT descending pathway depletion; indeed, $5HT_{1A}R$ and spinal β2 adrenergic blocking receptors abolish the effect of Cur [144]. Moreover, acute inhibition of *δ*-opioid receptors and μ-opioid receptors abolishes the analgesic effects of Cur on thermal hyper-

algesia and mechanical allodynia [144]. This result was also supported by cellular analysis using neuroglia cells, where it was found that the expression of the opioid-related nociceptin receptor 1 gene (OPRL1) was also down-regulated [145]. In an analogous model, the effect of chronic treatment with Cur was to block the expression of 11β-hydroxysteroid dehydrogenase type I enzyme ($11\beta HSD_1$) and to reduce thermal hyperalgesia and mechanical allodynia [146].

Mouse neuropathic pain model induced by formalin showed a response to Cur treatment inducing a noticeable hypoacetylation of histones H3 and H4 in dorsal root ganglia and down-regulation of the metabotropic glutamate receptor 2 (mGlu2) receptor in the spinal cord [147].

Comprehensive Curcumin Mechanisms in Neurological Diseases

We can identify common pathways by which Cur, regardless of the motivation for its use, can exert its effects.

Inflammation is a common factor in many neurological diseases. Although the diseases described above have many differences, one common factor is increased levels of IL2 and 6, TNFα, COX2, and MMP9 activity (Fig. 1) [148, 149]. In most cases, NFκB plays a pivotal role in this inflammatory response by inducing the production of TNFα, which also mediates ROS activation. Since Cur has an inhibitory effect on NFκB, its use in treatment can induce a reduction of the inflammation (Fig. 1) [148]. These effects can be also mediated by the MAPK pathway that leads to the production of TNFα, and, indeed, Cur has been proven capable of inhibiting this pathway (Fig. 1). Moreover, in AD, PD, MS, and SCI neuronal death in distinct regions of the CNS is also mediated by ROS, and oxidative stress in AD seems to be due to TNFα-mediated NFκb activation (Fig. 1) [148].

Cur is also able to modulate apoptosis in PD, SCI and Stroke, most likely by enhancing NFκB-reduced expression of Bcl2 and BclXL and by reducing the NFκB-induced expression of Bax, BAD and caspases (Fig. 1) [16]. Another interesting mechanism that can be modulated by Cur is monocyte chemotaxis and T-lymphocyte differentiation. Inflammatory diseases such as MS, SCI, and AD are characterized by the phlogosis invasion of various areas [84, 118, 119, 150]. MCP1 is the pivotal controller of monocyte recruitment and activation of T-lymphocyte via the binding of the CCR2 receptor. This chemokine is modulated by various pathways including AP1, JNK, NFκb, and MAPK that could be negatively regulated by Cur (Fig. 1) [149, 151].

Conclusions

Mens sana in corpore sano relates not only to physical exercise [152, 153] but also to other lifestyle factors such as healthy rest and good diet, which nowadays includes a wide range of "old" supplements that have arrived from eastern cultures, one of which is Cur. Our increased understanding of its proven protective capacity against many different diseases, including the neurological ones, and of its molecular actions, have encouraged researchers to find ways of making it work more efficiently. The recently developed formulations represent new pathways for the treatment of many neurological diseases, some of which previously had no effective treatment.

AUTHOR CONTRIBUTIONS

XY wrote the paper. XX prepared the tables and the graphical abstract. XY prepared Fig. 1. XX and XY revised and discussed the text figures and tables.

CONFLICT OF INTEREST

The Authors declare no conflicts of interests.

Figure Legend

Effects of Cur on common pathways involved in different neurological diseases.

Cur induces a suppressive activity on different pathways, reducing the recruitment of monocytes, apoptosis, and inflammation.

Blue: pathways affected by NDs; red: pathways affected by cellular activation; orange: pathways affected by apoptosis; pink: pathways affected by inflammation.

➡ indicate positive effects, ⊥ indicate negative effects.

Abbreviations as in the abbreviation list.

Graphical abstract

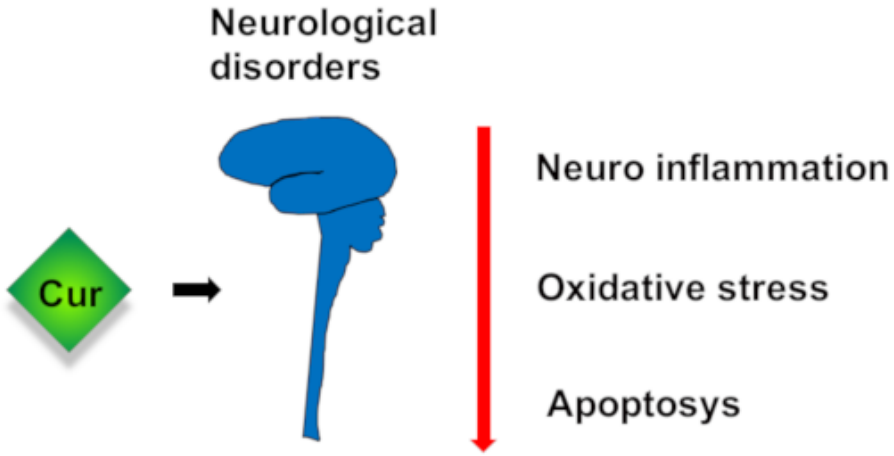

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Figure

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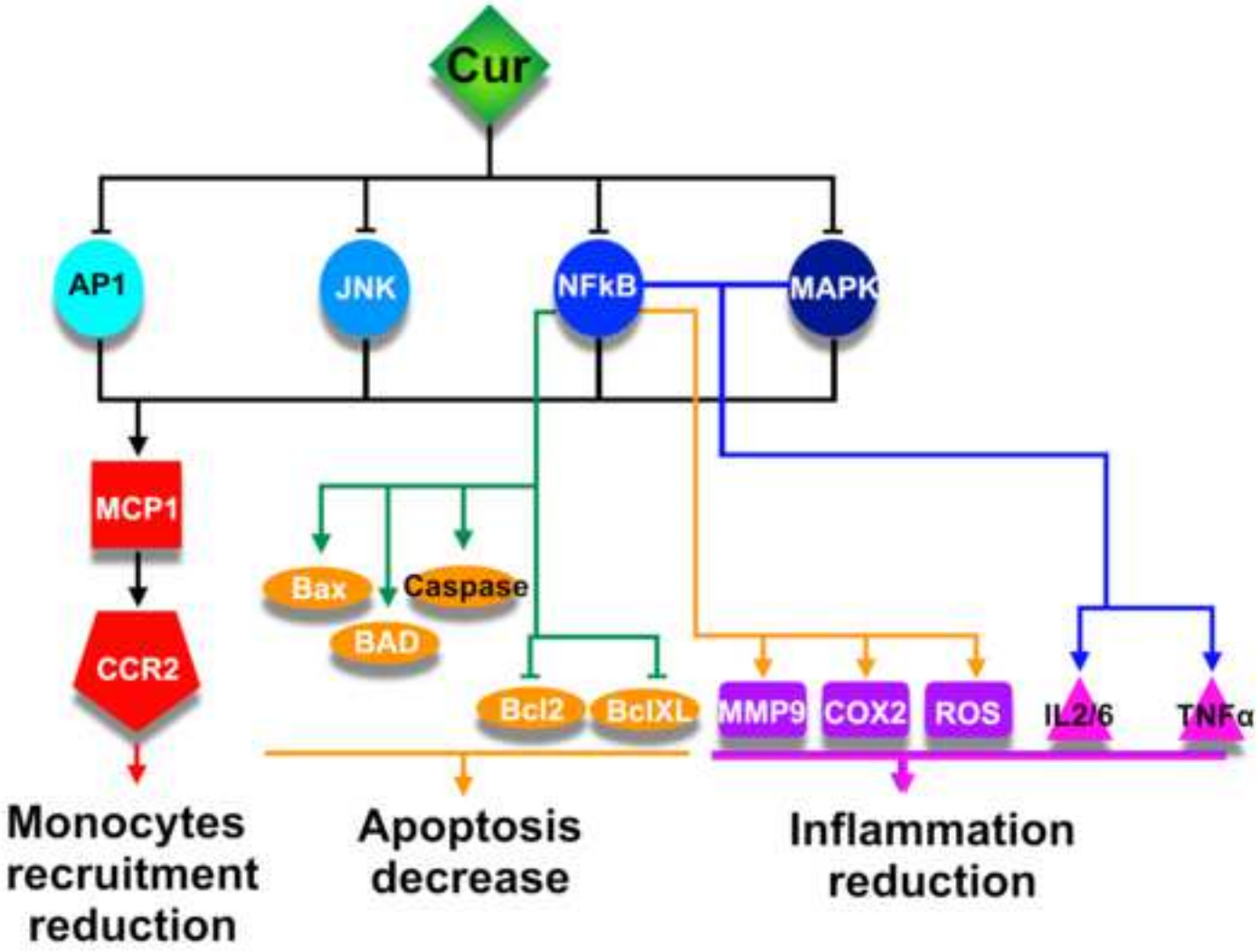

Table 1 Cur treatments in neurological diseases.

Condition	NTC IDs and Title	Intervention	Study goals	Main eligibility criteria	Outcome
Healthy adults	01925287 Oral Bioavailability of Curcumin From Micronized Powder and Liquid Micelles in Healthy Young Women and Men	Oral administration of native curcumin powder (500 mg), or micronized curcumin powder (500 mg), or curcumin micelles (500 mg)	Early Phase 1. Plasma determination of AUC, Cmax and Tmax of total curcumin, total bisdemethoxycurcumin and total demethoxycurcumin. Serum blood determination of routine chemistry values	Healthy aged 18 to 35, no metabolic or endocrine diseases, no pregnancy or breastfeeding, no smoking or drug abuse	Micronized powder administration induces 27-fold higher total curcumin AUC than native powder. Micelle formulation promotes 185-fold higher availability considering all the subjects enrolled; women absorb curcumin more efficiently. All Cur preparations were safe (Schiborr et al., 2014)
	01982734 Improved Oral Bioavailability of Curcumin Incorporated Into Micelles	Oral administration of native curcumin (active comparator, 80 mg), or native curcumin (80 mg) plus phytochemicals (sesamin 80 mg + narigenin 40 mg + ferulic acid 40 mg + xanthohumol 40 mg), or curcumin micelles (80 mg), or curcumin micelles (80 mg) plus phytochemicals (sesamin 80 mg + narigenin 40mg + ferulic acid 40 mg + xanthohumol 40 mg)	Early Phase 1. Plasma determination of AUC, Cmax and Tmax of total curcumin, total bisdemethoxycurcumin and total demethoxycurcumin. Serum blood determination of routine chemistry values	Aged 18 to 35 or >60, routine blood chemistry normal values, no metabolic and endocrine diseases, no pregnancy or breastfeeding, no smoking, no drug abuse	The administration of Cur micelles induces 88-fold higher Cur AUC than native powder, the phytochemical co-administration did not enhance this result. The phytochemical co-administration of the native curcumin improves availability modestly, 8-fold. Gender and age analysis did not reveal significant differences. All curcumin preparations were safe (Kocher et al., 2015)
	02474953 A Study to Compare the Pharmacokinetic Profile of a Proprietary Curcumin Formulation to a Comparator Curcumin Product	Oral administration of curcumin (proprietary formulation) and comparator curcumin (unformulated product)	Phase 1. Plasma comparison of AUC Cmax and Tmax of curcumin, verification of changes in several blood parameters	Aged 18 to 45, healthy by medical history, agrees to avoid Indian and Thai cuisine, black or white pepper, curry curcumin for the period of the study, no pregnancy or breastfeeding, no smokers, no severe disease	Results not yet available

Table 1 Cur treatments in neurological diseases.

Condition	NTC IDs and Title	Intervention	Study goals	Main eligibility criteria	Outcome
	01330810 Curcumin Pharmacokinetics	4 g C3 tablet (standardized curcumin supplements containing curcumin, demethoxycurcu- min, bisdemethoxycurcumin) or 2 g Meriva powder (standardized curcumin supplements containing curcumin, demethoxy curcumin and bisdemethoxy curcumin)	Phase 1. Plasma determination of AUC, Cmax, Tmax, T1/2, elimination rate and volume of distribution of total curcumin. Geometric AUC ratio of the two formulations. Bioequivalence of rectal tissue curcumin concentration	Aged 18 to 65, good general health, no history of acute or chronic illness, no pregnancy or breastfeeding, no allergy to studied agent	The Meriva powder induces similar plasma curcumin concentration to the C3 tablet, even though the Cur content was less in the Meriva. Conversely, demethoxycurcumin and bisdemethoxycurcumin levels were proportionately lower than with C3 tablet administration, suggesting a reduced uptake or faster metabolism. Standard curcumin also induces higher tissue curcumin concentrations, likely due to luminal rather than plasma inflow (Asher et al., 2017)
	00895167 The Effects of Oral Curcumin on Heme Oxygenase-1 (HO-1) in Healthy Male Subjects	Oral administration of Curcumin C3 Complex caplets containing 1000 mg curcumin and 5 mg Bioperine	Phase 1. Determination of HO-1 mRNA expression and protein level in PBMC, plasma bilirubin level	Healthy males aged 18 to 45, ECG without clinically relevant abnormalities, clinical chemistry in the normal range, no hypersensitivity to the treatment, no clinical evidence of severe disease	Results not yet available
	01403545 Evaluation of Liposomal Curcumin in Healthy Volunteers	Intravenous infusion of liposomal Curcumin, dose escalation 10, 20, 40, 80, 120, 180 mg/m² or placebo infusion	Phase 1. Safety and tolerability of increasing doses of intravenous liposomal Curcumin	Healthy aged 18 to 45, normal range body mass index, vital signs within the normal range, no concomitant medications, no unstable medical conditions, no pregnancy or breastfeeding	Cur plasma concentration increase was dose-dependent and was safe up to the dose of 120mg/m^2. Higher doses were associated with changes in red blood cell morphology as adverse effects (Storka et al., 2015)
	01489592 Effect of Curcumin on Iron Metabolism in Healthy Male Volunteers	Oral administration of: Curcumin (6 g) or placebo	Phase 2. Serum evaluation of hepcidin, iron, ferritin and transferrin levels	Healthy aged 18 to 35, male, normal range body mass index, normal clinical exam, no C282Y mutation within the HFE gene, no chronic or evolutive disease	Results are not yet available

Table 1 Cur treatments in neurological diseases.

Condition	NTC IDs and Title	Intervention	Study goals	Main eligibility criteria	Outcome
	03085680 Curcumin and Function in Older Adults	Oral administration of curcumin (1000 mg/day) or placebo capsules	Phase 2-3. Physical function changes in walking speed and in hand-grip strength dynamometer test. Cognitive improvement in attention and memory. Effect on pain symptoms. Change in inflammatory biomarkers blood concentrations, IL-2, C-reactive protein	Aged 65 to 99, walking speed <1 m/s and > 0.44 m/s on the 4 m walk, sedentary lifestyle, no significant cognitive impairment, no severe diseases	Results are not available yet
SCI	02099890 The Effect of Diet on Chronic Inflammation and Related Disorders Following Spinal Cord Injury	Oral administration of: InflanNox capsule (curcumin 1200 mg /day), or anti-oxidant Network capsule (1230 mg/day), or Vegetation Protein Powder (45 g/day), or Omega-3 pill (1500 EPA /750 DHA/day), or Chlorella tablet (6000 mg/day)	Phase 3. Median nerve conduction velocity evaluation (motor and sensory components), Function scores in Autonomic Standards Assessment and Neuropathic Pain questionnaires. Determination of PGE2, LTB4, PGE3 and LTB5	Individuals with Spinal Cord Injury over the age of 18. No allergies or food intolerances to any supplements used in the study. No pregnancy or breastfeeding, diabetic, or kidney disease	The treated group showed a reduction in pro-inflammatory mediators IL1β and IFNγ serum concentration and Center for Epidemiologic Studies Depression Scale scores. Serum amino acid concentrations were detected, included tryptophan, phenylalanine, tyrosine, and branched-chain amino acids (Allison et al., 2015)
MS	03150966 The Immunomodulatory Effects of Oral Nanocurcumin in Multiple Sclerosis Patients	Oral administration of nanocurcumin (80 mg/day) or placebo capsules	Phase 2. Disability Status neurologic test. PBMC isolation to measure Treg and Th17 frequency and expression levels of miRNA-106b, miRNA-25 and miRNA-326, transcription factors Foxp3 and RORγt, specific cytokine TGF-β and IL-17	Aged 18 to 65, diagnosis of MS by a neurologist, RRMS, EDSS <5/5. No history of diabetes and other chronic diseases	Results are not yet available
	01514370 Dietary Supplement of Curcumin in Subjects With Active Relapsing Multiple Sclerosis Treated With Subcutaneous IFN-β	IFN-β 1a 44 μg TIW, Curcumin BCM95 1000 mg/day or placebo	Phase 2. Assessment of subjects with active (new or enlarging) lesions by MRI. Determination of percentage of Relapse-Free and EDSS Progression-Free subjects	Aged 18 to 60, MS diagnosis, in treatment with IIFN-β 44 mcg TIW, EDSS between 0-5.5, no pregnancy and breastfeeding, no alcohol or drug abuse, no inadequate haematological functions	The results have not yet been analyzed

Table 1 Cur treatments in neurological diseases.

Condition	NTC IDs and Title	Intervention	Study goals	Main eligibility criteria	Outcome
AD	00164749 A Pilot Study of Curcumin and Ginkgo for Treating Alzheimer's Disease	Oral administration of curcumin (1 or 4 g/day) and ginkgo extract (120 mg/day), or placebo and ginkgo extract (120mg/day)	Phase 1-2. Plasma level of IsoPs, serum level of Aβ, MMSE score test. Level of curcumin in plasma vs. dose	50 Years and older. Ethnic Chinese, diagnosis of possible or probable AD, mild to severe dementia with Cantonese version of MMSE scores between 0 and 28, no anticoagulant or antiplatelet treatment or bleeding risk factors, no severe illness	Serum level of Aβ did not differ among curcumin doses groups. Cur did not affect serum cholesterol or triacylglycerol concentrations. MMSE score test did not show differences. Cur did not appear to cause side effects (Baum et al., 2007, Baum et al., 2008)
	01001637 Efficacy and Safety of Curcumin Formulation in Alzheimer's Disease	Dietary Supplement: Curcumin Formulation 2000 mg or 3000 mg daily BID and placebo	Phase 2. MMSE score, plasma concentration of βA	Aged 50 to 80, AD diagnosis, MMSE score ≥5 and ≤20, no history of significant psychiatric or non-AD neurological disease, no significant uncontrolled systemic illness, no AD due to a mutation in a known gene	Results are not available yet

Table 2 Trials focused on Cur treatment studies in healthy people (no applicable phase)

NTC IDs and Title	Intervention	Study goals	Main eligibility criteria	Outcome
03746158 Interindividual Variation in Excretion of Curcumin	Oral administration of: Curcumin (990 mg/day)	Determination of curcumin in subjects fecal samples	Healthy aged 18 to 30, normal range body mass index, no severe diseases especially intestinal disorders, no pregnancy or breastfeeding	Results not yet available
03621865 A Comparative Pharmacokinetic Study to Evaluate the Ability of a New Formulation to Enhance Curcuminoids Bioavailability	Oral administration of TG, STE, NOV, PHYT, TEP	Plasma AUC of total curcuminoids determination (curcumin+bisdemethoxycurcumin+demethoxycurcumin and their metabolites)	Healthy aged 18 to 45, stable weight, no menopausal women, no suffering from a metabolic disorder or severe chronic disease	Results not yet available
03530436 Comparison of Curcumin Bioavailability	Oral administration of curcumin in different formulation A, B, C, D, E, F, G, H, equivalent to 207 mg of curcumin	Plasma AUC, Cmax and Tmax of total curcumin, total bisdemethoxycurcumin and total demethoxycurcumin determination	Healthy aged 18 to 35, the normal range of body mass index and blood chemistry values. No pregnancy or breastfeeding, no metabolic, malignant or endocrine diseases	Results not yet available
03289507 Longvida Curcumin Human Pharmacokinetics Study	Oral administration of Longvida formulation A and B, Curcuma longa extract of Rhizomes	Plasma and urine curcumin metabolites determination	Healthy aged 20 to 45, no smokers, no severe clinical diseases, no intolerance, allergies or hypersensitivity to treatment	Results not yet available
02815475 Turmeric Anti-Inflammatory and Cell-Damage Trial	Oral administration of curcumin (400 mg/day), turmeric powder (2 teaspoons) and placebo	DNA methylation analysis and oxidative stress determination by Illumina EPIC array and whole-blood chemiluminescence assays	Healthy aged 18 to 80, no pre-existing medical conditions, no taking prescribed drugs	Results not yet available
01288859 Physiological Effects of New Polyphenol-enriched Foods in Humans	Dietary supplement of: EC-enriched bread (2 g/day curcumin), bread enriched EC-PQG (2 g/day curcumin), nut cream enriched with FCP (1.5 g/day polyphenols), control nut cream, nut cream enriched with ECP (1.5 g/day polyphenols), free curcumin in bread (2 g/day curcumin)	Determination of serum, urine and fecal AUC of polyphenols and metabolites. Plasma AUC of gut hormones (ghrelin, insulin)	Healthy aged 18 to 45, healthy by medical assessment, no pregnancy or breastfeeding, no previous abdominal/gastrointestinal surgery, no regular consumption of medication, no food allergies and intolerances to treatments	The serum concentration of curcuminoids was lower in new bread groups. Encapsulation increases bioavailability by preventing biotransformations and bioconversion in phenolic acids, its major metabolite (Vitaglione et al., 2012)
00181662 Pharmacokinetics of Curcumin in Healthy Volunteers	Oral administration of: Curcumin (4 gm) alone or with piperine or with silybin	Determination of pharmacokinetic course in serial timed collected blood	Healthy aged 18 to older, female, no medication, no pregnancy or breastfeeding, no comorbid disease	Results not yet available
00768118 A Nutritional Supplement Capsule Containing Curcumin, Green Tea Extract, Polygonum Cuspidatum Extract, and Soybean Extract in Healthy Participants	Oral administration of curcumin, green tea extract, Polygonum Cuspidatum, soybean capsules	Determination of serum and lymphocyte NFkB levels. Measurement of the marker in urine samples	Healthy aged 18 and older, no medication	NFkB levels, as biomarker of relevance to oxidative stress, was found altered in serum, lymphocyte and urine samples
01752868 Can Fish Oil and Phytochemical Supplements Mimic Anti-Aging Effects of Calorie Restriction?	Dietary supplement of curcumin, fish oil, resveratrol, sesamin, Acetyl-L-carnitine, lipoic acid, green and black teas, quercetin, pomegranate, cinnamon bark	Determination of carotid-femoral pulse wave velocity	Healthy aged 40 to 60, normal body mass index, sedentary to moderately active, eating a typical US diet, no chronic disease, no smoking, no use of nutritional supplements	Results not yet available