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Application of curcuminoids in inflammatory, neurodegenerative and aging conditions - Pharmacological potential and bioengineering approaches to improve efficiency

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ABSTRACT

Curcumin, a natural compound found in turmeric, has shown promise in treating brain-related diseases and conditions associated with aging. Curcumin has shown multiple anti-inflammatory and brain-protective effects, but its clinical use is limited by challenges like poor absorption, specificity and delivery to the right tissues.

A range of contemporary approaches at the intersection with bioengineering and systems biology are being explored to address these challenges. Data from preclinical and human studies highlight various neuroprotective actions of curcumin, including the inhibition of neuroinflammation, modulation of critical cellular signaling pathways, promotion of neurogenesis, and regulation of dopamine levels. However, curcumin's multifaceted effects - such as its impact on microRNAs and senescence markers - suggest novel therapeutic targets in neurodegeneration. Tetrahydrocurcumin, a primary metabolite of curcumin, also shows potential due to its presence in circulation and its anti-inflammatory properties, although further research is needed to elucidate its neuroprotective mechanisms.

Recent advancements in delivery systems, particularly brain-targeting nanocarriers like polymersomes, micelles, and liposomes, have shown promise in enhancing curcumin's bioavailability and therapeutic efficacy in animal models. Furthermore, the exploration of drug-laden scaffolds and dermal delivery may extend the pharmacological applications of curcumin. Studies reviewed here indicate that engineered dermal formulations and devices could serve as viable alternatives for neuroprotective treatments and to manage skin or musculoskeletal inflammation. This work highlights the need for carefully designed, long-term studies to better understand how curcumin and its bioactive metabolites work, their safety, and their effectiveness.

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1. Introduction

Curcumin and curcuminoids are among the most investigated natural bioactive compounds, mainly regarding their medicinal properties against cancer, inflammation and oxidative stress (Russo et al., 2024; Soo et al., 2020; Yeung et al., 2019). Curcumin shows important pharmacological effects in some gastrointestinal cancers and leukemia, including in clinical trials (Lagoa et al., 2020, 2022; Pal et al., 2023; Ruszkowska-Ciastek et al., 2024; Yeung et al., 2019). The antioxidant activity and the regulation of inflammatory processes are also widely established biological activities of turmeric, curcumin, and polyphenols in general (Lagoa et al., 2022; López-Sánchez et al., 2024; Milenkovic et al., 2013; Peng et al., 2021; Russo et al., 2024; Yeung et al., 2019). The research in neurodegeneration and aging is much less prevalent in the scientific literature of curcumin, and only in the 21st century the *in vitro* and *in vivo* anti-amyloidogenic activity start being reported attracting attention to curcumin for the treatment of Alzheimer's disease (AD) in specialized references (Yeung et al., 2019). Interestingly, a 2001 publication early pointed out that the pharmacological action of curcumin could surpass a conventional anti-inflammatory drug (ibuprofen) against amyloid-induced neuropathology (Frautschy et al., 2001). At present, supported by mounting data from laboratory studies and human trials referred in the following sections, curcumin is one of the natural compounds presenting more potential for ameliorating neurodegenerative and age-related pathologies, such as AD and the progression of cognitive dysfunction.

Despite its therapeutic potential, curcumin use has still not reached clinical approval. As with other polyphenols and phytochemicals, the rapid metabolization of curcumin limits its bioavailability, and the multi-target low-potency mechanisms of action of these compounds hinder their translation to therapies with recognized efficacy (Cas and Ghidoni, 2019; Metzler et al., 2013; Milenkovic et al., 2013; Silva et al., 2021). A variety of pharmacological and pharmaceutical approaches in the frontier with bioengineering and systems biology is currently being employed to deal with these difficulties and improve targeted therapeutic options with more success potential. While tests of improved cancer treatments are advancing with phase I/II trials completed and on course (Cheng et al., 2001; Lagoa et al., 2020, 2022), the applied research in neurodegenerative or aging conditions remains in infanthood. The sustainable production of curcumin and active metabolites for the growing nutraceutical and therapeutic markets is another challenge calling the deployment of specific biotechnological tools (Gurung et al., 2017; Patil and Gaikar, 2011; Rainha et al., 2024).

The aims of this work were to revise and refine the bioengineering approaches showing high potential contributing to the progress in the therapeutic applications of curcumin. With a focus on inflammatory, neurodegenerative and aging conditions, specific issues like the identification of pharmacologically relevant curcumin metabolites and biological targets, as well as alternative delivery methods (*e.g.* to the brain), were addressed. Data with diverse sources and biological significance were integrated to extract critical information for future research.

2. Zingiberaceae medicinal plants and curcuminoids

The Zingiberaceae family, which includes plants like turmeric and ginger, is found across Asia, Africa, and the Americas, with about 50 genera and 1600 species (Abubakar et al., 2018; Alolga et al., 2022; Matin et al., 2024b; Tushar et al., 2010). They are widely used as kitchen spice to enhance food's taste, colour, and aroma for thousands of years (Destryana et al., 2024), and contain important bioactive compounds deemed responsible for various pharmacological effects (Alolga et al., 2022; Matin et al., 2024b). One of the chief groups of phytochemicals in this family are the curcuminoids, characteristic of the genus *Curcuma*. Around 100 *Curcuma* species are distributed in India, Australia, and Africa (Rodrigues et al., 2015b), and it is a top food crop covered by functional food innovations (Matin et al., 2024a). The few species both cultivated and wild are *Curcuma angustifolia* Roxb., *C. aromatica* Salisb., *C. longa* L., *C. amada* Roxb., and *C. zedoaria* (Christm.) Roscoe, of which the most commonly available cultivated species is *C. longa* L., shown in Fig. 1.

C. longa (synonym, *C. domestica* Valeton; common name, turmeric) is a perennial herbaceous plant that grows up to 2 m in height. It is a tall herb, root-stock large, ovoid, with sessile cylindric tubers and orange inside. The rhizome of the plant grows beneath the surface of the earth, grown mostly for its rough, segmented skins on the rhizome. The rhizomes expand to 2.5 cm in diameter and up to 2.5–7.0 cm in length or more, taste harsh, and smell balm, while the leaves are large, in tufts, oblong-lanceolate, tapering to the base (Fig. 1). Flowers in autumnal spike 4-6 by 2 in.; peduncles 6 in. long, hidden by the sheathing petiole; flowering bracts pale green; bracts of the coma tinged with pinky. The *C. longa* plant requires tropical and subtropical climatic conditions with an optimum temperature of 20-30 °C, and adequate rainfall is necessary for the plant's growth. The plant is indigenous and widely cultivated throughout India for the turmeric obtained from its rhizomes, but it is also common in Iraq, Sri Lanka, Madagascar, China, Bangladesh, and Southeast Asia in general (Iweala et al., 2023; WHO, 1999).

For over 2500 years, curcuma species, particularly *C. longa*, have been integral to traditional medicine across Asia, being used to treat a variety of conditions—such as respiratory issues, gastrointestinal disorders, rheumatism, and infectious wounds (Abe and Ohtani, 2013; Gupta et al., 2024; Iweala et al., 2023; Jacob, 2016; Tejada et al., 2016). A heated poultice made of slaked lime and turmeric is applied to relieve muscle inflammation and pain from injuries. In India, turmeric is valued not only as a spice, but also in religious rites dating back 4000 years (Adamczak et al., 2020; Sharifi-Rad et al., 2020), and it is used for skin, respiratory, joint, and digestive health (Fuloria et al., 2022). It is also employed in the form of paste for beautification (Gopinath and Karthikeyan, 2018) and taken as a health tonic with milk (Ahmad et al., 2020). In China, turmeric is used orally for digestive issues and topically for skin conditions (Pradeep et al., 2019). It is also present in traditional Thai and Islamic medicine (Ayati et al., 2019; Kanjanahattakij et al., 2019). The versatility and pharmacological properties of turmeric have sustained its use across cultures, regarded as beneficial for a wide range of conditions from acne and arthritis to cancer (Abe and Ohtani, 2013; Ahmed, 2016; Gupta et al., 2013).

The diarylheptanoids present in turmeric rhizomes (in about 1.5 to 5 %) are known as curcumin or curcuminoids (Anand et al., 2008; Evans, 2002; Li et al., 2019b; Prasad et al., 2014), key phytoconstituents with numerous pharmacological effects. Three major curcuminoids (Fig. 2) are found in the rhizomes of *C. longa* as a mixture: curcumin (75-80 %), demethoxycurcumin (15-20 %) and bisdemethoxycurcumin (<5 %), being curcumin the most recognized for having pharmacological activities (Agrawal et al., 2012). The term curcumin is sometimes used as an umbrella name for the natural-occurring curcuminoid compounds. These compounds have also been reported in other species of *Curcuma*, as well as in other Zingiberaceae plants (Matin et al., 2024b; Rodrigues et al., 2015b).

As illustrated with curcumin in Fig. 2 the curcuminoids can interconvert between two tautomers, the di-keto (or bis-keto) and the enolate forms, in an equilibrium that depends on the media conditions. This is important as the enolate form can bind to amyloid protein, whereas the antioxidant activity is mainly provided by the di-keto tautomer (Kazakova et al., 2022). The ratio of keto to enol tautomers is altered in curcumin chemical derivatives (Yanagisawa et al., 2015).

3. Trends in the biotechnological production of curcuminoids

The production and isolation of medicinal phytochemicals from natural products still represent a costly method of obtaining secondary metabolites, especially because the natural compounds are often present at the level of parts per million in the complex extract of a plant (Harvey et al., 2015; Manasa et al., 2023). Even with the progress of modern

analytical and preparative separation techniques, the isolation of pure constituents from these complex mixtures remains laborious (Enke and Nagels, 2011). Curcuminoids can be obtained by extraction from turmeric plants or chemical synthesis in the laboratory. They have been isolated as a mixture of curcumin, demethoxycurcumin, bisdemethoxycurcumin, and other curcuminoids from the rhizomes of *C. longa* (Roth et al., 1998). The process of isolating pure curcuminoids from crude extracts is often time-consuming, and large-scale production of these compounds is also challenging since they can only be isolated in low yields and may not meet the increasing demand (Rainha et al., 2024). Chemical synthesis of these compounds involves several synthetic steps and the use of toxic reagents (Venkata Rao and Sudheer, 2011).

3.1. Microbial production of curcuminoids

Efforts have been devoted to produce curcuminoids using synthetic biology and metabolic engineering. Fig. 3 illustrates engineered biosynthetic pathways and Table 1 summarizes different strategies of heterologous production of curcumin. *Escherichia coli* and *Saccharomyces cerevisiae* are the microbe hosts adopted, and different optimization strategies are enabling the production of major curcuminoids in sizeable titers.

By modifying metabolic pathways, ferulic acid (Fig. 3A) can be used as substrate to produce curcumin in large amounts and with high purity (Chen et al., 2024; Rainha et al., 2022, 2024; Rodrigues et al., 2015a; Wu et al., 2020), by expressing the enzyme curcuminoid synthase and ensuring the supply of malonyl-CoA (Fig. 3). Latest alternatives allowed production from glucose in engineered *S. cerevisiae* (Rainha et al., 2024), and from phenylalanine (Fig. 3B) or tyrosine in *E. coli* by a combinatorial approach using six enzymes (Rodrigues et al., 2015a; Rodrigues et al., 2020). In a recent work (Chen et al., 2024), Chen and co-authors optimized different metabolic steps and intermediates' detoxification in an *E. coli* strain, reaching >100 mg/L curcumin titers, and even higher in a pilot bioreactor with pH adjusted control (Table 1).

These cutting-edge advancements mark the first reports of *de novo* biosynthesis of curcumin in yeast applying the clustered regularly interspaced short palindromic repeats (CRISPR) technology (Rainha et al., 2024; Utomo et al., 2024). CRISPR-Cas9 was previously employed to construct plasmids transformed into *E. coli* (Chen et al., 2024; Chu et al., 2020) or *S. cerevisiae* (Rainha et al., 2022), aiming to delete specific genes and enhance the production yields of curcuminoids. Now, CRISPR-Cas9 has been used to integrate several curcumin biosynthesis genes into the yeast genome (Fig. 3B). In the work by Utomo et al. (2024), the alternative caffeoyl-shikimate esterase phenylpropanoid pathway (Fig. 3B) showed higher titers of curcumin production (Utomo et al., 2024). Without needing precursor supplementation, nor plasmids and antibiotic selection, the CRISPR-based genome edition allowed stable expression of the curcumin pathway genes in an approach more suitable for large-scale production (Rainha et al., 2024; Utomo et al., 2024).

3.2. Purification technologies of curcuminoids and active metabolites

Curcuminoids have been extracted and purified using traditional and cutting-edge separation techniques, such as high-performance liquid chromatography (HPLC), thin-layer chromatography, supercritical liquid and enzyme-assisted extraction, and crystallization methods, including many of their variants (Gurung et al., 2017; Li et al., 2009; Manasa et al., 2023). In addition to the microbial production discussed above, the sustainable supply of curcuminoids to their growing market can also benefit from more efficient and scalable extraction and purification techniques like those based on adsorption (Manasa et al., 2023; Patil and Gaikar, 2011).

A recent advancement important for the pharmacological research and applications of curcumin is the production of tetrahydrocurcumin, a bioactive metabolite with relevant pharmacological properties that might be used instead of curcumin (Zhu et al., 2023b). The industrial production of tetrahydrocurcumin is mainly based on chemical hydrogenation methods. But the bioconversion of curcumin to tetrahydrocurcumin becomes an alternative method, potentially less expensive, involving mild reaction conditions and simple operation, though the yield is low coupled to complex by-products (Martin et al., 2017; Shimoda et al., 2012, 2019; Wu, 2019; Zhu et al., 2023b). In a recent work, plant cells of *Morus sp.* were employed in the transformation of curcumin

Fig. 1. *Curcuma longa* (Zingiberaceae), India (Photo- Logesh Rajan). a) Cultivation of *C. longa*, b) Flowering of *C. longa*, c) Close-up of the flowering, d) Fresh rhizomes, and e) Dried rhizomes of *C. longa*.

into dihydrocurcumin and tetrahydrocurcumin (Shimoda et al., 2019). The compounds dihydrocurcumin (5 %) and tetrahydrocurcumin (90 %) were isolated from the ethyl acetate fractions and then analyzed using HPLC. The structure of the metabolites was determined using nuclear magnetic resonance spectroscopic techniques assisted with electrospray ionization mass spectrometry. Moreover, tetrahydrocurcumin showed a significant anti-inflammatory potential by decreasing nuclear factor-kappa B (NF-κB) activity in HeLa cells, although inferior to the effect of curcumin (Shimoda et al., 2019). Enzyme-catalyzed conversion of curcumin into tetrahydrocurcumin is another option for tetrahydrocurcumin biosynthesis, making use of the specificity of enzymes and the possibilities to improve their catalytic efficiency by protein engineering (Feng et al., 2023). Integration of curcumin reductases into the synthetic metabolic pathway in *E. coli* for the microbial synthesis of tetrahydrocurcumin has also been reported (Zhu et al., 2023b).

4. Anti-inflammatory and neuroprotective actions of curcuminoids

Following widespread use from ancient times by virtue of its efficacy and safety profile, turmeric is approved as GRAS by FDA (FDA, 2024), and various turmeric-based products have been commercialized in the global market (CBI, 2022; MFPI, 2024). Recently, an Indian Pharmaceutical company has developed the Ayurvedic turmeric spray bandage named Relispray® (MidasCare, 2024).

Modern research across the world has shown interest in curcumin due to its diverse biological activities, including anti-inflammatory (Edwards et al., 2017; Peng et al., 2021; Zhao et al., 2024), anticancer (Lagoa et al., 2022; Wilken et al., 2011), antimicrobial (Hassan et al., 2024; Mabood Husain et al., 2024), anti-obesity (Akbari et al., 2019), cardioprotective (Li et al., 2023b), and neuroprotective effects (Donadio et al., 2022; Frautschy et al., 2001; Subedi and Gaire, 2021). Furthermore, curcumin accumulates in the gastrointestinal tract, where, in addition to undergoing biotransformation by gut microbiota, it influences microbial composition, diversity and richness (Pluta et al., 2020), acting on the gut-brain axis (Enayati et al., 2023). The remarkable anti-inflammatory properties of curcumin and its related compounds make curcuminoids a potential class of molecules for the management of neurodegenerative diseases. Inflammation in the brain plays a key role in diseases like Alzheimer's and Parkinson's (Frautschy et al., 2001; Zhang et al., 2023). Although neuroinflammation, triggered by diverse factors, such as infection, injury, toxins or pathological injuries, initially acts as a defense mechanism that protects the brain from pathogens, chronic neuroinflammation is detrimental and may lead to the onset and progression of neurodegenerative diseases (Kwon and Koh, 2020; López-Sánchez et al., 2024).

Detailed in the next section, different clinical trials are indicating beneficial effects of curcumin in inflammatory, AD, Parkinson's disease (PD) and aging-related conditions. Meanwhile, various studies demonstrated therapeutic effects of curcuminoids in classical models of AD and PD pathologies (Table 2). These studies are discussed herein offering insights into the *in vivo* capacities of curcuminoids to modulate brain inflammation and other pathological processes in neurodegeneration. Since curcuminoids' poor pharmacokinetic properties limit their bioavailability in the body, as detailed in the following chapters, several alternative oral formulations have been developed. The bioavailability and therapeutic effects of these novel formulations in animal models are also considered in this section.

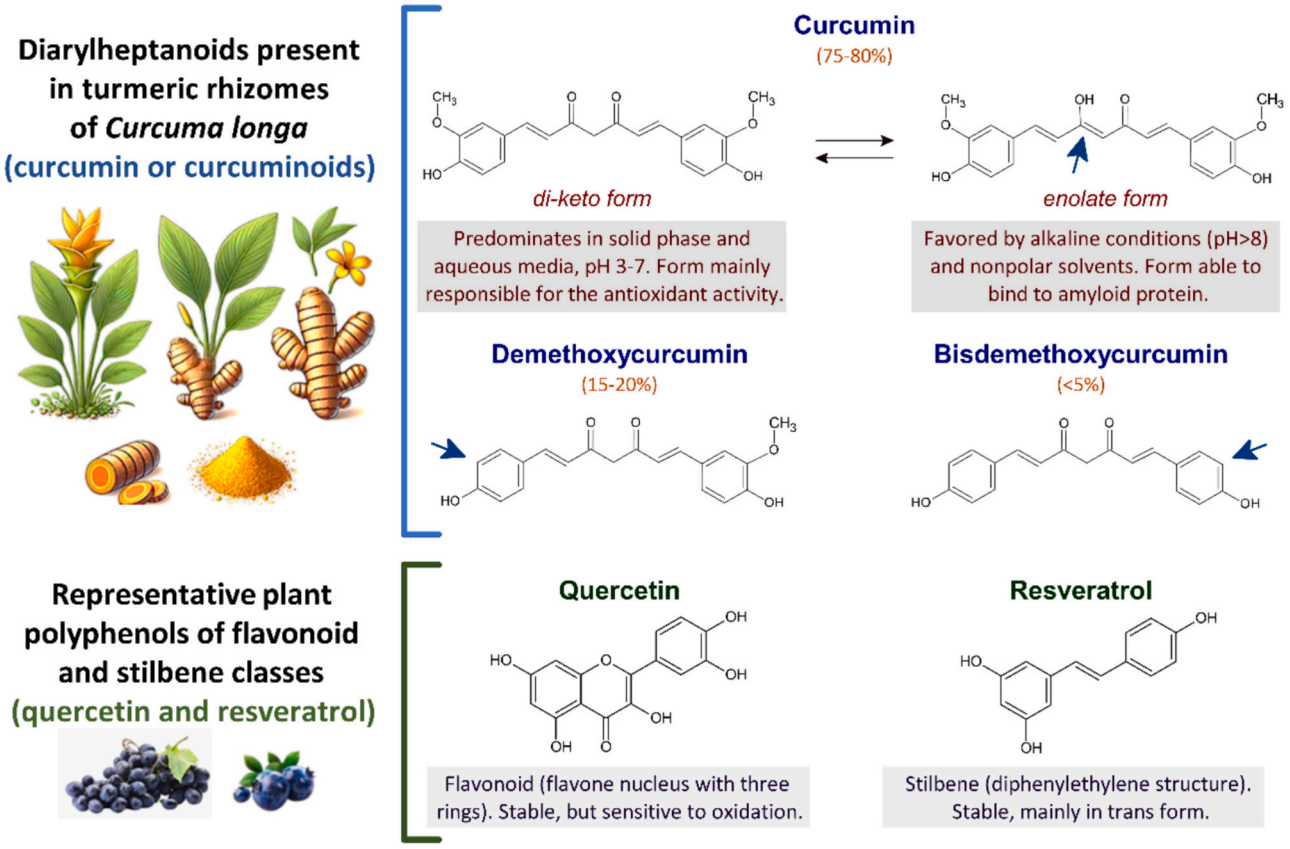

Fig. 2. Diarylheptanoids present in turmeric rhizomes of *Curcuma longa* (curcumin or curcuminoids) - curcumin, demethoxycurcumin and bisdemethoxycurcumin - along with major representative plant polyphenols of the flavonoid (quercetin) and stilbene (resveratrol) classes. The arrows point to differences in the chemical structures of the curcuminoids. The equilibrium between the tautomeric forms of curcumin is represented.

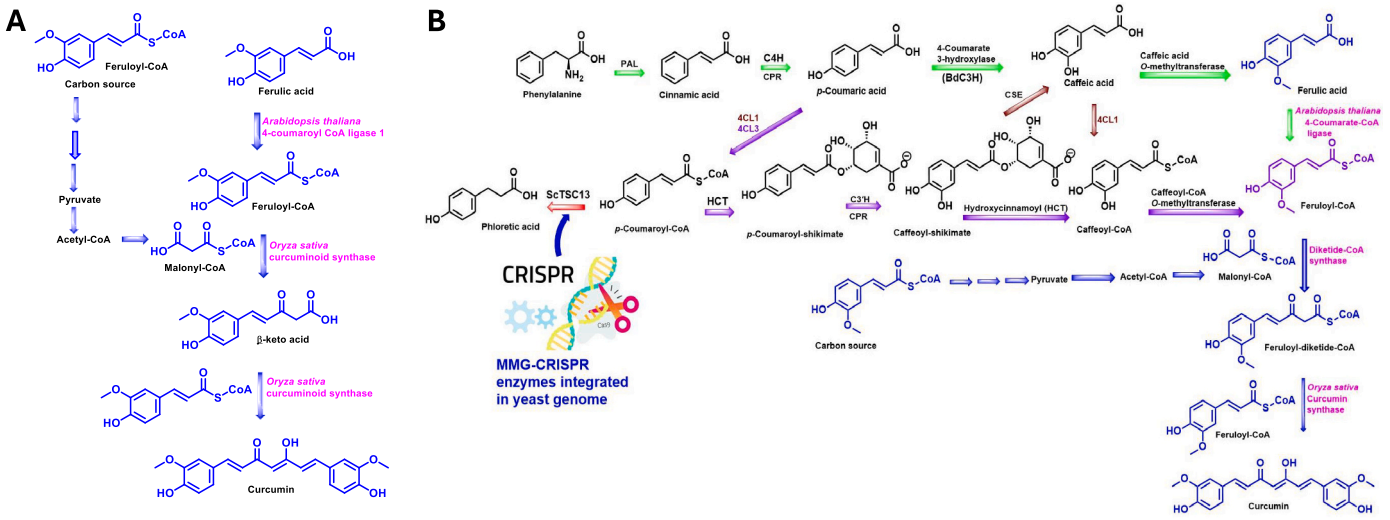

Fig. 3. (A) Engineered biosynthetic pathway of curcumin from ferulic acid. (B) Combinatorial approach in engineered biosynthesis of curcumin with CRISPR-Cas9. The green arrows pathway corresponds to the BdC3H pathway, cyan the HCT pathway, red the HCT-CSE pathway, and blue the engineered biosynthesis pathway of curcumin. Adapted from (Rainha et al., 2024; Utomo et al., 2024; Wu et al., 2020). Abbreviations: BdC3H, 4-coumarate 3-hydroxylase; C4H, trans-cinnamate-4-hydroxylase; CPR, cytochrome P450 reductase; CRISPR, clustered regularly interspaced short palindromic repeats; CSE, caffeoyl shikimate esterase; C3′H, p-coumaroylshikimate/quinate 3′-hydroxylase; HCT, hydroxycinnamoyl-CoA:shikimate hydroxycinnamoyl transferase; MMG: modular multiplex genome; PAL, phenylalanine ammonia lyase; ScTSC13, yeast endogenous enoyl reductase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. Alzheimer's disease

AD is the most common type of age-related neurodegenerative disease, characterized by the presence of intraneuronal neurofibrillary tangles and extracellular amyloid-β (Aβ) plaques, that lead to neuronal loss and brain atrophy (Oyovwi et al., 2025). *Via* antioxidant and anti-inflammatory activities, curcumin has shown great potential for AD management in many preclinical studies (Table 2). Moreover, curcumin also fosters Aβ degradation, reinforcing the neuroprotective effect (Genchi et al., 2024).

Oral supplementation of curcumin ameliorated abnormal cognitive behavior, biochemical parameters and histopathological features in AD rats, which is partially attributed to its antioxidant potential (Agrawal et al., 2010; Frautschy et al., 2001; Ishrat et al., 2009; Kumar et al., 2011; Samy et al., 2015; Sun et al., 2013). Moreover, a combination of antioxidants such as curcumin and piperine/hesperidin exhibited superior therapeutic response in galactose-induced senescence in rats as compared to monotherapy (Banji et al., 2013a, 2013b, 2014). Similarly, a combination of curcumin and mitoquinone mesylate, a synthetic analogue of coenzyme Q10, effectively mitigated typical AD pathological features, and demonstrated superior efficacy over individual drugs (Xie et al., 2024a). In another study, curcumin was reported to improve

Table 1
Production titers of curcuminoids by heterologous production in microbes. The studies are ordered by publication date, first those using *Escherichia coli* and afterwards *Saccharomyces cerevisiae*.

Curcuminoid	Titer (mg/L)	Bioprocess	Reference
Bisdemethoxycurcumin Curcumin	53.40 113.0	*E. coli* systems carrying artificial biosynthetic pathway Exogenous supplementation of tyrosine or phenylalanine, or ferulic acid (rice bran pitch)	(Katsuyama et al., 2008)
Curcumin	6.26	Engineered *E. coli* using heat shock promoters Use of *Arabidopsis thaliana* 4-coumaroyl-CoA ligase, *C. longa* diketide-CoA synthase and curcumin synthase	(Rodrigues et al., 2015a)
Bisdemethoxycurcumin Dicinnamoylmethane	4.63 6.95	Engineered *E. coli* Shikimic acid biosynthetic pathway to increase substrate supply	(Kim et al., 2017)
Curcumin	0.54	Engineered *E. coli* Overexpression of monoglucosyldiacylglycerol synthase from *Acholeplasma laidlawii*; media supplementation with unsaturated fatty acid	(Wu et al., 2020)
Curcuminoids	15.9	Combinatorial approach from tyrosine in *E. coli* Use of caffeic acid *O*-methyltransferase in monoculture and co-culture	(Rodrigues et al., 2020)
Dicinnamoylmethane	0.7 to 3.8	Engineered *E. coli* with *Oryza sativa* curcuminoid synthase and *Petroselinum crispum* 4-coumarate-CoA ligase, and CRISPR-knock down of genes in the tricarboxylic acid cycle and fatty acid biosynthesis pathway Scale-up of the recombinant strain to a 3-L fermenter, using cinnamic acid as substrate	(Chu et al., 2020)
Curcumin	696	Engineered *E. coli* Pilot-scale (5 L) fermentation, with three-stage pH management	(Chen et al., 2024)
Curcumin	2.7	Synthesis from ferulic acid in *S. cerevisiae* Maximum titer obtained with a bacterial feruloyl-CoA synthetase combined with *C. longa* polyketide synthase	(Rainha et al., 2022)
Curcumin	1.5 to 4.2	CRISPR-engineered *S. cerevisiae* Multiple genes integrated into yeast genome, enabling *de novo* production of curcumin without precursor supplementation	(Rainha et al., 2024; Utomo et al., 2024)

Table 2
Summary of preclinical *in vivo* studies demonstrating neuroprotective effects of curcuminoids.

Intervention and *Disease model*	Results
Alzheimer's disease (AD) and related pathology models	
Curcumin *STZ-induced dementia*	Ameliorated cognitive deficits (Agrawal et al., 2010; Bassani et al., 2017; Ishrat et al., 2009; Isik et al., 2009; Samy et al., 2015) Decreased oxidative stress (Agrawal et al., 2010; Awasthi et al., 2010; Ishrat et al., 2009; Samy et al., 2015) Decreased Aβ accumulation (Samy et al., 2015) Restored anticholinesterase activity, and the protein levels of insulin receptors in hippocampus and cerebral cortex (Agrawal et al., 2010) Suppressed Fas ligand apoptotic mechanism and neuronal death (Samy et al., 2015) Improved cerebral blood flow (Awasthi et al., 2010) Ameliorated memory impairment and cholinergic dysfunction (Awasthi et al., 2010) Normalized the level of insulin-like growth factor-1 in serum (Isik et al., 2009) Protected pyramidal neurons in the hippocampus (Isik et al., 2009)
Curcumin *Aβ-induced AD*	Ameliorated memory impairment (Frautschy et al., 2001) Decreased oxidative stress (Frautschy et al., 2001) Suppressed synaptophysin loss (Frautschy et al., 2001) Reduced microgliosis (Frautschy et al., 2001) Improved cognitive functions in a dose-dependent manner (Zhang et al., 2015) and neurogenesis (Lou et al., 2024) Increased levels of BDNF and phosphorylated ERK (Zhang et al., 2015) Improved spatial learning and memory abilities (Wang et al., 2013; Yin et al., 2014) Decreased expression of hippocampal NgR (Yin et al., 2014) Increased axonal protein expression (Yin et al., 2014) Increased CRMP-2 and NF-200 levels, and reduced hyperphosphorylation of CRMP-2 (Wang et al., 2013) Regulated the PI3K/Akt – GSK - Wnt/β-catenin and BDNF pathways (Lou et al., 2024)
Curcumin *D-galactose-induced senescence*	Ameliorated cognitive deficits and improved locomotor activity (Kumar et al., 2011) Decreased oxidative stress and restored mitochondrial enzyme complex (Kumar et al., 2011) Increased acetylcholine esterase activity (Kumar et al., 2011)
Curcumin *SAMP8 mice*	Attenuated cognitive deficits in a dose-dependent manner (Sun et al., 2013) Decreased oxidative stress (Sun et al., 2013) Increased levels of p-CaMKII and p-NMDAR1 (Sun et al., 2013)
Curcumin *APP/PS1 double transgenic mice*	Improved cognitive function, reduced deposition of Aβ, induced autophagy, and inhibited the PI3K/Akt/mTOR signaling pathway (Wang et al., 2014)
Curcumin *3xTg AD mice fed a high-fat high-sugar diet*	Improved behavioral and cognitive functions (Lamichhane et al., 2024) Enriched beneficial gut microbiota, including *Oscillibacter*, *Alistipes*, *Pseudoflavonifractor*, *Duncaniella*, and *Flintibacter* (Lamichhane et al., 2024)
Curcuminoid mixture, individual components *Aβ-induced AD*	Memory-enhancing effect (Ahmed et al., 2010) Increased expression of PSD-95, synaptophysin, and CaMK4 in the hippocampus (Ahmed et al., 2010)
Curcumin, Tetrahydrocurcumin *Aged Tg2576 APPsw mice*	Both reduced IL-1beta, and phospho-JNK (Begum et al., 2008) Only curcumin reduced amyloid plaque burden, insoluble Aβ, and protein carbonyls (Begum et al., 2008)
Curcumin combinations *D-galactose-induced senescence*	Curcumin and piperine improved spatial memory, reduced oxidative stress, in synergy with piperine (Banji et al., 2013b) Curcumin and hesperidin improved cognition, reduced levels of cleaved caspase-3 and malondialdehyde, and increased mitochondrial enzymes and glutathione levels (Banji et al., 2014)
Curcumin and mitoquinone mesylate *3 × Tg-AD mice*	Superior efficacy over individual drugs (Xie et al., 2024a) Mitigated Aβ aggregation, tau phosphorylation, and synaptic damage (Xie et al., 2024a)
Curcumin-loaded carriers *Aβ-induced cognitive impairments*	Targeted polymersomes ameliorated cognitive dysfunction (Jia et al., 2016) Lipid-core nanocapsules prevented cognitive impairments, increased BDNF expression and suppressed tau phosphorylation, more effectively than non-encapsulated curcumin (Hoppe et al., 2013) Polymeric nanoparticles induced neural stem cells proliferation and neuronal differentiation (Wnt/β-Catenin pathway), and reversed learning and memory impairments (Tiwari et al., 2014)
Curcumin nano-formulations *STZ-induced dementia*	Polycaprolactone nanocapsules coated with polysorbate reversed memory deficits, attenuated elevated acetylcholinesterase activity, and mitigated oxidative stress and neuroinflammation (Savall et al., 2024) Bovine serum albumin nanoparticles ameliorated learning and memory deficits, reduced caspase-3 cleavage and restored Akt and CaMKII-α signaling in the hippocampus (Moosavi et al., 2024)
Curcumin solid lipid particles (Longvida®) *Assessed in different models*	In the hTau transgenic mice model, it suppressed levels of soluble Tau dimers, increased synaptic proteins (PSD95, NR2B) and heat shock proteins (HSP90 and HSC70), and corrected behavioral deficits (Ma et al., 2013) In the p25 transgenic mice model, it inhibited glial activation and pro-inflammatory cytokines production (Sundaram et al., 2017)
Inhalational curcumin *5XFAD mice*	Reduced plaque formation, improved cognitive function, without toxicity detected (McClure et al., 2017)
Curcumin derivatives *APP/PS1 transgenic mice*	FMeC1 derivative reduced cognitive deficits, Aβ deposits and glial cell activity (Yanagisawa et al., 2015) Derivative-27 prevented short-term spatial memory loss, decreased IL-1β, and amyloid precursor protein and Aβ in hippocampus and plasma (Rodrigues et al., 2025)
PE859 curcumin derivative *SAMP8 mice*	Inhibited Aβ and tau aggregation and ameliorated cognitive dysfunction (Okuda et al., 2017)

(*continued on next page*)

Table 2 (*continued*)

Intervention and *Disease model*	Results
Parkinson's disease (PD) and related pathology models	
Curcumin *6-OHDA model*	Increased tyrosine hydroxylase levels (Du et al., 2012; Khuwaja et al., 2011) and positive cells (Zbarsky et al., 2005) Improved dopamine levels (Du et al., 2012; Lv et al., 2014; Song et al., 2016; Zbarsky et al., 2005) Enhanced antioxidant ability (Song et al., 2016) (Khuwaja et al., 2011) (Lv et al., 2014) Promoted neural regeneration by activating BDNF/TrkB-dependent pathway (Yang et al., 2014) Reduced lipotoxicity (Song et al., 2016) Upregulated bFGF, NGF, TrkA and HSP70 expression in the substantia nigra (Song et al., 2016) Dose and duration dependence of the neuroprotective effect (Liu et al., 2023)
Curcumin *MPTP mice model*	Restored dopamine and tyrosine hydroxylase levels (Muthian et al., 2018) Alleviated motor deficits, regulated gut microbiota composition, maintained the levels of short chain fatty acids (Cai et al., 2023)
Curcumin *Rotenone-induced PD*	Improved behavioral alterations and mitochondrial enzyme complex activities (Khatri and Juvekar, 2016) Attenuated oxidative stress (Fikry et al., 2022; Khatri and Juvekar, 2016)
Curcumin *Transgenic Drosophila*	Dose-dependent delay in the loss of activity pattern, reduced oxidative stress and apoptosis (Siddique et al., 2014) Decreased ROS level, improved locomotor activity, and reduced degeneration of dopaminergic neurons (Nguyen et al., 2018)
Curcumin *Lipopolysaccharide-induced PD*	Inhibited astrocytic activation, improved glutathione parameters, prevented iron deposition and α-synuclein aggregation in dopaminergic neurons, and downregulated NF-kB, proinflammatory cytokines (TNF-α, IL-1β, and IL-1α), and inducible nitric oxide synthase (Sharma and Nehru, 2018)
Curcumin *Copper-induced PD*	Increased tyrosine hydroxylase level and improved locomotor activity (Abbaoui and Gamrani, 2018)
Curcumin *Syn-GFP mice*	Improved gait impairments and increased phosphorylated forms of α-synuclein (Spinelli et al., 2015)
Curcumin, demethoxycurcumin, and bisdemethoxycurcumin *6-OHDA model*	Efficacy: Curcumin > Demethoxycurcumin > Bisdemethoxycurcumin (Agrawal et al., 2012)
Curcumin, Tetrahydrocurcumin *MPTP mice model*	Both reversed the decrease in dopamine and DOPAC, and inhibited monoamine oxidase-B (Rajeswari and Sabesan, 2008)
Curcumin combinations *Rotenone-induced PD*	Curcumin-piperine nano-formulation enhanced bioavailability, improved motor dysfunction, and reduced dopaminergic neuronal degeneration (Kundu et al., 2016) Curcumin, niacin and ZM241385 increased dopamine levels and attenuated neuroinflammation and oxidative stress (Motawi et al., 2020)
Curcumin formulations *MPTP mice model*	Curcumin in oil offered higher bioavailability and better neuroprotection (Geng et al., 2022) Curcumin loaded polysorbate 80-modified cerasome provided longer circulation lifetime (after IV), high permeation through blood-brain barrier, and improved behavior disorder and dopamine depletion (Zhang et al., 2018)
Curcumin/alginate nanocomposite *Transgenic Drosophila*	Delayed climbing disability and reduced oxidative stress and apoptosis (Siddique et al., 2013)
Curcumin loaded nanoemulsion *Rotenone-induced PD*	Improved motor impairment, reduced lipid oxidation and modulated complex I inhibition (Ramires Júnior et al., 2021)
Curcumin-pyrazole derivative *MPTP mice model*	Ameliorated behavioral impairments, oxidative stress, and mitochondrial deficits (Jayaraj et al., 2014) Increased expression of tyrosine hydrolase, dopamine transporter, and vesicular monoamine transporter 2 (Jayaraj et al., 2014)

Abbreviations: 6-OHDA: 6-hydroxydopamine; Aβ: amyloid-β; AD: Alzheimer's disease; BDNF: Brain derived neurotrophic factor; bFGF: basic fibroblast growth factor; CaMKII-α: Calcium/calmodulin-dependent protein kinase II-α; CRMP-2: Collapsin response mediator protein 2; DOPAC: 3,4-dihydroxy phenyl acetic acid); ERK: extracellular signal-regulated kinase; GSK: glycogen synthase kinase; HSP70: heat shock protein 70; IL: Interleukin; JNK: c-Jun N-terminal kinase; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NgR: Nogo receptor; NGF: Nerve growth factor; p-CaMKII: p-calcium/calmodulin-dependent kinase II; PD: Parkinson's disease; PI3K: Phosphatidylinositol 3-kinase; p-NMDAR1: p-*N*-methyl-D-aspartate receptor subunit 1; ROS, reactive oxygen species; SAMP8: senescence-accelerated mouse prone 8; STZ: streptozotocin; TrkA: tyrosine kinase A; TrkB: tyrosine kinase B.

cerebral blood flow in a dose-dependent manner, along with amelioration of memory impairment and oxidative stress (Awasthi et al., 2010). This improvement in cerebral blood flow may potentially contribute to enhanced clearance of toxic protein aggregates and delivery of nutrients to affected brain regions. Also in the streptozotocin AD model, the increased level of insulin-like growth factor-1 (IGF-1) was associated with the neuroprotective effect of curcumin (Isik et al., 2009). Upregulation of brain-derived neurotrophic factor (BDNF)-extracellular signal-regulated kinases (ERK) signaling (Zhang et al., 2015), lowering of hippocampal Nogo receptor expression (Yin et al., 2014), and inhibition of collapsin response mediator protein-2 (CRMP-2) hyperphosphorylation (Wang et al., 2013) are other mechanisms implicated in the beneficial effect of curcumin countering cognitive impairment. Curcumin also decreased Aβ deposition, and induced autophagy in association to the inhibition of phosphatidylinositol 3-kinase (PI3K)/phosphorylated protein kinase B (Akt)/rapamycin (mTOR) signaling, while in another AD model it rescued impaired adult neurogenesis at the hippocampus (Lou et al., 2024; Wang et al., 2014). Curcumin supplementation also affected the gut-brain axis by protecting the intestinal barrier integrity and function and modulating microbiota composition, demonstrating potential to modulate the crosswalk between gut microbiota and brain for regulating metabolic and cognitive functions (Lamichhane et al., 2024; Scazzocchio et al., 2020). In a comparative study, individual curcuminoids exhibited better memory-enhancing effect in AD rats than a curcuminoid mixture (Ahmed et al., 2010). Both curcuminoid mixture and individual components showed beneficial effects, although variable depending on the dose and duration of treatment, on the expression of genes involved in synaptic plasticity. Demethoxycurcumin (30 mg/kg) showed high efficacy to induce the expression of PSD-95, synaptophysin and CaMK4 in the hippocampus of the Aβ-infused rats (Ahmed et al., 2010). In a different model (Table 2), administration of curcumin at a dose of 25-100 mg/day did not exhibit any beneficial effect in short-term spatial memory impairment, but only slight improvements in neuroinflammation (Bassani et al., 2017). The

metabolite tetrahydrocurcumin also showed anti-inflammatory action in the g2576 APPsw mice model of AD, although only curcumin administration reduced plaque deposition and protein oxidation (Begum et al., 2008).

To overcome the issue of curcumin's low bioavailability, various strategies such as derivatization and novel formulations have been deployed. Curcumin-loaded lipid-core nanocapsules exhibited similar neuroprotective effect compared to free curcumin, but at lower dose (Hoppe et al., 2013). Curcumin encapsulated in nanoparticles (NPs) of polylactide-*co*-glycolic acid (PLGA) was found to induce neurogenesis in AD mice through activation of the canonical Wnt/β-catenin pathway (Tiwari et al., 2014). Brain-targeting polymersomes with curcumin, after intravenous administration (IV), also enhanced cognitive performance of AD mice (Jia et al., 2016). Other nano-formulations (Moosavi et al., 2024; Savall et al., 2024) showed higher efficiency than unencapsulated curcumin for ameliorating cognitive deficits in AD mice, in association to beneficial modulation of different biochemical markers (Table 2). Curcumin-derived carbon quantum dots simultaneously mitigated Aβ aggregation and tau hyperphosphorylation (Lim et al., 2024). Oral supplementation with Longvida® (Verdure Sciences), a commercial formulation of curcumin in the form of solid lipid particles, reduced the levels of soluble Tau oligomer and increased heat shock proteins (HSPs) implicated in Tau clearance, in association with behavioral improvements (Ma et al., 2013), and also inhibited neuroinflammation (Sundaram et al., 2017), in different transgenic mice (Table 2). This formulation is also being trialed in humans (Table 3). Inhalational delivery of curcumin *via* aerosol significantly reduced plaque fraction in AD mice, without any systemic or pulmonary toxicity (McClure et al., 2017).

The chemically modified curcumin derivative FMeC1 inhibited the cognitive deficits, Aβ deposition and glial cell activity in AD transgenic mice, and was able to attenuate cell toxicity of Aβ (Yanagisawa et al., 2015). Another semi-synthetic derivative, the dual Aβ and tau aggregation inhibitor PE859, was found to ameliorate cognitive dysfunction in senescence-accelerated mouse prone 8 (Okuda et al., 2017).

4.2. Parkinson's disease

PD is the second most common age-related neurodegenerative disease, pathologically characterized by the loss of dopaminergic neurons in the substantia nigra region of the brain, resulting in dopamine deficiency within the basal ganglia, leading to the development of characteristic parkinsonian motor symptoms, with further appearance of non-motor symptoms as the disease progresses (Patel et al., 2022; Xiao et al., 2025). Curcumin shows promise as a supportive treatment for PD, particularly when used in specially designed forms (Donadio et al., 2022; Patel et al., 2022). The beneficial effects of curcumin in PD are attributed to augmentation of cerebral dopamine levels *via* inhibition of monoamine oxidase (MAO) enzyme (Rajeswari and Sabesan, 2008), prevention of mitochondrial dysfunction (Jayaraj et al., 2013; Liu et al., 2011), inhibition of α-synuclein aggregation (Pandey et al., 2008), thereby reducing Lewis body formation, and anti-inflammatory activity (Xu et al., 2023).

A significant neuroprotective effect of curcumin-loaded lactoferrin NPs has been observed in cell line experiments, which was justified by increased intracellular drug uptake and sustained retention of NPs. Pretreatment of dopaminergic cell line SK-N-SH with curcumin NPs induced tyrosine hydroxylase expression and a decrease in α-synuclein levels (Bollimpelli et al., 2016). Sookhaklari et al. (2019) reported approximately four times higher efficacy of a nano-formulation of curcumin (with bovine serum albumin) in protecting human neuroblastoma cells against 6-hydroxydopamine-induced death, an *in vitro* model of PD (Sookhaklari et al., 2019). Curcumin is also reported to protect against α-synuclein-induced cell death *via* inhibition of oxidative stress and the mitochondrial cell death pathway (Liu et al., 2011; Wang et al., 2010). Cytoprotective effects of curcumin have been associated to downregulation of p53 phosphorylation and Bax/Bcl-2 ratio (Jaisin et al., 2011; van der Merwe et al., 2017), as well as modulation of NF-kB translocation (Wang et al., 2009) and Bcl-2-mitochondria-reactive oxygen species (ROS)-nitric oxide synthase (NOS) pathway (Chen et al., 2006). Pretreatment with the CNB-001 curcumin-pyrazole derivative protected neuronal cells against rotenone-induced toxicity through antioxidant and anti-apoptotic actions (Jayaraj et al., 2013). In another study, curcumin-pyrazole and *N*-(3-nitrophenylpyrazole) curcumin exhibited remarkable inhibition of α-synuclein aggregation (Ahsan et al., 2015). A glucoside form of curcumin also inhibited the fibrillization of α-synuclein (Shrikanth Gadad et al., 2012).

In addition to *in vitro* studies, the PD therapeutic potential of curcumin and its novel formulations is also being investigated in various animal models (Table 2). Siddique et al. used a transgenic *Drosophila* flies' model to evaluate the efficacy of curcumin and its alginate nanocomposite against PD pathology (Nguyen et al., 2018; Siddique et al., 2013, 2014). Both free curcumin and its nanocomposite improved the locomotor activity of the transgenic flies, reduced oxidative stress and apoptosis in the brain in a dose-dependent manner, among other effects (Table 2).

Intraperitoneal (IP) administration of curcumin for 21 days, to rats injected lipopolysaccharide (LPS) into the substantia nigra, was reported to inhibit astrogliosis, as revealed by glial fibrillary acidic protein (GFAP), a marker of neuroinflammation (Sharma and Nehru, 2018). In accordance, the polyphenol modulated NF-kB activity, proinflammatory cytokines, and inducible NOS (Table 2). Moreover, it regulated glutathione levels, prevented iron deposition and α-synuclein aggregation (Sharma and Nehru, 2018). The modulation of the NF-kB signaling pathway is one of the more supported action mechanisms of curcuminoids in opposing inflammation and neurodegeneration, hence it is detailed in section 4.3.

Curcumin was also reported to promote neural regeneration of hippocampal tissue by activation of BDNF/tyrosine receptor kinase B-dependent pathway (Song et al., 2016; Yang et al., 2014). In another study, dietary curcumin intervention improved gait impairments, and increased the phosphorylated forms of α-synuclein in a genetic synucleinopathy mouse model (Spinelli et al., 2015). In addition to antioxidant effects, pretreatments with curcumin restored dopamine and tyrosine hydroxylase levels in different animal models of PD (Abbaoui and Gamrani, 2018; Du et al., 2012; Fikry et al., 2022; Khatri and Juvekar, 2016; Khuwaja et al., 2011; Muthian et al., 2018; Zbarsky et al., 2005). Indeed, both curcumin (80 mg/kg, IP) and tetrahydrocurcumin (60 mg/kg, IP) counteracted the drop in dopamine, and decreased MAO-B activity, in a mice model of PD (Rajeswari and Sabesan, 2008).

Curcumin's antioxidant action is partially due to its ability to bind to iron (Du et al., 2012), and a combination of curcumin and deferoxamine was more effective than single therapy (Lv et al., 2014). Curcumin supplementation also restored the altered gut microbiota composition of PD rats and normalized the levels of short-chain fatty acids (Cai et al., 2023); in addition, it was suggested that the neuroprotection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated PD mice (improved motor deficits, glial cell activation, and the aggregation of α-synuclein) is associated with modulation of the gut microbiota-metabolite axis, viewed by a strong correlation among crucial taxa (such as Lactobacillaceae, and Aerococcaceae*)*, key metabolites (namely tyrosine, and dopa) and the motor function and pathological results (Cui et al., 2022).

Among the various curcuminoids, curcumin was the most effective, followed by demethoxycurcumin, and bisdemethoxycurcumin, in protecting against neuronal degeneration in PD mice model (Agrawal et al., 2012). The neuroprotective effect of curcumin in PD was dose- and duration-dependent with the daily intervention of 160 mg/kg for 2 weeks showing optimal therapeutic effect (Liu et al., 2023).

Recently, a curcumin oil formulation demonstrated better bioavailability and efficacy in PD mouse model (Geng et al., 2022). Similarly, IV curcumin-loaded cerasome NPs (Zhang et al., 2018) returned improved

pharmacokinetics and therapeutic effects in PD mice (Table 2). The CNB-001 derivative also ameliorated behavioral impairments and mitochondrial deficits in the MPTP mouse model (Jayaraj et al., 2014). A lipid-based nano-formulation containing both curcumin and piperine exhibited neuroprotective effects *via* suppression of α-synuclein levels, oxidative stress and apoptosis in PC12 cells, together with activation of autophagy. Further, in an *in vivo* model, the dual drug-loaded NPs rescued rotenone-induced motor impairment and dopaminergic neuronal degeneration (Kundu et al., 2016). Another combination - curcumin, niacin and ZM241385 (non-dopaminergic) - was reported to be more effective in ameliorating Parkinson's symptoms in PD mice when compared to single treatment (Motawi et al., 2020). In the same model (Table 2), curcumin loaded into a nanoemulsion was more effective in preventing motor impairment than free curcumin, both given orally for 30 days (Ramires Júnior et al., 2021).

4.3. *Major cell signaling pathways modulated by curcuminoids in inflammation*

A significant number of animal studies and a few clinical studies implicate the modulation of NF-κB, PI3K/Akt, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways (Fig. 4) in the beneficial effects of curcuminoids in inflammatory and neurodegenerative conditions (Alvarenga et al., 2020; Azimzadeh et al., 2024; Esmaealzadeh et al., 2024; Musso et al., 2025; Porro et al., 2019).

The NF-κB signaling pathway is a major player in inflammation, including in the nervous system. Microglial activation of NF-κB family induces transcription of proinflammatory genes like those encoding chemokines, cytokines, and other inflammatory mediators (Anilkumar and Wright-Jin, 2024). NF-κB activation is initiated by diverse stimuli that bind to various cell membrane receptors, which in turn activates IκB kinase (IKK). IKK further phosphorylates cytoplasmic inhibitory proteins IκB and triggers nuclear translocation of NF-κB members. The binding of NF-κB proteins to the specific DNA element, κB enhancer, mediates transcription of pro-inflammatory genes (Xu et al., 2024). NF-κB signaling also plays a crucial role in the priming phase of inflammasome activation (Capece et al., 2022), as well as in regulation of the proliferation and differentiation of innate immune cells and inflammatory T cells (Guo et al., 2024). Deregulated NF-κB activation has been implicated in the pathogenesis of both AD and PD (Anilkumar and Wright-Jin, 2024). Curcumin decreases inflammation by inhibiting NF-κB, which downregulates the production of pro-inflammatory cytokines, eventually by stimulation of peroxisome proliferator-activated receptor-γ (PPARγ) signaling (Alvarenga et al., 2020; Musso et al., 2025; Rodrigues et al., 2025; Sharma and Nehru, 2018). Curcumin was reported to inhibit

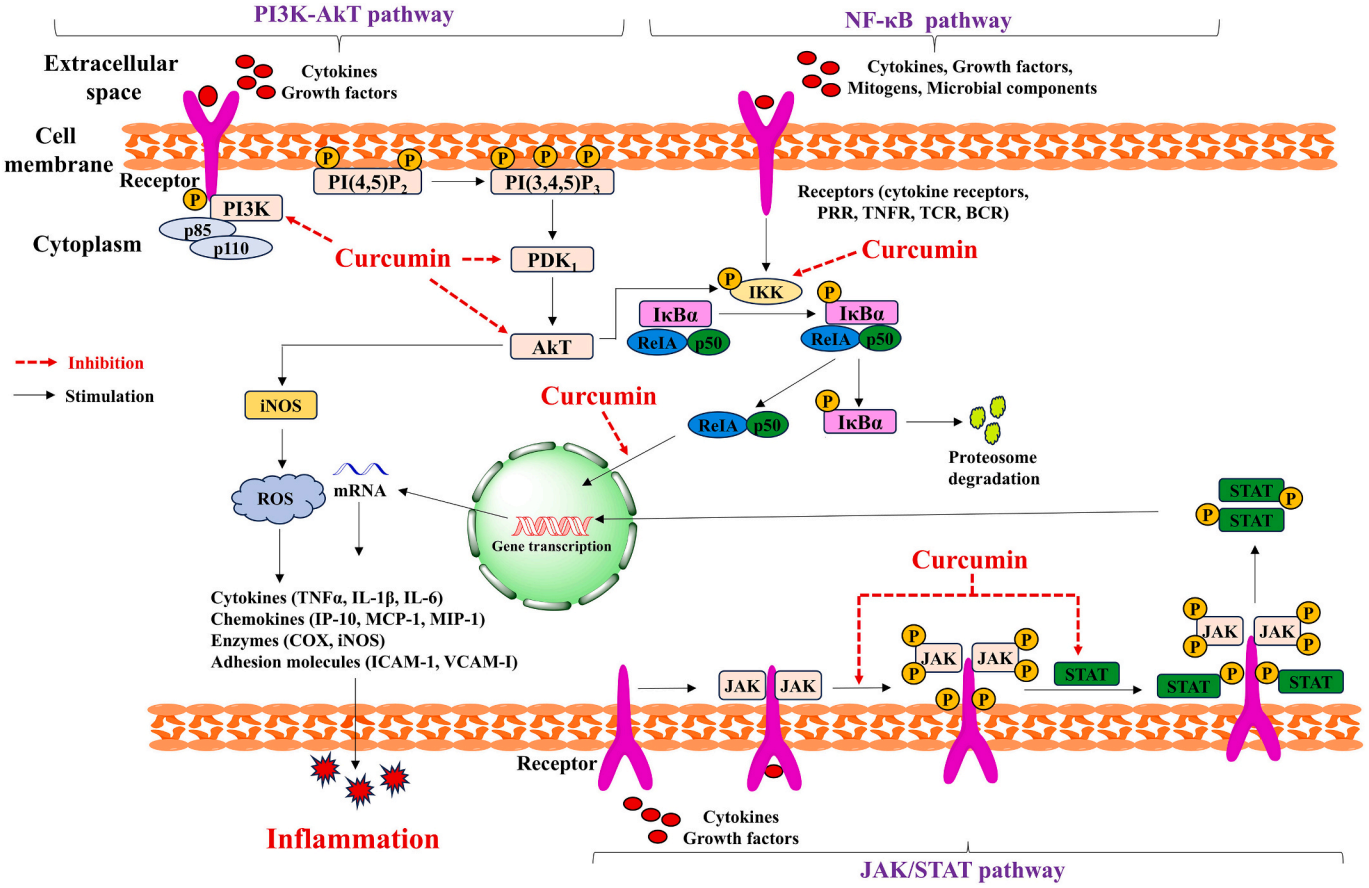

Fig. 4. Cell signaling molecular pathways modulated by curcuminoids in inflammation and neurodegeneration. NF-κB activation induces transcription of pro-inflammatory genes, including those encoding chemokines, cytokines, and other inflammatory mediators. Curcumin and related members inhibit the phosphorylation of IκB, and subsequent translocation of p50 subunit of NF-κB to the nucleus, thereby ameliorating inflammation. The PI3K cellular signaling pathway regulates microglial activation and inflammation. Curcuminoids also attenuate inflammatory response by suppressing PI3K and protein kinase B (Akt) signaling. In addition, curcuminoids suppress phosphorylation of JAK and STAT, which are critical steps in JAK-STAT pathway, responsible for expression of various critical inflammatory mediators. Abbreviations: AkT, protein kinase B; BCR, B-cell receptor; COX, cyclooxygenase; ICAM, intercellular adhesion molecule; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IP, inducible protein; JAK, Janus kinase; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NF-κB, nuclear factor-kappa B; PDK, phosphoinositide-dependent protein kinase; PI(3,4,5)P3, phosphatidylinositol 3,4,5 trisphosphate; PI(4,5)P2, phosphatidylinositol 4,5 bisphosphate; PI3K, phosphatidylinositol 3-kinase; PRR, pattern recognition receptors; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TNF, tumor necrosis factor; TNFR, TNF receptor; VCAM, Vascular cell adhesion molecule.

the phosphorylation of IκB, and subsequent translocation of p50 subunit of NF-κB to the nucleus (Fig. 4), thereby ameliorating neuroinflammation (Karunaweera et al., 2015). Curcumin also blocks ERK2, which is one of the mediators in NF-κB pathway that mediates phosphorylation of IκBα *via* activation of IκB kinases (Tang et al., 2017).

PI3K is another key cellular regulator of various functions like microglial activation and inflammation (Wright et al., 2024). It is a heterodimer composed of p85 regulatory subunit that recruits the enzyme to the plasma membrane and a p110 catalytic subunit that phosphorylates phospholipids mediating the downstream signaling. Upon activation, PI3K phosphorylates D-3 position of phosphatidylinositol 4,5 bisphosphate PI(4,5)P_2, generating the second messenger phosphatidylinositol 3,4,5 trisphosphate (PI(3,4,5)P_3), which further leads to activation of protein kinase B (Akt) and NF-κB (Chu et al., 2021; Zhuang et al., 2004). Aberrant PI3K-Akt signaling alters the microglial activity and exacerbates neuroimmune responses (Goyal et al., 2022). Additionally, PI3K-mediated Akt signaling influences the generation of ROS *via* inducible NOS (Fig. 4), triggering oxidative stress, that further amplifies neuroinflammation (Wright et al., 2024). Impairment of PI3K/Akt pathway also increases glycogen synthase kinase (GSK)-3β activity, which aggravates Tau hyperphosphorylation and aggregation that ultimately forms neurofibrillary tangles in AD (Desale et al., 2021). Curcumin supplementation attenuated the inflammatory responses in microglial cells through down-regulation of PI3K/Akt signaling (Cai et al., 2024; Cianciulli et al., 2016). Curcumin also inhibited nitric oxide secretion and the expression of inducible NOS, as well as phosphorylation of mitogen-activated protein kinase (MAPK) including ERK, Akt and translocation of NF-κB (Yu et al., 2018). Studies in PD and AD models associated the neuroprotective effects of curcumin to the modulation of the BDNF and PI3K/Akt signaling pathways (Jin et al., 2022; Lou et al., 2024).

Inducing the expression of various critical inflammatory mediators, the JAK/STAT pathway is triggered by more than 50 types of cytokines, including interleukins, growth factors and interferons (Hu et al., 2021; Xue et al., 2023). Binding of these factors to their corresponding receptors causes the recruitment of related JAKs that initiate receptor phosphorylation and formation of docking sites for STATs (Fig. 4). When phosphorylated by JAKs, inactive phosphorylated STAT monomers dissociate from the receptors and undergo conformational changes to form active homodimers, heterodimers, or tetramers, that on translocation to nucleus regulate gene transcription (Hu et al., 2021). Dysregulation of JAK-STAT pathway is implicated in various neurodegenerative diseases including AD and PD (Lashgari et al., 2021) (Panda et al., 2024). The anti-inflammatory action of curcumin has been attributed to the suppression of JAK-STAT pathway. Curcumin markedly suppressed phosphorylation of JAK1 and 2 as well as STAT1 and 2, which are critical steps in this pathway (Kim et al., 2003). In addition to inhibition of JAK2 and STAT3 phosphorylation, curcumin also upregulated the expression of suppressors of cytokine signaling (SOCS), an important regulator protein in JAK/STAT pathway (Porro et al., 2019).

5. Data from clinical trials guiding future research

The encouraging results obtained in preclinical studies led to the investigation of the therapeutic potential of curcuminoids in clinical trials.

To assess the effects of curcuminoids on inflammation and neurodegeneration conditions in clinical trials a search was performed mainly using ClinicalTrials.gov. At this platform, the keywords “curcumin OR curcuminoids” were introduced in the “intervention” field together with “Neurodegeneration OR Neurodegenerative diseases” OR “Age OR Ageing OR Aging OR Ageing-related diseases OR Aging-related diseases” OR “inflammation OR inflammatory diseases” in the “condition/disease” field. The trial reference number was also searched on the Pubmed database to complement the information collected.

The information obtained is summarized in Table 3 and shows the therapeutic effects of curcuminoids in inflammatory, cancer, neurodegenerative, and aging-related conditions. Moreover, the specific data on therapeutic and adverse outcomes extracted from these human trials provide valuable clues for the conditions and treatment options deserving more research efforts in the future.

Since inflammation is connected to many important pathologies, the search returned several trials on cancer, kidney and varied diseases where inflammatory processes receive special attention. In cancer patients, liposomal curcumin (IV) led to transient clinical benefits together with significant tumor marker responses, although only in 2 patients out of 32 (NCT02138955, (Greil et al., 2018)). In patients with familial adenomatous polyposis (NCT00641147, (Cruz-Correa et al., 2006, 2018)) and ulcerative colitis (NCT02683733, (Banerjee et al., 2021)), beneficial molecular changes and clinical response were reported, respectively (Table 3). Curcuminoids helped reduce the severity of symptoms in children with inflammatory bowel disease, and gassiness was the only adverse effect observed in a part of the group (NCT00889161, (Suskind et al., 2013)). In acute pancreatitis, curcuminoids reduced the hospital length of stay and the need for analgesics, and increased the appetite of the patients (NCT04989166, (Chegini et al., 2023)). Although an acute condition, only patients diagnosed by at least two of three criteria were enrolled in this trial, ensuring the subjects had a rightly defined inflammatory pancreatitis condition.

In chronic kidney disease, two trials were conducted with the same curcuminoid dose, 500 mg thrice daily (Table 3). In one, the plasma levels of MDA reduced after 12 weeks (NCT04413266, (Reis et al., 2024)), while important anti-inflammatory activity was detected in the other, namely decreases in NF-kB mRNA expression and plasma high sensitivity C-reactive protein (NCT03475017, (Alvarenga et al., 2020)). Another trial with a lower dose (320 mg/day, only 8 weeks) also reported antioxidant effects of curcumin given to patients with proteinuric chronic kidney disease (Jiménez-Osorio et al., 2016). A recent trial in patients with nonalcoholic steatohepatitis (NASH) tested 2 g, corresponding to 400 mg curcuminoids, of the phytosomal formulation Meriva® daily (Musso et al., 2025). After 72 weeks of treatment, a high effect size was registered in NASH resolution and regression of chronic kidney disease, in addition to other clinical and biochemical improvements (Table 3). Moreover, the inhibition of hepatic NF-kB was predictive of NASH resolution and fibrosis improvement (Musso et al., 2025). Antioxidant and anti-inflammatory activities were also registered in conditions of alcoholism (CTRI/2018/03/012385, (Krishnareddy et al., 2018)) and occupational stress (Sudheeran et al., 2016) with daily doses up to 500 mg for some weeks (Table 3). The trial NCT03475017 (Alvarenga et al., 2020) suggests the inhibition of NF-kB signaling as a specific and antioxidant-independent effect of curcumin, as changes in the NLRP3 inflammasome and nuclear receptor factor-2 (Nrf2) pathways were not detected, and the effect was observed despite the patients taking curcumin with orange juice and carrots equal to the placebo group.

The formulation Curcuphyt/Meriva showed immunomodulatory effects in patients with endometrial carcinoma (NCT02017353, 2013-001737-40, (Tuyaerts et al., 2019)) and leukemia (Golombick et al., 2015), but only in small groups and less encouraging results were reported in other trials (NCT01740323 and NCT02782949 in Table 3). Still regarding inflammatory conditions, the results from our trials' search also reveal the interest in curcumin for periodontitis, skin inflammation, and osteoarthritis, although without available results in most cases (Table 3). For osteoarthritis, a recent trial of a topical organogel revealed to alleviate pain and stiffness, without adverse effects (IRCT20220531055045N1 (Baharizade et al., 2024)).

Combinations of curcumin with other compounds are also trialed, namely with piperine (or bioprine), described to increase the curcumin bioavailability (Shoba et al., 1998), and with other polyphenols having algo important pharmacological actions. Combinations with quercetin or Ginkgo leaf extract have already revealed positive clinical and pharmacokinetic results (NCT00164749, (Baum et al., 2007, 2008;

Table 3
Registered clinical trials of curcuminoid formulations in inflammation, neurodegeneration, and aging-related conditions. Trials are denoted by the ClinicalTrials.gov identifier, EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/), Clinical Trials Registry of India (https://ctri.nic.in/), Australian New Zealand Clinical Trial Registry, Iranian Registry of Clinical Trials, or by a bibliographic reference. The administration route is specified when it is different from oral. The table is divided into 3 parts, according to the general condition, and the trials within each part are ordered by increasing daily dose. According to the information available on the formulation, the actual dose of curcuminoids was calculated and indicated.

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Inflammation-related conditions (including cancer)					
Lipocurc®, liposomal curcumin (Intravenous)	Patients with locally advanced or metastatic cancer	Phase II Completed	- No toxicity for doses between 100 and 300 mg/m2 over 8 h - hemolysis and hemoglobin decrease for doses of 300 mg/m2 over 6 h - stable curcumin plasma concentrations during infusion but undetectable after the infusion - Significant tumor marker responses and transient clinical benefit observed in two patients	8-24.4 mg (~57-171 = 100-300 mg/m2 weekly) for 8 weeks	NCT02138955 (Greil et al., 2018)
Nano-curcumin soft gels	Patients with mild and moderate acute pancreatitis	Completed	- Decreased hospital length of stay (LOS) - Reduced need for analgesics over time - Increased overall appetite score over the study period - No adverse effects or mortality reported	80 mg (40 mg twice daily) for 2 weeks	NCT04989166 (Chegini et al., 2023)
Nano-micelle curcumin	Patients with metabolic syndrome	Unknown status	No study results published	80 mg once daily for 12 weeks	NCT03514667
Curcuminoid from turmeric extract in capsules	Patients with a clinical diagnosis of osteoarthritis	PhaseI/II Completed	No study results published	90 mg (30 mg thrice daily) for 3 weeks	NCT06105840 (Mahanani et al., 2024)
Curcumin nanoemulsion	Obese women at high risk for breast cancer	Completed	No study results published	100 or 200 mg (50 or 100 mg twice daily) for 3 months	NCT01975363
Valdone, bio-enhanced curcumin soft gelatin capsule	Patients with mild to moderate ulcerative colitis	Phase III Completed	- Higher clinical remission, clinical response, and endoscopic remission rates at different periods - No significant side effects.	100 or 200 mg (50 or 100 mg twice daily) for 12 months	NCT02683733 (Banerjee et al., 2021) NCT02683759
SinaCurcumin®, nanocurcumin as a nanomicelle	Patients undergoing radiotherapy for prostate cancer	Phase II Recruiting	- Good toleration - No significant differences in the occurrence of radiation-induced proctitis or cystitis	120 mg once daily for 6 days	NCT02724618 (Saadipoor et al., 2019)
Puritans Pride Turmeric curcumin®, capsule	Diabetic patients with atherosclerotic cardiovascular risk	Phase II Recruiting	No study results published	150 mg (50 mg thrice daily) for 14 weeks	NCT05753436
Surface-controlled water-dispersible curcumin	Patients with advanced cancer	Phase I Completed	No study results published	200 mg (100 mg twice daily) for 28 days	NCT01201694
Meriva®500, curcumin formulation (+ phosphatidylcholine) (20 % curcuminoids)	Chemotherapy-treated breast cancer patients undergoing radiotherapy	Phase II Completed	- Serious adverse effects reported - Non-serious adverse effects reported	200 mg Curcuminoids (100 mg twice daily) for 6 weeks	NCT01740323
Micellar curcumin	Subjects at risk for metabolic syndrome	Phase II Completed	No study results published	240 mg (80 mg thrice daily) for 6 weeks	NCT01925547
Curcumin	Patients with nondiabetic or diabetic proteinuric chronic kidney disease	Completed	- No effects on proteinuria, estimated glomerular filtration rate, lipid profile, antioxidant enzyme activities, or Nrf2 activation - Attenuated lipid peroxidation in non-diabetic patients - Enhanced antioxidant capacity in diabetic patients	320 mg once daily for 8 weeks	(Jiménez-Osorio et al., 2016)
BCM-95® or Bio-curcumin, capsule	Healthy overweight adults	Completed	No study results published	350 mg (95 % curcumin) daily for 21 days	NCT03329781
CurQfen® (curcumin-galactomannoside) (70 % curcuminoids)	Subjects experiencing occupational stress-related anxiety and fatigue	Completed	- Increase in antioxidant markers - Decrease in lipid oxidation - Increase in quality of life	350 mg Curcuminoids (175 mg twice daily) for 30 days	(Sudheeran et al., 2016)

(*continued on next page*)

Table 3 (*continued*)

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Meriva®, curcuphyt capsule (phytosome lecithin-based curcumin)	Patients with endometrial carcinoma	Phase II Completed	- Downregulation of Major Histocompatibility Complex expression on leucocytes - Upregulation of CD96 levels on CD16- cells - Reduction of monocyte frequency - Decreased inducible costimulator expression by CD8+ T cells	400 mg daily for 2 weeks	NCT02017353 2013-001737-40 (Tuyaerts et al., 2019)
Curcumin combination	Patients with knee osteoarthritis	Unknown status	No study results published	400 mg (200 mg twice daily) for 6 weeks	NCT04207021
Meriva® formulation (phytosome lecithin-based curcumin, 20 %)	Patients with stage 0/1 chronic lymphocytic leukemia	Completed	In 20 % of patients - Reduction in absolute lymphocyte count - Increase in CD4, CD8 and NK cells	400 mg Curcuminoids daily for 6 months	(Golombick et al., 2015)
Meriva®, curcumin phytosome formulation (20 % curcuminoids)	Nonalcoholic steatohepatitis patients (52), biopsy-proven	Completed	- Hepatic NF-kB inhibition - Compared with placebo, improved levels of eGFR, fasting glucose, HbA1c, LDL-C, glycerides, HDL-C, and inflammatory markers - NASH resolution in 62 % of patients (12 % on placebo) - Fibrosis improvement by ≥1 stage in 50 % of patients (8 % on placebo) - F ≥ 2 stage fibrosis improvement in 42 % of patients (0 % on placebo) - Chronic kidney disease regression in 50 % of patients (0 % on placebo) - Adverse events were rare, mild, and evenly distributed.	400 mg Curcuminoids (200 mg twice daily) for 72 weeks	(Musso et al., 2025)
Curcumin solid lipid particles (Longvida®)	Kidney transplant recipients	Active, not recruiting	No study results published	460 mg once daily for 12 months	NCT03935958
CurQfen® (curcumin-galactomannoside)	Chronic alcoholics	Completed	- Decrease of 31 % of serum transaminases and 29 % of serum GGT - Decrease of IL-6 and CRP - Increase of GSH, SOD and GPx	500 mg (250 mg twice daily) for 8 weeks	CTRI/2018/03/012385 (Krishnareddy et al., 2018)
Curcumin capsule	Patients with type 2 diabetes	Unknown status	No study results published	500 mg for 12 weeks	NCT02529969
B-Turmactive® pill of curcuminoids (+ vitamin C)	Healthy subjects with mild and moderate knee pain	Completed	No study results published	519.5 mg once daily for 1 week	NCT03202901
Turmeric-based tablets	Subjects undergoing fitness tests	Completed	No study results published	700 mg once daily for 2 weeks	NCT04765527
Curcumin capsules	Pediatric patients on regular hemodialysis	Phase III Recruiting	No study results published	1 g once daily for 3 months	NCT05627843
Curcumin	Pediatric patients with inflammatory bowel disease	Phase I Completed	- improvement in PUCAI/PCDAI score of disease severity at 9 weeks - adverse effect (increase in gassiness) at 3 weeks.	1 g (500 mg twice daily) for 3 weeks followed by 2 g (1 g twice daily) for 3 weeks, and followed by 4 g (2 g twice daily) for 3 weeks	NCT00889161 (Suskind et al., 2013)
Turmeric (95 % curcumin, 5 % piperine) in carrot+orange juice	Patients with chronic kidney disease	Completed	- Decreased NF-kB mRNA expression and plasma high sensitivity CRP in peripheral blood mononuclear cells - No change in the other evaluated markers (Nrf2, NLRP3 inflammasome, IL-1beta), blood biochemistry, and other parameters	~ 1.1 g daily (2.5 g three times a week) for 3 months	NCT03475017 (Alvarenga et al., 2020)
Curcumin (+ quercetin)	Familial adenomatous polyposis	Completed	- Decreased number and size of rectal polyps	1.44 g (480 mg thrice daily) for 6 months	(Cruz-Correa et al., 2006)

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Table 3 (*continued*)

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Turmeric 95 % curcumin	Cardiovascular risk in patients with coronary artery disease	Withdrawn	No study results published	1.5 g (500 mg thrice daily) for 1 month	NCT04458116
Curcumin capsules	Patients with chronic kidney disease on peritoneal dialysis	Completed	- reduced plasma levels of MDA after 12 weeks - a trend for p-CS plasma level reduction - no changes in protein thiols, mRNA expression of Nrf2, HOX-1, NF-κB, and cytokines plasma levels.	1.5 g (500 mg thrice daily) for 4 or 12 weeks	NCT04413266 (Reis et al., 2024)
Diet with curcumin supplementation	Patients with Hashimoto's disease	Not yet Recruiting	No study results published	1.5 g (500 mg thrice daily) for 3 months	NCT05975866
Curcumin	Diagnosis of diabetes mellitus type 2 and proteinuric kidney disease	Phase II Unknown status	No study results published	1.67 g (557 mg thrice daily) for 6 months	NCT03019848
Curcumin	Pediatric patients with mild to moderate ulcerative colitis	Phase III Withdrawn	No study results published	1-4 g (0.5-2 g twice daily) for 6 months	NCT02277223
Curcumin	Smokers with aberrant crypt foci	Phase II Completed	- No differences in PGE, 5-HETE, COX-1, COX-2, 5-LOX and ki-67, number of aberrant crypt foci - Some adverse effects reported	2 or 4 g once daily up to 30 days	NCT00365209
Curcumin (+ piperine)	Chronic obstructive pulmonary disease	Completed	No study results published	2 g (1 g twice daily) for 1 month, followed by 3 g (1.5 g twice daily) for 1 month, 4 g (2 g twice daily) for 1 month	NCT01514266
Curcumin	Patients with ulcerative colitis	Terminated	No study results published	3 g daily for 12 months	NCT03122613
Curcumin	Patients with familial adenomatous polyposis	Phase II Completed	- Decreased polyamine mean level changes at month 8-baseline - Decreased change in microRNA mean activity level at 8 months compared to baseline - Decreased change in apoptosis index levels at 8 months (cleaved Caspase-3) - No difference in the mean number or size of lower intestinal tract adenomas - Adverse effects: abdominal pain, facial abscess	3 g (1.5 g twice daily) for 12 months	NCT00641147 (Cruz-Correa et al., 2018)
Curcumin combined with plant exosomes tablets	Patients with colon cancer	Recruiting	No study results published	3.6 g daily for 7 days	NCT01294072
Curcumin supplementation (in addition to treatment)	Patients with inflammatory bowel diseases	Unknown status	No study results published	4 g daily for 12 months	NCT03500653
Turmeric tablets Curcumin (+ piperine)	Skin inflammation	Completed	No study results published	6 g (1 g six times daily) for 8 weeks	NCT03066791
Turmeric and Turmeric-containing polyherbal combination tablets	Skin Inflammation	Completed	- Facial redness intensity and distribution down trended after 4 weeks based on clinical grading and photographic image analysis for the polyherbal combination group - The placebo and turmeric groups had no statistically significant changes in image analysis-based facial redness. - No reported adverse events	200 mg or 2 g twice daily or 4 weeks	NCT03065504 (Vaughn et al., 2019)
Curcumin pill	Hemodialysis patients	Completed	No study results published	Once daily for 12 weeks	NCT03144882
Curcuma extract ice cream	Soccer athlete after having strenuous exercise	Completed	No study results published	Once daily for 21 days	NCT04439981
Curcumin	Patients with chronic inflammatory bowel disease	Completed	No study results published	Once daily for 28 days	NCT04879810
Meriva® curcuminoids	Patients with chronic atrophic gastritis and/or gastric intestinal metaplasia	Phase II Recruiting	- No differences in histological gastric score nor gastric levels of IL-1 beta, TNF alpha, IP-10, and DNA damage.	Twice daily for 180 days	NCT02782949

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Table 3 (*continued*)

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Curcumin C3 complex® (+bioperine)	Patients with clonal cytopenia of undetermined significance, low-risk myelodysplastic syndrome, and myeloproliferative neoplasms	Phase II Recruiting	No study results published	Twice daily for 12 months	NCT06063486
Liposomal curcumin in a high-protein oral supplement	Adults with chronic kidney disease undergoing hemodialysis	Recruiting	No study results published	7 mL thrice weekly for 8 weeks equivalent to a total of 24 treatments	NCT06381076
1 % Curcumin oral gel	Chronic periodontitis patients with periodontal pockets	Early Phase I Unknown status	No study results published	1 time application during the periodontal pack application	NCT04355416
Curcumin chip: 1 % curcumin in biodegradable hydroxy propyl methyl cellulose vehicle (Oral implant)	Patients with periodontitis	Phase III Unknown status	No study results published	1 time application after scaling and root planning. The chip will be replaced after two weeks	NCT03790605
Organogel of Curcumin for topical application	Osteoarthritis patients (75), age 50 to 70 years old	Completed	- Decrease of pain score, 72 % - Decrease of stiffness, 62 % - Decrease in physical function difficulty, 46 % - Decrease in the need of anti-inflammatory/analgesic drugs throughout the study - No serious adverse effects	1.5 g of gel (40 % of the curcumin dose estimated to permeate skin), daily for 2 months	IRCT20220531055045N1 (Baharizade et al., 2024)
Neurodegeneration and aging-related conditions					
Curcumin solid lipid particles (Longvida®, 23 %)	Healthy older population free from a history of neurological conditions or psychiatric disorders and any significant current illness	Phase III/IV	- Improved performance on sustained attention, working memory, and mood - Effect on alertness and contentedness - Significantly reduced total and LDL cholesterol - No effect on hematological safety measures	92 mg once daily for 4 weeks	ACTRN12612001027808 (Cox et al., 2015)
Turmeric powder capsules	Alzheimer's disease patients (3) with disturbed memory and orientation	Completed	- Significant improvement of the behavioral symptoms, memory - No adverse reactions detected	100 mg daily for 12 months	(Hishikawa et al., 2012)
Theracurmin®	Patients with amyotrophic lateral sclerosis	Phase II Completed	- No differences in microbiome (oral, stool) - Serious adverse effects reported among other adverse effects	180 mg (90 mg twice daily) for 6-months	NCT04499963
Theracurmin® capsules	Diagnostic for mild cognitive impairment or age-related memory decline without significant cerebrovascular disease with adequate visual and auditory acuity (age interval: 50-90 years; mean above 60 years)	Phase II Completed	- Improved memory and attention - Decreased accumulation of amyloid and tau in brain regions modulating mood and memory - Some adverse effects described -Peak of curcumin (108 nM, at 2 h), superior to those observed with other two formulations	180 mg (90 mg twice daily) for 18 months	NCT01383161 (Small et al., 2018)
Curcumin and Resveratrol Liposomes With G04CB02	Patients with amyotrophic lateral sclerosis	Phase II Completed	No study results published	200 mg (total) daily for 4 months	NCT04654689
Curcumin solid lipid particles (Longvida®, 23 %)	Mild cognitive impairment or Subjective cognitive Impairment	Phase II	No study results published	368 mg (184 mg twice daily) for 12 months	NCT01811381
Curcumin phytosome (Meriva®, 20 %)	Idiopathic Parkinson's Disease	Completed	- Ameliorated motor and non-motor symptoms - Tendency to decrease misfolded phosphorylated α-synuclein deposits in skin nerves - Increased levels of curcuminoids in plasma, and curcumin metabolites in cerebrospinal fluid - No adverse effects	400 mg (200 mg twice daily) for 12 months	(Donadio et al., 2022)

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Table 3 (*continued*)

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Curcumin	Leber hereditary optic neuropathy patients with 11,778 point mutation	Phase III Completed	No study results published	500 mg (250 mg twice daily) for 1 year	NCT00528151
Curcumin solid lipid particles (Longvida®)	Diagnosed with probable Alzheimer's disease	Phase II Completed	No study results published	920 or 1380 mg (460 or 690 mg twice daily) for 60 days	NCT01001637
Curcumin, C3 Complex® capsules	Aging subjects at increased risk for disability (> 65 years old)	Phase II/III Completed	- No significant changes in physical measures, neurological functions or inflammation - No adverse effects reported	1 g once daily for 3 months	NCT03085680
Curcumin in capsules or powder mixed with food (+ Ginkgo leaf extract)	Progressive decline in memory and cognitive function for 6 months	Phase I e II Completed	- Peak plasma levels of curcumin: 250 nM at 1.5 h with food; and 270 nM at 4 h with only water - Higher total curcuminoid levels in the high-dose group - Higher concentration of curcumin after capsules than powder administration - Increased vitamin E level - Increased serum Aβ40 levels - No side effects	1 g or 4 g once daily for 6 months	NCT00164749 (Baum et al., 2007, 2008)
HP-EVOO (dietary Supplement: curcumin, high phenolic extra virgin olive oil)	Adult Neurofibromatosis-1 patients with cutaneous neurofibromas	Phase I Recruiting	No study results published	1, 2, 4 g (500, 1000 and 2000 mg twice daily) for 12 months	NCT05363267
BCM-95® (Bio-curcumax)	Good health, no significant cerebral vascular disease, no significant cognitive impairment	Completed	- No difference in cognitive performance between the groups - Gastrointestinal-related adverse events	1.5 g (500 mg thrice daily) for 12 months	ACTRN12611000437965 (Rainey-Smith et al., 2016)
Galactomannan formulation, capsule form with Resveratrol, Quercetin, and Curcumin	Stage 1 or 2 Alzheimer's disease	Phase II Not yet recruiting	No study results published	2 g (1 g twice daily) for 24 months	NCT06470061
Curcumin C3 Complex®	Mild to moderate Alzheimer's disease	Phase II Completed	- No differences in clinical or biomarker efficacy measures - Low plasma native curcumin and tetrahydrocurcumin levels, and higher of the glucuronidated forms - Curcumin undetectable in cerebrospinal fluid - Gastrointestinal side effects	2 or 4 g daily for 24 weeks	NCT00099710 (Ringman et al., 2012)
Curcumin capsules	Healthy middle-aged smokers (50-70 years old)	Phase I/II Completed	- Significant effect on FMD in women and subjects presenting lower cardiovascular risk - Changes in gene expression are observed when analyzed according to gender - Substantial variability in the efficacy of curcumin exists across individuals	5 g once	NCT01543386 (Barber-Chamoux et al., 2018)
Curcumin powder	Older people (60-85 years old)	Completed	- During exercise, changes in cerebral oxygenation and blood volume were higher - No significant changes in heart rate, systolic blood pressure, and diastolic blood pressure	10 g once	NCT04119752 (Rezende et al., 2022)
Population without specific condition					
Curcumin C3 tablet and Meriva phytosome	Healthy subjects	Phase I Completed	- Maintained detectable curcuminoids at a steady state in plasma and rectal tissues	4 g once daily for 3 months	NCT01330810 (Asher et al., 2017)

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Table 3 (*continued*)

Curcumin form	Population	Study Information	Most relevant results	Curcuminoid Daily Dose	Reference
Liposomal curcumin (Intravenous)	Healthy subjects	Phase I Completed	- Dose-dependent increases in the plasma concentrations of curcumin and its metabolite tetrahydrocurcumin were detected - After the end of drug infusion, curcumin and metabolite plasma concentrations decreased within 6 - 60 min below the limit of quantification - Mean urinary excretion was ~0.1 % of total systemic clearance - Good tolerance to liposomal curcumin but a transient red blood cell echinocyte formation was observed at dosages ≥69 mg	~6, 11, 23, 46, 69, 103 mg (10, 20, 40, 80, 120, 180 mg/m^2 over 120 min)	NCT01403545 (Storka et al., 2015)
Curcumin Intravaginal capsules	Normal population of women	Phase I Completed	- No toxicity - Without systemic absorption or significant local absorption	500-2000 mg once daily for 14 days	NCT01035580

Abbreviations: 5-HETE, 5-hydroxy-eicosatetraenoic acid; COX, cyclooxygenase; CRP, C-reactive protein; FMD, flow-mediated dilation; GGT, gamma-glutamyl transferase; GPx, glutathione peroxidase; GSH, reduced glutathione; GST, glutathione S-transferase; IL, interleukin; IP, inducible protein; Ki-67, proliferation marker; LOX, lipoxygenase; MDA, malondialdehyde; NF-kB, nuclear factor-kappa B; Nrf2, nuclear receptor factor-2; PGE2, prostaglandin E2; PUCAI/PCDAI, Pediatric Ulcerative Colitis Activity Index/Pediatric Crohn's Disease Activity Index; SOD, superoxide dismutase; TNF, tumor necrosis factor.

Cruz-Correa et al., 2006)), and trials with resveratrol are registered for neurodegenerative diseases (Table 3).

In patients with mild cognitive impairment or age-related memory decline, curcuminoids in the format of Theracurmin® capsules resulted in improved memory and attention, and decreased accumulation of amyloid and tau in brain regions modulating mood and memory, but some adverse effects were described (NCT01383161, (Small et al., 2018)). A previous small study revealed improvement in behavioral symptoms of AD patients with disturbed memory and orientation ingesting turmeric powder capsules (Hishikawa et al., 2012). When the Meriva formulation was administered to PD patients, there was a tendency for a decrease in the misfolded α-synuclein deposits in skin nerves together with ameliorated motor and nonmotor symptoms (Donadio et al., 2022). In a healthy older group, Longvida® improved the performance on sustained attention, working memory, and mood, affected alertness and contentedness, and reduced total and LDL cholesterol (ACTRN12612001027808, (Cox et al., 2015)). In healthy middle-aged smokers, 5 g curcuminoids ingested once showed effects on flow-mediated dilation (endothelial function) in women and subjects presenting lower cardiovascular risk, although variability in the efficacy of curcumin was underlined (NCT01543386, (Barber-Chamoux et al., 2018)). Also, in older people, 10 g curcuminoids enabled changes in cerebral oxygenation and blood volume during exercise (NCT04119752, (Rezende et al., 2022)).

Despite no significant changes in selected gut microbiota diversity, a curcumin extract (500 mg, Curcugen) was able to improve digestive complaints, viewed by a decrease in several symptoms, including abdominal pain, reflux, diarrhea, indigestion, and constipation, which was accompanied by a reduction in anxiety levels (ACTRN12619001236189, (Lopresti et al., 2021)).

It should be noted that some trials failed to detect any beneficial effect of curcumin, even in antioxidant or inflammatory markers (*e.g.* NCT00365209, NCT02782949). In aging subjects and AD, some trials have also failed despite using significant doses for weeks or months, apparently due to insufficient bioavailability (Table 3). Most of the studies point to a good tolerance to curcumin, but adverse effects have also been reported that need attention. Fig. 5 depicts an overall view of the generalized outcome of the trials analyzed in this work according to the dose and period of treatment. It is clear that a large distribution of treatment doses and durations are tested, and the outcomes do not depend only on these factors. High doses seem to represent a risk without a noticeable gain in therapeutic efficacies, while lower doses -

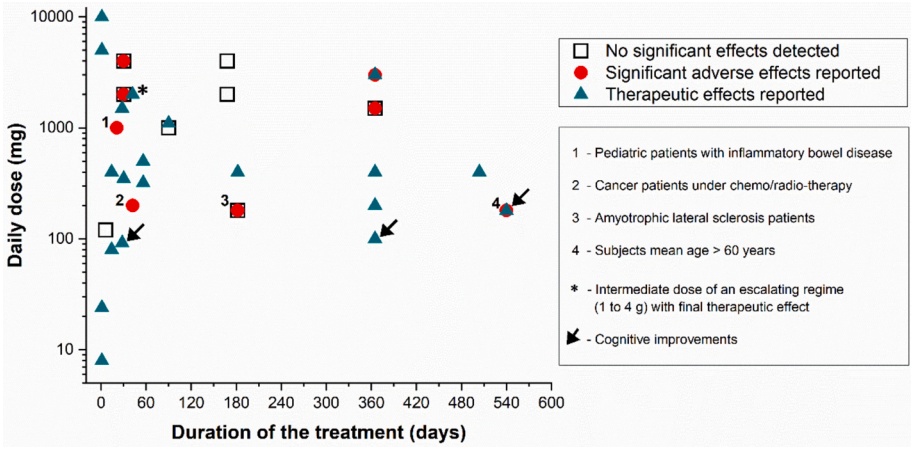

Fig. 5. Overview of the daily dose, duration, and general outcomes of clinical trials of oral curcumin in inflammation, neurodegeneration, and aging-related conditions. The trials reporting adverse effects of doses up to 1 g/day are annotated with numbers 1 to 4. The arrows point to trials describing cognitive improvements. Details provided in the main text and Table 3.

Table 4
Chemical structural properties of curcuminoids relevant for drug-likeness prediction, compared to other important polyphenols and a neuroprotective approved drug (donepezil).

Compound	Molecular weight	Log P (XLOGP)	H-bond donors	H-bond acceptors	Rotatable bonds
Curcumin	368.38	3.20	2	6	8
Demethoxycurcumin	338.35	3.32	2	5	7
Bisdemethoxycurcumin	308.33	3.26	2	4	6
Resveratrol	228.24	3.13	3	3	2
Kaempferol	286.23	2.05	4	6	1
Donepezil	379.49	4.28	0	4	6

up to 1 g daily - showed beneficial effects in cancer (NCT02138955, NCT02017353, 2013-001737-40, (Golombick et al., 2015; Greil et al., 2018; Tuyaerts et al., 2019)), pancreatitis (NCT04989166, (Chegini et al., 2023)), kidney and liver diseases (CTRI/2018/03/012385, (Jiménez-Osorio et al., 2016; Krishnareddy et al., 2018; Musso et al., 2025)), occupational stress-related anxiety and fatigue (Sudheeran et al., 2016) and neuroprotection (ACTRN12612001027808, (Cox et al., 2015; Donadio et al., 2022)). Serious adverse effects were also observed, nevertheless in patients expected to be more debilitated such as cancer patients under therapy (NCT01740323), or in the case of intravenous infusion (NCT01403545). Some formulations are obtained by processing curcuminoids with other components in substantial proportions that can influence the side effects. These results indicate that treatments of older or debilitated subjects should be carefully followed. However, it is noteworthy that low doses (up to 200 mg daily) were enough to promote cognitive improvements in different trials (ACTRN12612001027808, NCT01383161, (Cox et al., 2015; Hishikawa et al., 2012; Small et al., 2018)) highlighted in Fig. 5. Moreover, in trials returning positive outcomes in conditions of neuropathology and with pharmacokinetic data, it is remarkable that quite coherent levels of circulating curcumin were measured (Baum et al., 2008; Donadio et al., 2022; Small et al., 2018), allowing to point an interval of the probable therapeutic concentrations. The plasma levels of curcumin detected in these works were between 100 and 500 nM, while the other two curcuminoids were less concentrated, but the major metabolite tetrahydrocurcumin reached 2 microM. In cerebrospinal fluid (CSF), curcumin was not detected, even with supplementation to PD patients (Donadio et al., 2022), but tetrahydrocurcumin and hexahydrocurcumin were present, strong evidence of the importance of curcumin metabolism for the neuropharmacological effects. Tetrahydrocurcumin was the metabolite at higher concentration, and levels between 1 and 50 nM (in the order of ng/mL) could be recommended for future neuroprotective studies.

Some of the discussed studies reporting improved outcomes lack a placebo group and had a small sample size (NCT02017353, 2013-001737-40, Cruz-Correa et al., 2006; Golombick et al., 2015; Hishikawa et al., 2012; Tuyaerts et al., 2019)). While there are indications on the importance of sample size and its calculation methods, together with the defined statistical parameters (EMEA, 1998), general recommendations can be followed, for example a minimum of 20 to 100 study participants in phase I trials (FDA, 2018). A strong point, several of the previous trials are randomized double-blind placebo-controlled trials (RCT) with dozens of participants (NCT01543386, NCT02683733, NCT02724618, NCT03065504, NCT03475017, NCT04989166, ACTRN12619001236189, CTRI/2018/03/012385, IRCT20220531

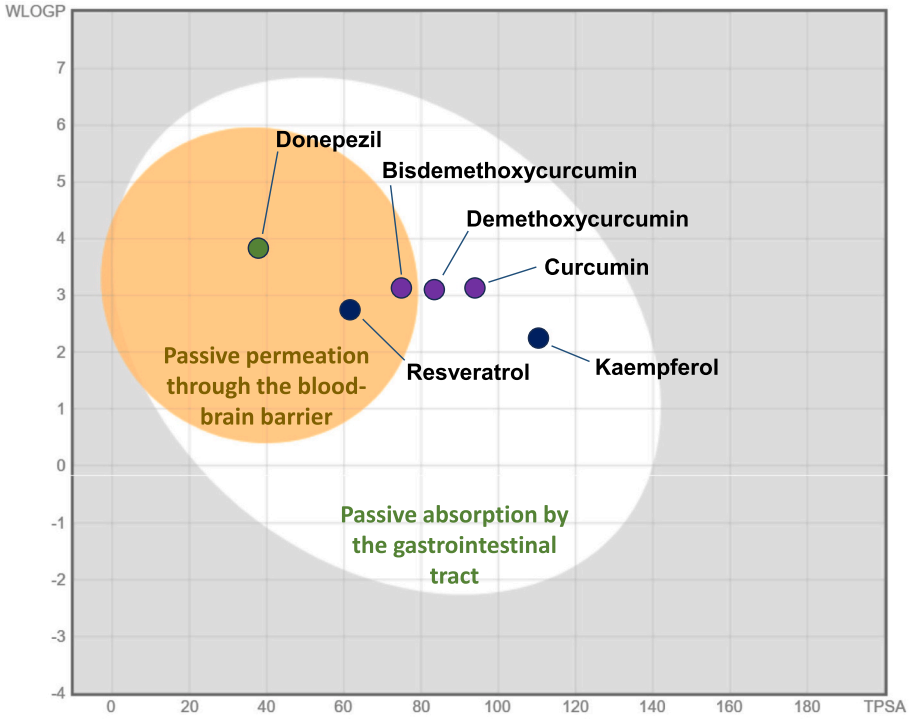

Fig. 6. Human intestinal absorption and brain penetration probability of curcuminoids, other important polyphenols, and a neuroprotective approved drug (donepezil). Image adapted from the basic construction generated at http://www.swissadme.ch/.

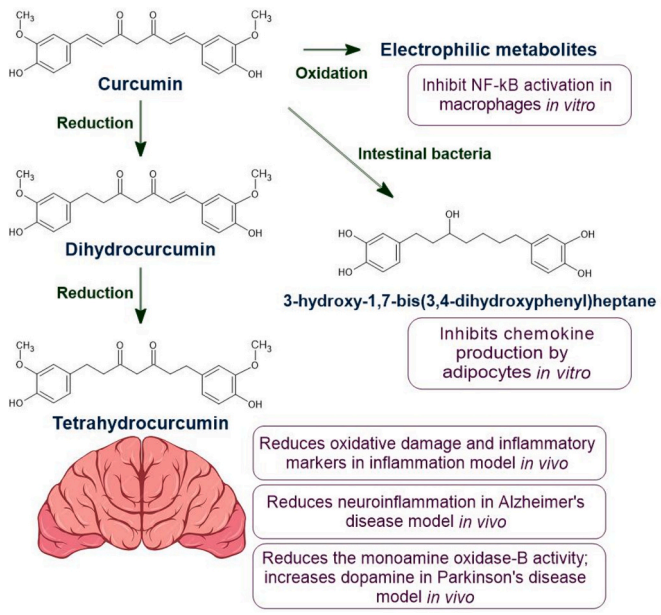

Fig. 7. Biological activities of different curcumin metabolites. Additional details can be found in the main text.

055045N1, (Alvarenga et al., 2020; Baharizade et al., 2024; Banerjee et al., 2021; Barber-Chamoux et al., 2018; Baum et al., 2008; Chegini et al., 2023; Jiménez-Osorio et al., 2016; Krishnareddy et al., 2018; Lopresti et al., 2021; Musso et al., 2025; Saadipoor et al., 2019; Sudheeran et al., 2016; Vaughn et al., 2019)), including some evaluating cognitive performance (NCT00099710, ACTRN12611000437965, (Rainey-Smith et al., 2016; Ringman et al., 2012)) like two key trials of those highlighted in Fig. 5 (ACTRN12612001027808, NCT01383161, (Cox et al., 2015; Small et al., 2018)). Equally important, the inhibition of NF-kB and additional inflammatory endpoints in various pathologies has been established in different other key RCT (NCT03065504, NCT03475017, CTRI/2018/03/012385, IRCT20220531055045N1, (Alvarenga et al., 2020; Baharizade et al., 2024; Krishnareddy et al., 2018; Musso et al., 2025; Vaughn et al., 2019)). Nevertheless, larger and multi-center trials are required for wider and regulatory acceptance.

Future trials should also consider pharmacokinetic parameters – like the maximum blood concentration - as a trial outcome due to the existence of a variety of curcumin formulations and related bioavailability (Funk and Schneider, 2021). In this respect, the trial NCT00099710 (Ringman et al., 2012) is an example of how the collected pharmacokinetic data, informing of the low bioavailability of curcumin (plasma levels <10 ng/mL), provides a hypothesis for the absence of beneficial effects and directs future efforts.

6. Bioavailability and the impact of metabolism

The drug-likeness of curcuminoids can be compared to other natural compounds and synthetic drugs approved for clinical use. Table 4 presents key properties for predicting the drug-likeness of the curcuminoids, along with two other polyphenols from different classes relevant in the context of aging, cancer and neurological protection (Lagoa et al., 2022; López-Sánchez et al., 2024; Rysz et al., 2022; Soo et al., 2020), and also with donepezil. Donepezil is an aceytilcholinesterase inhibitor approved to treat cognitive symptoms of AD, administered by oral or transdermal routes (Dinh et al., 2022). The 6 compounds have a good drug-likeness according to general rules for an orally bioavailable drug candidate (MW $\leq$ 500, cLog $P \leq 5$, H-bond donors $\leq$5, H-bond acceptors $\leq$10, and rotatable bonds $\leq$10) (Lipinski et al., 2001; Veber et al., 2002).

Curcuminoids are predicted to be passively absorbed by the gastrointestinal tract, as polyphenols in general (Fig. 6), providing support to these compounds as oral drug candidates. However, the likelihood that they passively permeate through the blood-brain barrier (BBB), to reach the CNS cells, is low. On the contrary, and consistent with its established neuroprotective action, donepezil is predicted as a brain penetrant (Fig. 6). Nevertheless, the potential efflux from the CNS should not be disregarded, namely of donepezil by P-glycoprotein, as well as the brain penetration by curcumin metabolites or carried by designed delivery systems (section 9).

In agreement with the prediction models, studies with radio-labeled curcumin showed that it is absorbed in the intestine, at least partially (Ravindranath and Chandrasekhara, 1981). After dosage, the excretion of the label was detected mostly in the feces and lasted for a few days. Other authors reported the urinary excretion of curcumin was undetectable (Cheng et al., 2001). Stimulating, the use of high doses enabled the retention of the radio-label in tissues for several days (Ravindranath and Chandrasekhara, 1981), although it was likely from metabolites generated by the different transformations curcumin undergoes in the body (Metzler et al., 2013).

The concentrations of curcumin in blood and tissues after oral intake are typically low. In addition to the chemical instability, the extensive metabolism in the liver and elimination through the gall bladder combine to a low systemic bioavailability of curcumin (Cas and Ghidoni, 2019; Metzler et al., 2013; Shoba et al., 1998). The pharmacokinetic profile of curcumin also seems to discourage therapeutic applications. Studied in patients and healthy volunteers, curcumin peak concentrations in blood were measured 1-2 h after the oral intake and then declined for 12 h (Cheng et al., 2001; Shoba et al., 1998). Concentrations in the order of μM were achieved with high dose of 8 g/day (Cheng et al., 2001), but sub-micromolar levels are commonly reported in trials of curcumin and turmeric (Asher et al., 2017; Cas and Ghidoni, 2019; Shoba et al., 1998; Small et al., 2018), including in AD and PD patients (Baum et al., 2008; Donadio et al., 2022; Ringman et al., 2012). The curcumin maximum concentrations (and time) can change with the formulation or food (Asher et al., 2017; Baum et al., 2008; Small et al., 2018), but very significant, the metabolite tetrahydrocurcumin is usually at higher concentrations (Asher et al., 2017; Baum et al., 2008; Donadio et al., 2022; Ringman et al., 2012).

Like other polyphenols, curcumin is metabolized by the gut microbiota, by enterocytes in the intestine, and by hepatocytes in the liver (Cas and Ghidoni, 2019). Bacteria in the intestine reduce the double bonds (Fig. 7) and demethylate curcumin (Cas and Ghidoni, 2019; Hassaninasab et al., 2011; Niwa et al., 2019). A NADPH-dependent reductase (named CurA) was described in *Escherichia coli* to reduce curcumin as depicted in Fig. 7, first to dihydrocurcumin and, then, to tetrahydrocurcumin (Hassaninasab et al., 2011). Reductive metabolism to different hydrocurcumin species continues in enterocytes and in the liver, together with conjugation to glucuronate and sulfate (Cas and Ghidoni, 2019). The β-diketone group in curcumin is a substrate of aldo-keto reductases in the liver and may be a reason for the fast metabolization of the compound after absorption (Rosemond et al., 2004). This suggests that curcumin derivatives modified at the hemiacetal moiety may present better pharmacokinetics than the parent compound.

Proving the influence of the conjugative metabolism, glucuronides and sulfates of curcumin are frequently found in the blood after oral administration, typically at levels superior to the parent compound (Cas and Ghidoni, 2019; Ringman et al., 2012). Curcuminoids and conjugates have also been detected in the human liver and intestinal tissues, as well as in mice's brain (Asher et al., 2017; Cas and Ghidoni, 2019; Lagoa et al., 2022). Tetrahydrocurcumin was found in the brain and plasma of mice fed curcumin (Begum et al., 2008). In PD patients taking curcumin for 12 months, the 3 major curcuminoids increased in plasma to detectable levels (up to 50 ng/mL), as well as the metabolites tetrahydrocurcumin and hexahydrocurcumin (up to 800 ng/mL), but only these

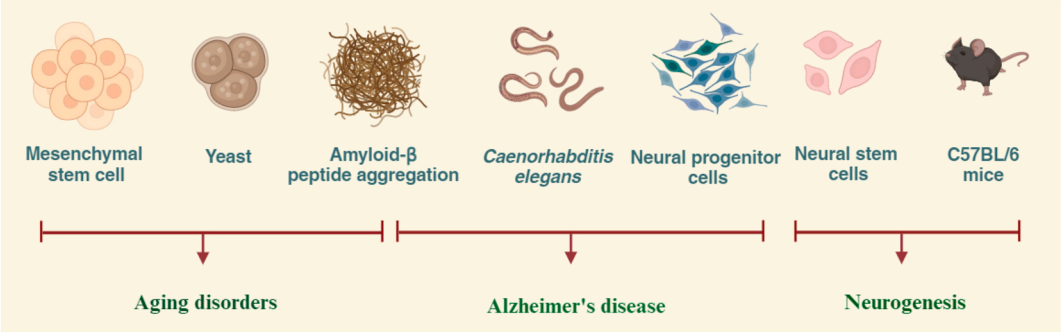

Fig. 8. Different bioassays and models have been used to study how curcumin affects neurodegeneration and aging.

metabolites became detectable in CSF (Donadio et al., 2022). In AD patients, curcumin was also undetectable in CSF, and glucuronidated curcumin and tetrahydrocurcumin dominated in the plasma (Ringman et al., 2012).

However, the plasma levels of hydrocurcumin metabolites also decrease steadily after the peak concentrations. Studying two formulations, curcumin peaked at 60-70 ng/mL, demethoxycurcumin and bis-demethoxycurcumin 20-70 ng/mL, while tetrahydrocurcumin and hexahydrocurcumin reached maximums 80-250 ng/mL and at later (> 1.5 h) times, but then all forms of curcumin declined at similar rates (Asher et al., 2017). Nevertheless, the concentrations of tetrahydrocurcumin at both 24 and 48 h were higher.

Importantly, some curcumin metabolites present antioxidant and pharmacological activities *per se* (Begum et al., 2008; Cas and Ghidoni, 2019; Edwards et al., 2017; Hassaninasab et al., 2011; Niwa et al., 2019). Facing the low bioavailability of curcumin, these metabolites are increasingly regarded as key mediators of the beneficial actions of curcumin and turmeric (Cas and Ghidoni, 2019; Metzler et al., 2013; Zhu et al., 2023b). In an *in vivo* PD model, tetrahydrocurcumin administration showed neuroprotective effects (Fig. 7) like curcumin (Rajeswari and Sabesan, 2008). Tested in two mice models, tetrahydrocurcumin at low μM concentrations showed very relevant anti-inflammatory actions and potential to attenuate amyloid-related pathologies (Begum et al., 2008). In LPS-injected mice, the metabolite alleviated the activation of inducible NOS and the increase of oxidative and nitrosative stress markers at the animals' brains. Also in aged Tg2576 APPsw mice, tetrahydrocurcumin and curcumin reduced the production of the proinflammatory interleukin (IL)-1beta, the measured levels of soluble Aβ peptides and of phospho-c-Jun N-terminal kinase (JNK). However, the metabolite showed no effect on Aβ aggregation and only curcumin alleviated the plaques or insoluble Aβ burden (Begum et al., 2008).

Another microbial metabolite, 3-hydroxy-1,7-bis(3,4-dihydroxyphenyl)heptane (Fig. 7), was reported to have a lower cytotoxicity and to inhibit chemokine production by murine adipocytes *in vitro* as curcumin (Niwa et al., 2019). In a different track, reactive metabolites produced by curcumin oxidation were demonstrated to have anti-inflammatory activity by inhibiting NF-kB in LPS-stimulated macrophages with a luciferase reporter (Edwards et al., 2017). The potency of the different curcumin analogs to inhibit NF-kB activity correlated with their rate of autoxidation.

Despite that the bioactivities of the curcumin metabolites are still being uncovered, it is clear that the degradation/oxidation and metabolization routes of the polyphenol have a strong impact on its bioavailability and play an important role in the pharmacological actions of curcumin. Tetrahydrocurcumin arises as the metabolite with more important pharmacological activity for anti-inflammatory and neuroprotective applications.

7. Bioassays and models for neurobiological disease and aging

The interest in the neuroprotective effects of curcuminoids and potential implications for age-related disorders prompted the use of less conventional bioassays and models for challenging specific mechanistic hypotheses. Fig. 8 illustrates the models considered from the literature and Table 5 summarizes the results reported.

7.1. *In vitro models*

Various bioassays and models have been used to understand curcumin's effect on neurodegenerative and aging disorders. In a study with neural progenitor cells, curcumin inhibited histone acetyltransferase, and suppressed the differentiation in astrocytes while promoting neurogenesis, in correlation with the observed decrease of histone H3 and H4 acetylation (Kang et al., 2006), in divergence to the observed in leukemic cells (Pal et al., 2023). Another work by Kaltschmidt et al. showed that curcumin was able to inhibit the NF-κB pathway in IL1-treated mesenchymal stem cells and showed increased production of type-II collagen and cartilage-specific proteoglycans (Buhrmann et al., 2010; Kaltschmidt et al., 2021). Pirmoradi et al. showed that curcumin significantly increases cell proliferation, decreases the senescent cell number, and enhances the *tert* gene expression in mesenchymal stem cells (Pirmoradi et al., 2018).

Stępień and co-workers have studied the effects of curcumin supplementation in wild-type and SOD-depleted yeast strain BY4741 chronological aging model. Curcumin delayed aging of the wild-type strain, but there was a decrease in the survival rate of the cells lacking the antioxidative protection. And, the treatment with curcumin showed a significant rise in the ROS levels of all yeast mutant strains (Stępień et al., 2020). In a study by Yang and colleagues, curcumin was encapsulated in silk fibroin films and NPs to investigate the antiaging effects. The results showed that when curcumin was presented to stem cells, it significantly inhibited cell senescence by downregulating p53 and p16 genes and thus decreasing the SA-β-Gal staining (Yang et al., 2017).

Chen et al. (2021) explored the effects of curcumin on neural stem cells (NSCs). The results showed that curcumin promoted NSCs proliferation, migration, and the formation of neurospheres, and it also upregulated the expression of SDF-1 and promoted the formation of SDF-1/CXCR4 complex in NSCs (Chen et al., 2021). Another study carried out by Wang and their co-workers examined curcumin effects in NSCs on autophagy, differentiation, cell cycle and apoptosis. The results showed that it inhibited the differentiation of GFAP+ astrocytes or DCX+ immature neurons and decreased the expression of Atg7 and p62 proteins, respectively (Wang et al., 2018).

In a different approach, Thew et al. (2024) recently employed a dot-bot assay to probe Aβ aggregation and the effect of potential natural drugs, with curcumin revealing an inhibitory effect at sub-micromolar concentrations. A work with rat primary hippocampal cultures and human neurons (Mishra et al., 2011) showed that tetrahydrocurcumin inhibited Aβ cytotoxicity (Table 5).

Table 5
Bioassays and models revealing curcuminoids' roles in neurobiology and aging disorders.

Assay or Model	Dose/Frequency	Effect of curcuminoid treatment	Ref.
***In vitro*models**			
Dot-blot of amyloid-β(42) oligomer	Curcumin (0.1–1.0 μM)	Inhibition of amyloid-β aggregation	(Thew et al., 2024)
Yeast strains BY4741 chronological aging model	Curcumin (200 and 300 μM)	Decreased the survival rate of the Δsod strain and increased ROS levels, while it delayed aging of wild-type strain	(Stępień et al., 2020)
Neural progenitor cells	Curcumin (1 μg/mL)	Inhibited histone acetyltransferase, decreased H3 and H4 acetylation, and promoted neurogenesis	(Kang et al., 2006)
Mesenchymal stem cells	Curcumin (0.5 - 5 μM)	Inhibited NF-κB and increased production of type II collagen and cartilage-specific proteoglycans	(Buhrmann et al., 2010; Kaltschmidt et al., 2021)
Human mesenchymal stem cells	Curcumin (0.125 and 0.05 mg/mL)	Inhibited cell senescence by downregulating p53 and p16 genes	(Yang et al., 2017)
Mesenchymal stem cells	Curcumin (1 and 5 μM)	Increased cell proliferation, decreased the number of senescent cells, and enhanced the expression of the TERT gene	(Pirmoradi et al., 2018)
Neural stem cells	Curcumin (1 μM)	Up-regulated the expression of SDF-1 and promoted the formation of SDF-1/CXCR4 complex	(Chen et al., 2021)
Neural stem cells	Curcumin (10 μM)	Inhibited the differentiation of GFAP+ astrocytes or DCX+ immature neurons and decreased the expression of Atg7 and p62	(Wang et al., 2018)
Neuronal cells	Tetrahydrocurcumin (5 μM)	Reduced amyloid-β cytotoxicity, the increase in ROS, the drop in mitochondrial membrane potential, and caspase activation	(Mishra et al., 2011)
***In vivo*models**			
C. elegans model (wild-type and R406W)	Curcumin (100 mg/plate; 30 μM)	Reduced both Unc and the neuritic abnormalities, in both wild-type and R406W tau-expressing worms	(Miyasaka et al., 2016)
Transgenic *C. elegans* model	Curcumin (0.5 and 1.0 mg/g)	Caused cell cycle arrest, enlarged lysosome, and breaks the DNA double-strand, and activation of DNA damage	(Bahrami et al., 2021)
C57BL/6 transgenic APP/PS1 mice model	Curcumin (150 mg/kg)	Increased the new NSCs (BrdU+/Nestin+) and neurons (NeuN/kI67+) in the hippocampus, and decreased the number of apoptotic neurons (TUNEL+ and Caspase-3/NeuN+), resulting in the improvement of Alzheimer's disease	(Li et al., 2019a)
Neural progenitor cells Male C57BL/6 mice (adult)	Curcumin	Increased proliferation of primary embryonic neural progenitor cells *in vitro* (0.1 and 0.5 μM) *via* activation of extracellular signal-regulated kinases and p38 kinases Low intraperitoneal dose (<0.2 mg/kg) increased the number of newly generated cells in the dentate gyrus of the hippocampus - neuronal (NeuN) type and less glial (GFAP) new cells.	(Kim et al., 2008)
Male C57BL/6 mice	Tetrahydrocurcumin	Increase or no effect in lifespan, depending on factors like the starting age of treatment	(Kitani et al., 2007; Soo et al., 2020)

7.2. *In vivo models*

Curcumin has been shown to increase the lifespan of small organisms like worms and fruit flies, while data for tetrahydrocurcumin in mice is not so clear (Kitani et al., 2007; Soo et al., 2020). The nematode *Caenorhabditis elegans* is invaluable for the *in vivo* investigation of biomolecular mechanisms involved in different diseases and aging. A study by Miyasaka et al. (2016) investigated how curcumin could improve tau-induced neuronal dysfunction in a transgenic *C. elegans* model (wild-type and R406W). The results showed that curcumin reduced Unc and neuritic abnormalities in wild-type and R406W tau-expressing worms (Miyasaka et al., 2016). More recently, Bahrami et al. (2021) found that curcumin causes cell cycle arrest, enlargement of the lysosome, and breaks the DNA double-strand, senescence-associated heterochromatin foci, and DNA damage response activation in *C. elegans* (Bahrami et al., 2021). These observations reinforce the potential of curcumin to alleviate pathological processes associated with tau in AD and aging.

A study carried out by Li et al. investigated the curcumin role in the proliferation of NSCs and hippocampal neurogenesis using a C57BL/6 transgenic APP/PS1 mice model. Curcumin has been shown to significantly improve the animal's memory and learning functions, in direct association with increased new NSCs (BrdU+/Nestin+) and neurons (NeuN/kI67+) in the hippocampal region and reduced apoptotic neurons number (TUNEL+ and Caspase-3/NeuN+). Thus, curcumin was found to activate the proliferation of NSCs, enhance neurogenesis, and improve cognitive ability in AD (Li et al., 2019a).

Another exciting work explored the curcumin effects in neural progenitor cells *in vitro* and *in vivo* (Kim et al., 2008). Neural progenitor cells differentiate into neurons and glial cells during embryonic development and the adult brain also maintains some populations of these cells. In cultured neural progenitor cells, curcumin at sub-micromolar levels activated ERK and p38 kinases, pathways well-recognized in stress response but also involved in neuronal plasticity. The IP administration to adult C57BL/6 mice increased the newly generated neural cells in the hippocampus, but only with a low dose of curcumin (<0.2 mg/kg). Higher dose showed no toxicity but failed to promote neurogenesis in the hippocampus (Kim et al., 2008).

Overall, these data from various *in vitro* and *in vivo* models (Table 5) suggest that, in addition to anti-inflammatory action, the curcumin's (neuro-)pharmacological effects can result from other critical cellular and molecular mechanisms, like the stimulation of hippocampal neuroplasticity.

8. System pharmacology to reveal key targets and biomarkers

Systems pharmacology has great potential for understanding the action and identifying key therapeutic targets of natural compounds, like curcuminoids, characterized by a multi-target pharmacological

activity (Silva et al., 2021). The advances in bioinformatic and experimental tools have expanded the capacities of systems pharmacology through network analyses of "omics" data at multiple scales of biological organization (Zhao and Iyengar, 2012).

In the case of curcumin and polyphenols, microRNA (miRNA) and messenger RNA (mRNA) transcriptomics are the levels accumulating more data enabling system or network pharmacology applications (Devi et al., 2017; Kim et al., 2019; Lagoa et al., 2022; Milenkovic et al., 2013). In a previous work, curcumin was found to share a set of four target miRNAs with other polyphenols (tea catechins, quercetin and resveratrol), and the corresponding protein targets were associated with different signaling pathways regulating pluripotency of stem cells, carcinogenesis processes, inflammation and immunity (Lagoa et al., 2022).

In the present work, miRNAs associated with neurodegenerative diseases and regulated by curcuminoids were identified, and the corresponding protein targets were analyzed for further insight into the mechanism of action of curcumin. The miRNAs affected by curcuminoids were listed from different studies *in vitro* and *in vivo* (Devi et al., 2017; Gao et al., 2019; Milenkovic et al., 2013), but only those reported in two or more studies were considered, a total of 106 miRNAs. In parallel, the miRNAs associated with neurodegenerative diseases were collected at miRTarBase database (Huang et al., 2022), a total of 67. Five miRNAs were common to both groups: let-7b, miR-21, miR-22, miR-26a, and miR-146a. Afterwards, the protein targets of these miRNAs were searched at miRDB (Chen and Wang, 2020) and those with a target prediction score minimum of 90 were analyzed in STRING (Szklarczyk et al., 2023). The functional analysis of the group of proteins revealed 3 pathways from Encyclopedia of Genes and Genomes (KEEG) more enriched: insulin resistance, long-term potentiation (LTP) and autophagy. Fig. 9 shows the functional network of the proteins from these pathways, that includes different components of protein kinases and NF-kB complex. The PI3K family and protein kinase C (PRKC) are the protein kinases more represented. Compared to NF-kB signaling and inflammation, the curcumin regulation of PRKC and of LTP are effects much less investigated. Abnormalities in the insulin signaling system are associated with AD, and curcumin was shown to restore IGF-1 and brain insulin receptor levels in streptozotocin rat models (Agrawal et al., 2010; Isik et al., 2009), and to be able to modulate the PI3K pathway (Lagoa et al., 2022; Lou et al., 2024; Moosavi et al., 2024; Wang et al., 2014). The above group of miRNAs and the related functional pathways are potential targets or biomarkers of curcumin action deserving further studies preventing neurodegeneration pathologies.

9. Modern approaches for efficient delivery of curcumin

Numerous tools and methods have been implemented to develop formulations and delivery systems for optimizing the therapeutic

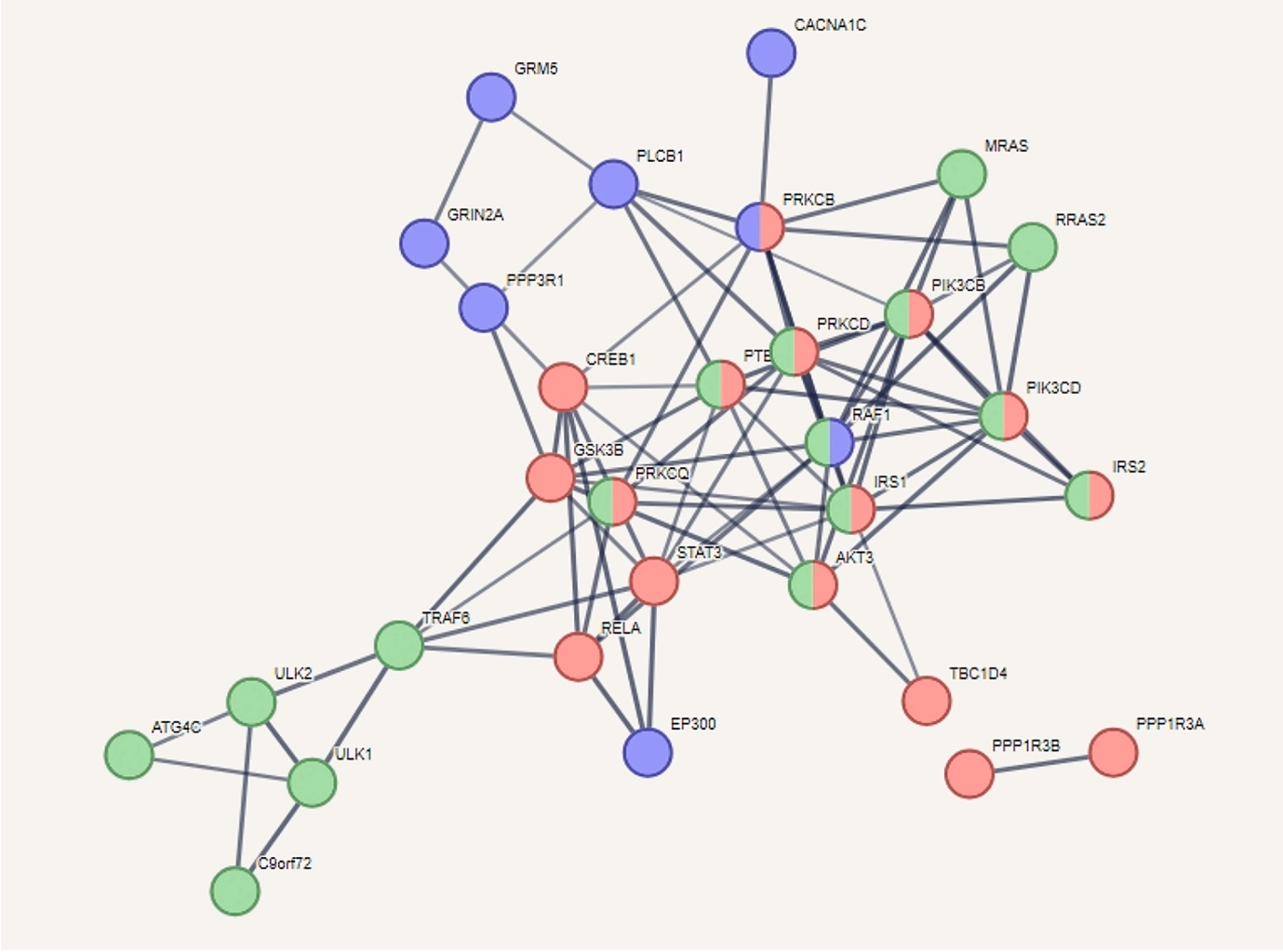

Fig. 9. Network of protein targets of the microRNAs associated with neurodegenerative diseases and regulated by curcuminoids. Only the candidate protein targets belonging to the KEEG pathways insulin resistance (in red), long-term potentiation (in blue) and autophagy (in green) are represented. More information is described in the main text. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potential of curcumin. Two general objectives are pursued: increase the systemic bioavailability (blood concentration and half-time), and deliver curcumin to the desired site of action. Having in mind some inflammatory conditions and, especially, novel approaches for counteracting chronic neurodegenerative and aging-related disorders, interesting systems being fabricated to deliver curcumin through the skin and others to release it into the brain are discussed in following sections.

9.1. Strategies to improve curcumin oral bioavailability

Bioavailability is significantly influenced by various factors, including the physicochemical properties of the medication, interactions with other substances, absorption, hepatic metabolism, excretion, and most importantly, the route of drug administration (Stielow et al., 2023). Oral administration is very convenient, but the bioavailability of drugs taken orally can be ruined by metabolism in the gastrointestinal system (Helen Chan and Stewart, 1996; Prausnitz and Langer, 2008). The IV route offers the highest drug bioavailability, avoiding the extreme conditions of the gastrointestinal system and the first-pass metabolism, but with significantly higher risks (Gibaldi et al., 1971; Lee and Chiou, 1983; Stielow et al., 2023).

As expectable from the bioavailability limitations discussed in section 6, a variety of strategies have been implemented to achieve high and sustained levels of curcumin in the blood after oral intake. Table 6 lists the main approaches and gives indications of their success in increasing curcumin's bioavailability. A simple and classic strategy is to use the bioavailability enhancer piperine (Shoba et al., 1998). Although transient, high concentrations of curcumin are reached with piperine co-administration (Table 6). Combinations of curcumin with piperine showed therapeutic effects in rodents (Banji et al., 2013a, 2013b; Kundu et al., 2016), and are used in formulations trialed in humans (Table 3). One prodrug of curcumin obtained by succinylation has been tested orally in rats but yielded no bioavailability increase (Table 6). Effective delivery of curcumin in micro/nano-sized vehicles is affording significant bioavailability and pharmacokinetics improvements. In a direct comparison in rats, NPs of PLGA yielded better results than piperine co-administration (Shaikh et al., 2009). Plain or coated with polyethylene glycol (PEG), oral PLGA NPs maintained therapeutically relevant concentrations of curcumin in animals' plasma for several hours (Table 6). Curcumin-loaded PLGA NPs have also been tested by IV administration (Tsai et al., 2011), as well as curcumin liposomes (Table 3). Solid lipid particles and phytosomes were reported to extend the absorption of curcumin, delaying peak concentrations (Cmax) to >2 h after intake (Table 6). An extended pharmacokinetic profile with high concentrations for hours was also observed with curcumin dispersed as NPs by high-pressure homogenization. Nevertheless, the greatest bioavailability increases reported are with micelles (Table 6), though some results of curcumin concentrations should be approached with caution, as it may be an amalgamation of native and conjugated forms of curcumin (Jamwal, 2018). The success of these formulations is attributed to different factors that probably contribute cumulatively, namely the ability to stabilize curcumin, promote intestinal absorption, and delay the metabolization and rapid elimination from the body (Cas and Ghidoni, 2019; Lagoa et al., 2020).

Some of these formulations increasing the curcumin's bioavailability and circulation time in the body are commercially available as dietary supplements - identified in Table 6 – and were used in clinical trials returning positive results listed in Table 3. In different cases, they benefit from relatively simple manufacturing processes and increasing use of non-synthetic components (Meriva). The progress of curcumin approval in therapy will be facilitated with the development of increasingly reliable nano-sized delivery systems, along with optimization of formulations and manufacturing processes, which are key for clinical translatability (Zhang et al., 2025). Most of the approved oral drug nanomedicines are nanocrystals, which can be industrially produced by methods like milling and high-pressure homogenization, but also lipid and polymer NPs can be obtained by some scalable and cost-effective precipitation-based techniques (Chow et al., 2015; Zhang et al., 2025).

9.2. Dermal delivery of curcumin

Applying drugs through the skin is an alternative method for both local and whole-body treatments with varied drugs, including phytochemicals (Benson and Watkinson, 2011; Lagoa et al., 2020; Prausnitz

Table 6
Summary of the strategies to improve the oral bioavailability of curcumin. Pharmacokinetic data from human studies, except when indicated.

Strategy	Published results
Piperine co-administration	Increased the blood concentration and bioavailability of curcumin in rats and humans. In humans, the bioavailability increased by 20-fold (with 20 mg/kg piperine); piperine caused a fast and great increase in the serum concentration of curcumin in the first hour after intake (Cmax = 0.18 mg/L, Tmax = 0.69 h), but that rapidly declined to zero by 3 h (Shoba et al., 1998).
Prodrug	Curcumin diethyl disuccinate given orally (40 mg/kg) did not improve the bioavailability of curcumin, in rats (Bangphumi et al., 2016).
Polymer NP encapsulation	PLGA NPs (264 nm) exhibited good stability under freeze-drying and refrigerated storage. In rats, it enabled higher plasma concentrations (Cmax = 0.26 mg/L, Tmax = 2 h) and maintained >0.05 mg/L for more than 24 h. It enhanced the bioavailability more than 25 times compared to simple curcumin suspension, and more than 9 times relative to curcumin plus piperine (10 mg/kg) suspension (Shaikh et al., 2009). PEG-coated PLGA NPs (152 nm) extended the half-life of curcumin in rat plasma to 6 h, more than plain NPs (162 nm, 4 h). The Pegylated and plain particles increased the bioavailability about 16 and 55 times, respectively, compared to an aqueous suspension of curcumin (Khalil et al., 2013).
Solid lipid particles	Solid lipid NPs increased >30 times the plasma bioavailability in rats (Kakkar et al., 2013). Longvida® formulation increased the bioavailability of curcumin approximately 100 times, affording Cmax = 0.022 mg/L at Tmax = 2.4 h (Jamwal, 2018).
Colloidal NP dispersion	Submicron crystal dispersion of curcumin (Theracurmin®) having a 27-fold higher bioavailability than standard curcumin powder increased Cmax to 0.04 mg/L (Tmax 2 h), and maintained >0.01 mg/L for at least 6 h (Small et al., 2018).
Micelle encapsulation	Micellization with Tween-80 polysorbate enabled a bioavailability 185 folds higher than unformulated curcumin, Cmax >1 mg/L (native plus conjugated curcumin) at Tmax = 1.1 h (Jamwal, 2018). The nanomicelle (10 nm) formulation SinaCurcumin® improved the bioavailability of curcumin 59 times, in mice, increasing the Cmax more than 10-fold and extending the half-life from 0.48 to 1.44 h (Saadipoor et al., 2019).
Phytosomes/phospholipid complexes	Phosphatidylcholine complex Meriva® enhanced the bioavailability by about 48 times (Jamwal, 2018). It increased the levels of the 3 major curcuminoids 2.9- to 8.8-fold compared to a standard extract (dose-adjusted); the levels of curcumin and hydrocurcumin metabolites were maintained above 0.01 mg/L, and demethoxycurcumin and bisdemethoxycurcumin above 0.001 mg/L, for at least 24 h (Asher et al., 2017). Prolonged treatment resulted in plasma concentrations of the 3 major curcuminoids about 0.05 mg/L, while the metabolites tetrahydrocurcumin+hexahydrocurcumin were > 1 mg/L; these metabolites in CSF were < 0.01 mg/L (Donadio et al., 2022).

Abbreviations: Cmax, peak concentration; NP, nanoparticle; PEG, polyethylene glycol; PLGA, polylactide-*co*-glycolic acid; Tmax, time to reach the peak concentration after intake.

Table 7
Recent publications on the dermal delivery of curcuminoid compounds studied *in vivo*.

Biological Model	Formulation	Main results	Reference
Liposome-derived systems			
Balb/c mouse model of psoriasis (with *ex vivo* rat skin and HaCat cells *in vitro*)	TD Peptide-modified curcumin-loaded liposome (CRC-TD-Lip)	The CRC-TD-Lip formulation improved intracellular uptake, the inhibitory effects on HaCaT cells, and the skin permeation compared to curcumin-loaded liposomes (CRC-Lip). CRC-TD-Lip had higher encapsulation efficiency, stability, and released over 80 % curcumin in 96 h. The TD peptide temporarily opened the skin barrier, increasing curcumin's skin permeation quantity by 60 % in 24 h. *In vivo*, CRC-TD-Lip enhanced curcumin delivery and antipsoriasis efficiency. Curcumin internalization (green fluorescence) by cells from CRC-TD-Lip was 1.6 times higher than from CRC-Lip after 2 h.	(Yu et al., 2021)
Balb/c mouse model of psoriasis (and *ex vivo* porcine ear skin)	Curcumin-loaded invasomal gel composed of Carbopol934	The pH of the optimized gel was 6.20. Invasomal gel formulation improved entrapment efficiency, drug release, and skin permeation compared to a plain curcumin gel. Invasomal gel afforded a permeation flux 3 times greater than the plain gel. Psoriatic symptoms in mice treated with the invasomal curcumin gel subsided by day 10, while plain curcumin gel failed to fully cure them after 10 days (PASI score test and skin histology).	(Kumar and Sahoo, 2023)
Kunming mouse and C57BL/6 mouse models of melanoma (and B16F10 cells *in vitro*)	Curcumin-loaded liposomes with TD-1 peptide loaded in a gel	The liposome-gel formulation displayed higher cytotoxicity towards B16 cells, compared to curcumin in solution and curcumin liposomes. Topical application of the gel suppressed the growth of the melanoma and induced cell apoptosis in tumor tissues (histopathological examination).	(Zhu et al., 2023a)
Albino rat model of wound healing	Curcumin-loaded bilosomes (composed of cholesterol/Span 60 and sodium deoxycholate) loaded into alginate dialdehyde/chitosan hydrogel (cross-linked with calcium chloride)	The optimal formulation achieved the highest drug release over 3 days (≈96 %). Loaded hydrogel showed sustained drug release for five days (≈100 %). Curcumin-loaded bilosomal hydrogel showed superior wound healing properties, with complete wound closure after 3 weeks (histopathology, compared to the curcumin dispersion and plain hydrogel).	(Sideek et al., 2024)
Emulsion and micelle-derived systems			
Balb/c mouse model of psoriasis (with *ex vivo* mouse skin and A-431 cells *in vitro*)	Nanoemulsion gel composed of Oleic acid+Tween20 + PEG200 and Carbopol940, with curcumin, resveratrol, and thymoquinone	The pH of the optimized gel was 6.45. Higher growth inhibition of psoriatic epidermal keratinocytes (A-431 cells) and enhanced permeability through mouse skin in Franz diffusion cells compared to the free drugs in solution. Good anti-angiogenic activity (HET-CAM test) and anti-psoriatic activity comparable to a commercial formulation. No skin irritation potential was detected.	(Khatoon et al., 2021)
Wistar rat with carrageenan-induced hind paw edema (and *ex vivo* rat skin)	Curcumin dissolved in myrrh oil loaded into a nanoemulgel composed of Tween 80, NaCMC, PG, ethanol and water	The pH of the nanoemulgel was 6.2 and its viscosity 78,300 cP at 25 °C. The *ex vivo* skin permeation study demonstrated that the nanoemulgel formulation achieved the highest steady-state transdermal flux and enhancement ratio compared to curcumin loaded into a gel. The loaded nanoemulgel had a significant anti-inflammatory effect *in vivo*.	(Soliman et al., 2021)
Kunming mouse ear edema induced with croton oil (and *ex vivo* mouse skin)	Curcumin-enveloped MPEG-PVL-PCL micelles embedded into Carbopol940 hydrogel (CUR-H)	The hydrogel showed acceptable skin deposition, high antioxidant activity, and sustained curcumin release. The *ex vivo* permeation assay showed that curcumin-loaded micelles achieved significantly higher skin permeation than the CUR-H formulation at all four time-points over the 12-h experiment. Antioxidant activity surpassed that of other commercial formulation. *In vivo*, CUR-H accelerated collagen synthesis, fibroblast proliferation, and wound closure (histopathological examination).	(Song et al., 2022)

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Table 7 (*continued*)

Biological Model	Formulation	Main results	Reference
Sprague-Dawley rat model of acne (and *ex vivo* rat skin)	Curcumin-fusidic acid–loaded mixed micelles loaded into a nanogel	The pH of the nanogel formulation was 5.7 - 6.2, and its viscosity>13,000 cP. The micelles provided a 2-fold increase in skin permeation of both drugs, compared to the plain nanogel. It reduced inflammation by 70 % compared to the negative control. Biphasic release over 48 h and good colloidal stability. *In vivo*, the gel loaded with micelles decreased skin inflammation, epidermal hypertrophy, and congestion.	(Abdel-monem et al., 2023)
Mouse (and rat skin *ex vivo*)	Curcumin-loaded microemulsion loaded into keratin–chitosan gel	The pH of the formulation was 6.15. The gel showed slow and controlled release of curcumin (85 %, in 48 h), and significantly higher permeation through *ex vivo* skin compared to the drug in solution. The gel could effectively deliver curcumin to the deeper skin through the pathways of the stratum corneum and hair follicles. No erythema or edema detected *in vivo* (mice skin irritation test).	(Niu et al., 2023)
Rat with carrageenan-induced paw edema (*ex vivo* rat skin and HEPG2 cells *in vitro*)	Curcumin-loaded microemulsion (Geranium oil+Tween 80 + propylene glycol)	The pH of the formulation was 4.36. High ROS scavenging activity and inhibition of *Escherichia coli* and *Staphylococcus aureus*. Among the several formulations with different compositions of geranium oil and Tween80/PG, the formulation with the highest amount of oil (20 %) afforded the fastest skin permeation *ex vivo*: a flux of 130.9 μg/cm^2/h and a lag time of 0.08 h. Enhanced antioxidant activity compared to pure curcumin. *In vivo*, the emulsion reduced inflammation more effectively than pure curcumin, with reductions of 93 % *versus* 32 % at 6 h. The emulsion showed greater cytotoxicity against hepatocellular carcinoma cells than pure curcumin, with 96 % inhibition at 500 μg/mL compared to 68 % for pure curcumin.	(Hassan et al., 2024)
Solid lipid nanoparticles-based systems			
Human males, Wistar albino rats with carrageenan-induced paw edema (and *ex vivo* human skin)	Curcumin-loaded solid lipid nanoparticles (ceramide 2: palmitic acid) embedded into gel (Carbopol934)	The viscosity of the gel was 19,283 cP. *Ex vivo* fast dermal permeation lasted for up to 24 h, while the plain curcumin gel released the drug slowly only for up to 14 h. In rats, it greatly increased the plasma concentrations and showed a good edema inhibition of 90.75 % at 6 h. No significant skin irritation detected in humans.	(Gaur et al., 2016)
Swiss albino mouse model of rotenone-induced Parkinson's disease and Wistar rat (and *ex vivo* goat skin)	Curcumin-loaded solid lipid nanoparticles (glyceryl monostearate+Tween 80) incorporated into a microneedles patch	*Ex vivo* dermal permeation of curcumin over a 12-h time was 69.31 ± 0.67 %. Bradykinesia decreased, and motor coordination and balance improved in the group treated with the patch. No signs of irritation or sensitivity were found in the animals' skin.	(Prabhu et al., 2022)
Other delivery systems			
Balb/c mouse model of psoriasis (and *ex vivo* mouse skin)	Nanosponge-based gel composed of Beta-cyclodextrin (reticulated with dimethyl carbonate) + Carbopol934 + Guar gum, with curcumin and caffeine)	The pH of the optimized gel was <6 and viscosity >12,000 cP. Sustained drug release for 12 h, similar to a commercial formulation. *Ex vivo* assay showed that the drug produced a local effect in psoriatic lesions, without entering the systemic circulation. Anti-psoriatic activity *in vivo*.	(Iriventi et al., 2020)
Sprague-Dawley rat (and rat skin *ex vivo*)	Curcumin hybrid nanosuspensions with embedded aggregation-caused quenching probes	The nanosuspensions showed enhanced transdermal transport of curcumin compared to curcumin propylene glycol solution, but the permeated amount of curcumin was limited. Co-localization of curcumin and the probe signals indicated that curcumin nanosuspensions can infiltrate into the stratum corneum and accumulate in hair follicles.	(Shi et al., 2020)

and Langer, 2008). It offers several advantages over the oral route, especially for compounds subject to high first-pass metabolism in the gastrointestinal system (Prausnitz and Langer, 2008). Dermal systems are less invasive, can be self-administered, and allow for controlled release of compounds over extended periods.

However, an obstacle for dermal delivery is that only a limited number of compounds can effectively permeate the skin. In general, the transdermal absorption of hydrophilic compounds remains the main challenge (Paudel et al., 2010; Phatale et al., 2022). For successful applications, drugs must be formulated to penetrate the outer skin layers and reach the systemic circulation in sufficient quantities and within an appropriate time frame to exert therapeutic effects (Brown et al., 2006; Prausnitz and Langer, 2008).

The dermal permeability of curcumin is relatively low (Gaur et al.,

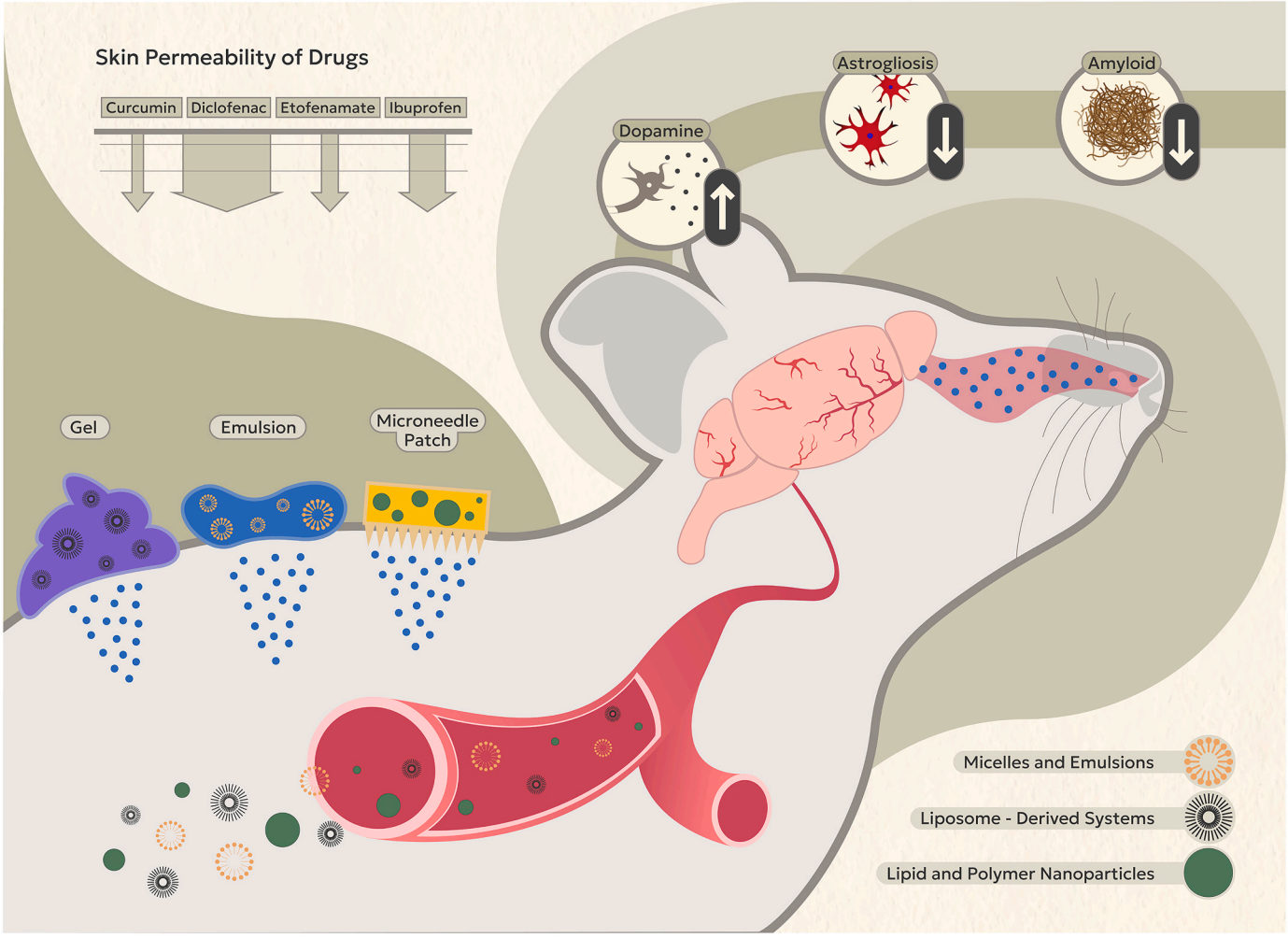

Fig. 10. Diversity of approaches for enhanced delivery of curcumin through the skin and targeting the brain. A variety of drug delivery systems have been used for dermal application, intravenous (and oral) administration or exploiting the nose-to-brain pathway. Important neuroprotective effects were reported in some cases: inhibition of astrogliosis and amyloid-β accumulation; and increase in dopamine levels, in association with behavior improvement. The top left panel compares the skin permeation fluxes of different drugs obtained using improved delivery systems. Detailed information can be found in the main text.

2016), inferior to the neuroprotective donepezil (Dinh et al., 2022) and common anti-inflammatory drugs dermally administered like diclofenac and etofenamate (Escribano et al., 2003; Mancini et al., 2021). Nevertheless, specially designed delivery systems increased more than an order of magnitude the skin permeation flux of curcumin (Gaur et al., 2016; Nair et al., 2022). Publications reporting the development of curcumin delivery systems for dermal application were searched in Web of Science using the keyword combination ("dermal delivery" OR "topical delivery" OR "transdermal delivery" OR "skin delivery") AND (curcumin* OR curcuminoid*) AND (*in vivo* OR "animal study" OR "clinical study") in (Topic). The recent studies that included the *in vivo* assessment of the developed formulations are presented in Table 7.

The collection of the found studies reveal the interest in applications against psoriasis and inflammatory conditions, and the tendency to employ liposome-derived carriers and emulsions to facilitate the skin absorption of curcumin (Table 7 and Fig. 10). In several cases, the micro/nano-encapsulating carriers are presented to skin by way of hydrogels, like those of carbomers (Carbopol), alginate and chitosan, polymers with wide acceptability for dermal use (Niu et al., 2023; Silva et al., 2020; Song et al., 2022). In varied studies, liposomes, invasomes, bilosomes and emulsions, as well as different micelles, were demonstrated to promote the permeation of curcumin through animal skin *ex vivo* in transdermal permeation assays, and exhibited therapeutic efficacy in pathology models *in vivo* (Table 7).

A group of formulations of curcumin-loaded solid lipid nanoparticles (SLNs) was tested in human skin and in rat (Gaur et al., 2016). They generally provided transdermal fluxes through human skin *ex vivo* superior to a commercial emulgel, and the pharmacokinetics in rat was reported to reach 100 to 300 μg/mL levels in plasma for several hours. Moreover, the more successful formulation reduced edema in inflammation and caused no skin irritation (Table 7). Using a more elaborated system, Prabhu et al. (2022) optimized the production of SLNs loaded with curcumin and their incorporation into microneedle arrays fabricated by micromolding. It was possible to reach encapsulation efficiencies of curcumin in the SLNs around 82 % and the drug release was observed for up to 12 h, including after incorporation into the polyvinyl alcohol microneedle patches assayed in skin permeation tests. The authors also tested the patches in an *in vivo* rotenone model of PD and registered motor improvements in the mice (Prabhu et al., 2022).

Although still not tested in humans, the technological options to deliver curcumin through the skin are broadening and showing encouraging pharmacological actions (Table 7 and Fig. 10). The skin permeation flux of curcumin carried by SLNs reached 7.84 μg/cm^2/h (Gaur et al., 2016), comparable to fluxes measured for clinically approved anti-inflammatory drugs (Escribano et al., 2003; Mancini et al., 2021), as illustrated in the top left panel of Fig. 10.

9.3. Curcumin delivery to the brain

A key issue for the pharmacological applications of curcuminoids in neurodegenerative conditions is their actual presentation to cells in the brain. Most of the drugs do not cross the BBB (Pardridge, 2022) and the properties of curcumin are also not favorable to brain penetration (Fig. 6). Accordingly, curcumin is not detected in the CSF from subjects taking common oral formulations (Donadio et al., 2022; Ringman et al., 2012). For the goal of acting at the CNS, drugs have been re-engineered in a variety of ways to transverse the BBB (Nguyen and Maeng, 2022; Pardridge, 2022). In the case of curcumin, the strategy of encapsulating the drug in lipid and vesicular nanosystems has been the most adopted (Fig. 10).

Curcumin delivered by SLNs showed one to two orders of magnitude increases in bioavailability and was detected in brain tissues (Kakkar et al., 2013). Using fluorescence microscopy and gamma scintigraphy techniques, the brain or intracranial accumulation of curcumin was demonstrated 1 to 4 h after oral and IV administration of the SLNs to mice and rabbits (Kakkar et al., 2013). Other NPs formulations of curcumin were argued to deliver the drug in the brain or specially designed to cross the BBB (Barbara et al., 2017; Neves et al., 2021; Tsai et al., 2011; Wang et al., 2019). NPs of PLGA distributed curcumin to the liver, heart, spleen, lung, kidney and brain of rats, with a noteworthy accumulation in the hippocampus (Tsai et al., 2011). Other authors functionalized PLGA NPs with a glycopeptide (g7), for BBB crossing, and tested the curcumin-loaded carrier in hippocampal cells (Barbara et al., 2017). These NPs showed no toxicity and reduced the Aβ aggregates. Later, Neves et al. (2021) decorated lipid nanocarriers with transferrin to mediate their transport through the BBB and, tested in transwells with hCMEC/D3 cells monolayers, a higher transmigration of curcumin was measured (Neves et al., 2021). In an *in vivo* model of cerebral damage after ischemia/reperfusion, curcumin-loaded NPs (IV) were reported to accumulate in the ischemic penumbra and protect the BBB integrity, reducing neuroinflammatory and brain injury markers (Wang et al., 2019).

Although a wider demonstration of the advantages of these formulations to deliver curcumin through functional BBB is necessary, significant CNS effects in preclinical models are rising (Jia et al., 2016; Narouiepour et al., 2022; Wang et al., 2019; Zhang et al., 2018). In another model of brain injury, curcumin-loaded niosome NPs were orally administered for 10 days to rats after traumatic brain injury and human neural stem/progenitor cells' transplantation into the lesion site (Narouiepour et al., 2022). The combined transplantation plus curcumin therapy improved the animals' locomotor activity, and reduced edema, astrogliosis and inflammation markers at the injury site, in comparison to the control groups. Interestingly, the beneficial effects in edema and inflammation were driven mostly by the drug formula. In this work, curcumin levels around 40 ng/g were measured in homogenized brain samples (Narouiepour et al., 2022). Jia et al. (2016) fabricated curcumin-loaded polymersomes functionalized with transferrin and Tet-1 peptide for enhanced brain delivery. The polymersomes (IV) ameliorated cognitive defects in AD mice (Jia et al., 2016). Loaded cerasomes with high BBB permeability improved behavior disorder and dopamine depletion in PD mouse model (Zhang et al., 2018). Furthermore, an ultrasmall micellar carrier able to cross a BBB *in vitro* model delivered curcumin intracranially with therapeutic effect against glioblastoma multiforme (Singh et al., 2016). In the case of these ultrasmall (<15 nm) particles based on the amphiphilic Pluronic polymer, the improved BBB-crossing efficiency was attributed to the polymer-facilitated passive endocytosis-mediated transendothelial migration and/or increased vesicular transport (Singh et al., 2016), while the functionalized systems mentioned above are expected to undergo receptor-mediated transport (Pardridge, 2022).

The nose-to-brain pathway is an attractive route for delivering drugs to the brain and promising data has been obtained with synthetic drugs and phytochemicals in animal models (Lagoa et al., 2020; Nguyen and Maeng, 2022; Pardridge, 2022). A moderate improvement in the brain availability of curcumin was achieved by using nanostructured lipid carriers (NLCs) nasally administered to rats (Nguyen and Maeng, 2022). Mishra et al. (2022) developed transferosomes of phosphatidylcholine and deoxycholate loaded with only curcumin, or combined with berberine (Mishra et al., 2022). Tested in mice, curcumin levels of ng/mL could be found in the brain (homogenized samples) 4 h after intranasal administration and the mean residence time in the brain (5 h) was longer than applying a simple curcumin solution (1.8 h). In animals treated with scopolamine (AD model), the nasal curcumin transferosomes and those co-loaded with berberine improved spatial memory, and reduced the expression of BACE-1 and Aβ accumulation in the hippocampus (Mishra et al., 2022). Very recently, PEG-decorated mesoporous silica NPs were also proposed for intranasal administration of curcumin so that high levels could be reached in mice brains as fast as 30 min (Sofi et al., 2024). There are still doubts about the clinical feasibility of using the nasal path of drug administration in CNS disease (Nguyen and Maeng, 2022; Pardridge, 2022), but the preclinical data with curcumin encourages the continued development of biomaterials suitable to explore this alternative route.

10. Curcumin-laden scaffolds in wound healing and tissue engineering

The pharmacological properties of curcumin have been further employed in the development of bioactive scaffolds for wound healing and tissue regeneration. In addition to the anti-inflammatory action, these applications explore the antibacterial and cell modulating activities of curcumin for example to accelerate wound closure. The antibacterial activity of curcumin is well established against *Escherichia coli* and *Staphylococcus aureus*, and delivery systems – liposomes, quantum dots, and others - have been specifically designed to promote its efficiency in opposing bacterial biofilms and infections (Arunachalam et al., 2023; Hassan et al., 2024; Mabood Husain et al., 2024). The antibacterial activity has also been demonstrated with curcumin-laden scaffolds that can be used to convey the drug at infection-prone tissues like surgical sites or bone grafts (Ji et al., 2023; Mahmoudi et al., 2023; Tarrahi et al., 2021; Wei et al., 2023; Xie et al., 2024b).

Various material platforms have been utilized to improve curcumin presentation in wound healing applications. Curcumin-loaded lignin NPs, electrospun polycaprolactone (PCL)/gelatin scaffolds containing curcumin-loaded chitosan NPs, and polyvinyl alcohol (PVA)/chitosan/curcumin patches showed enhanced wound healing properties (Azari Torbat et al., 2023). Loaded into cellulose acetate/PCL nanofibers obtained by electrospinning, curcumin increased the swelling of the matrix and fibroblast proliferation *in vitro* (Suteris et al., 2022). Studied *in vivo*, a fibrous electrospun mat containing PVA, bioactive glass, silver NPs and curcumin improved skin tissue regeneration after surgery (Mahmoudi et al., 2023).

The benefit of curcumin in scaffolds for tissue engineering is increasingly recognized. The ideal tissue scaffold presents a bioactive surface that favors cell adhesion, growth, and differentiation, as well as good biocompatibility, suitable mechanical properties, and a porous internal structure allowing nutrient flow and cell multiplication (Azari Torbat et al., 2023; Ji et al., 2023; Xie et al., 2024b). In scaffolds of crosslinked cellulose, chitosan/PVA/Carbopol/PCL, and silk, curcumin was demonstrated to support the proliferation of fibroblasts, mesenchymal stem cells and chondrocytes, respectively (Azari Torbat et al., 2023; Tarrahi et al., 2021). Curcumin has been incorporated in scaffold structures for varied applications, including inflamed dentin–pulp complex, corneal tissue engineering, cartilage regeneration and bone repair (Azari Torbat et al., 2023; Bhattacharjee et al., 2023; Lee et al., 2019; Mokhtarzadegan et al., 2024). The presence of curcumin in PCL scaffolds granted robust anti-inflammatory action (Yang et al., 2022). After chondrocyte seeding, these scaffolds showed biocompatibility and enhanced the regeneration of tracheal cartilage in rabbits.

Merged with the antibacterial and anti-inflammatory properties, the osteoinductive actions of curcumin raise great interest for bone healing or repair using both organic and inorganic supports (Azari Torbat et al., 2023; Bose et al., 2018; Mokhtarzadegan et al., 2024; Wei et al., 2023; Xie et al., 2024b). Third generation biomaterials combining cells, scaffolds and bioactive factors promise future bone grafts for complex skeletal defects requiring osseous reconstruction. Loaded into graphene oxide and incorporated in a collagen scaffold, curcumin promoted osteogenic differentiation of stem cells and prevented the growth of potentially infective bacteria (Xie et al., 2024b). Lu et al. (2025) developed an injectable cement formulation that can adapt to bone defects following tumor tissue excision from the bone. The curcumin-loaded calcium phosphate silicate cement was found to induce the death of osteosarcoma cells, due to curcumin, without toxicity to pre-osteoblast cells *in vitro* (Lu et al., 2025).

Three-dimensional (3D) printing offers important advantages for producing scaffolds with individual customization, complex shapes and interconnected porosity (Jaiswal and Wadetwar, 2025; Ji et al., 2023; Sarkar and Bose, 2019). Calcium phosphates and hydroxyapatite are common bioactive materials used for 3D printed bone scaffolds (Jaiswal and Wadetwar, 2025). 3D printed interconnected macroporous calcium phosphate scaffolds, coated with PCL-PEG polymer containing curcumin, were assessed in rats and increased the mineralized bone formation (Bose et al., 2018). These results were supported by an improved osteogenic and angiogenic ability of the scaffolds. In later approaches, curcumin only or combined with carvacrol was encapsulated in liposomes (Sarkar and Bose, 2019), in polymeric micelles (Bose et al., 2023), or in NPs (Dahiya et al., 2024), and incorporated into 3D printed calcium phosphate structures. In all cases, the drug eluting from the scaffolds reduced the viability of osteosarcoma cells but promoted osteoblast proliferation *in vitro*. An improved performance *in vitro* and *in vivo* was reported with curcumin-loaded magnesium oxide doped tricalcium phosphate printed grafts (Bhattacharjee et al., 2023). Implanted in rat femur, the polyphenol-loaded grafts prompted the formation of more new bone than unloaded scaffolds.

3D printed matrices with hydroxyapatite are also being explored by other authors to promote migration and differentiation of bone marrow mesenchymal stem cells (BMSC). A scaffold of hydroxyapatite and chitosan, bridged by tannic acid and sodium alginate, and incorporating curcumin-loaded dendritic mesoporous organic silica NPs, was described to induce proliferation and osteogenic differentiation of BMSC in a curcumin concentration-depended way (Ji et al., 2023). In other work, the osteoinductive activity of a scaffold combining calcium phosphate, hydroxyapatite, PCL and gelatin microspheres with curcumin was thoroughly studied (Wei et al., 2023). This scaffold induced the attachment, proliferation, osteogenesis, and migration of BMSC, and resulted in increased regenerated area of bone formation *in vivo*.

In addition to bone grafts, curcumin-laden 3D printed scaffolds reach further tissue engineering applications. Aiming cartilage regeneration, a curcumin-loaded polyurethane scaffold modified with gelatin was shown to enhance proliferation and differentiation of chondrocytes *in vitro* (Lee et al., 2019). Also with polyurethane, curcumin-incorporated vascular grafts were produced by the fused deposition modeling 3D printing technology (Basile et al., 2023). Printed curcumin-loaded poly (lactic acid) scaffolds (Vijayaraghavan et al., 2025) and gelatin hydrogels (Xia et al., 2022) promoted cell survival and accelerated wound healing in mouse models.

3D printed scaffolds were also developed to explore alternative curcumin delivery applications. Potentiating intracranial therapy of brain cancer, fused deposition modeling was used to produce curcumin-loaded PCL flexible porous scaffolds that released the drug for more than 3 days and showed toxicity against glioblastoma cells *in vitro* (Li et al., 2021). Dissolvable sublingual films with curcumin-loaded PLGA NPs showed neuroprotective effects *in vitro*, suggesting a novel treatment option, namely for AD patients with swallowing problems (Yekeler et al., 2024).

Many of these approaches were still not assessed *in vivo*, but the curcumin-laden bioengineered bone grafts returning positive results in animal models hold the higher potential for clinical translation (Fig. 11). In particular, the 3D printed bone substitutes can represent a scalable alternative to overcome the limitations associated with the current use of autologous bone grafts in bone repair. Printing technologies can form complex and defect-designed geometries, control internal features, and combine cells, bioactive molecules and different materials. The research discussed above demonstrates how the use of curcumin in scaffolds affords localized drug delivery and key pharmacological effects like osteoinduction, antibacterial protection, anti-cancer (osteosarcoma) and anti-inflammatory action.

11. Concluding remarks and future perspectives

Since the first reports on curcumin's anti-amyloidogenic activity at the beginning of the 21st century (Frautschy et al., 2001), the pharmacological exploration of curcumin against neuropathological disorders has seen significant progress. Despite this, substantial challenges remain to translate these findings into widely accepted therapies. Novel approaches are essential to overcome curcumin's bioavailability limitations, to identify the most relevant pathology-specific targets and mechanisms of action, and to ensure an effective delivery of bioactive forms to the affected tissues or organs.

Traditionally, turmeric has been used in ethnopharmacology mainly to treat respiratory, digestive, and musculoskeletal ailments, by combating infections, inflammation and pain. Following confirmation of curcumin's robust anti-inflammatory effects, there has been growing interest in its therapeutic potential, especially in addressing inflammation-related conditions and gastrointestinal cancers. A recent meta-analysis of clinical trials has reinforced curcumin's efficacy in managing knee osteoarthritis (Zhao et al., 2024). Despite the interest in curcumin against neuropathologies is contemporary, the *in vitro* and *in vivo* data reviewed in this work highlight the diversity of neuroprotective actions of curcuminoids with potential for applications in neurodegenerative and age-related neurological disorders. Beyond inhibiting neuroinflammation and Aβ deposition, curcumin promotes neurogenesis, modulates BDNF signaling, reduces tau and α-synuclein alterations, regulates synaptic plasticity-related genes, and increases dopamine levels in PD models, among other effects. Curiously, curcumin is simultaneously a substrate for gut microbes, by whom is biotransformed into distinct metabolites, and a modulator of the intestinal microbiota composition and diversity, which could play a major role in the gut-brain axis-evoked neuroprotection in AD and PD.

Associated with these cellular and molecular actions, curcumin

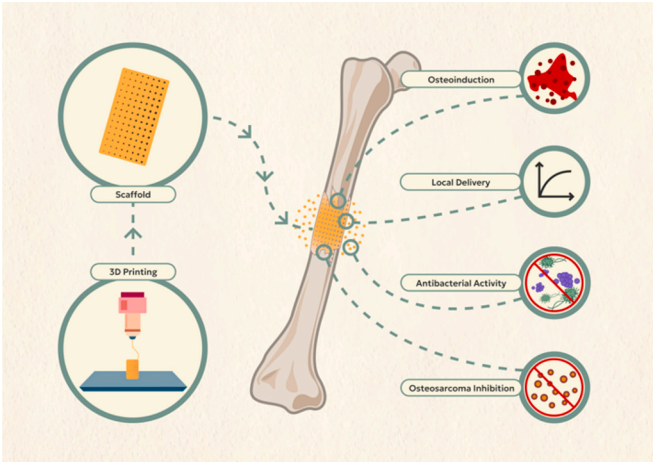

Fig. 11. Application of 3D printed curcumin-laden bone graft substitutes and reported biological activities (Bhattacharjee et al., 2023; Bose et al., 2018; Wei et al., 2023). Detailed information can be found in the main text.

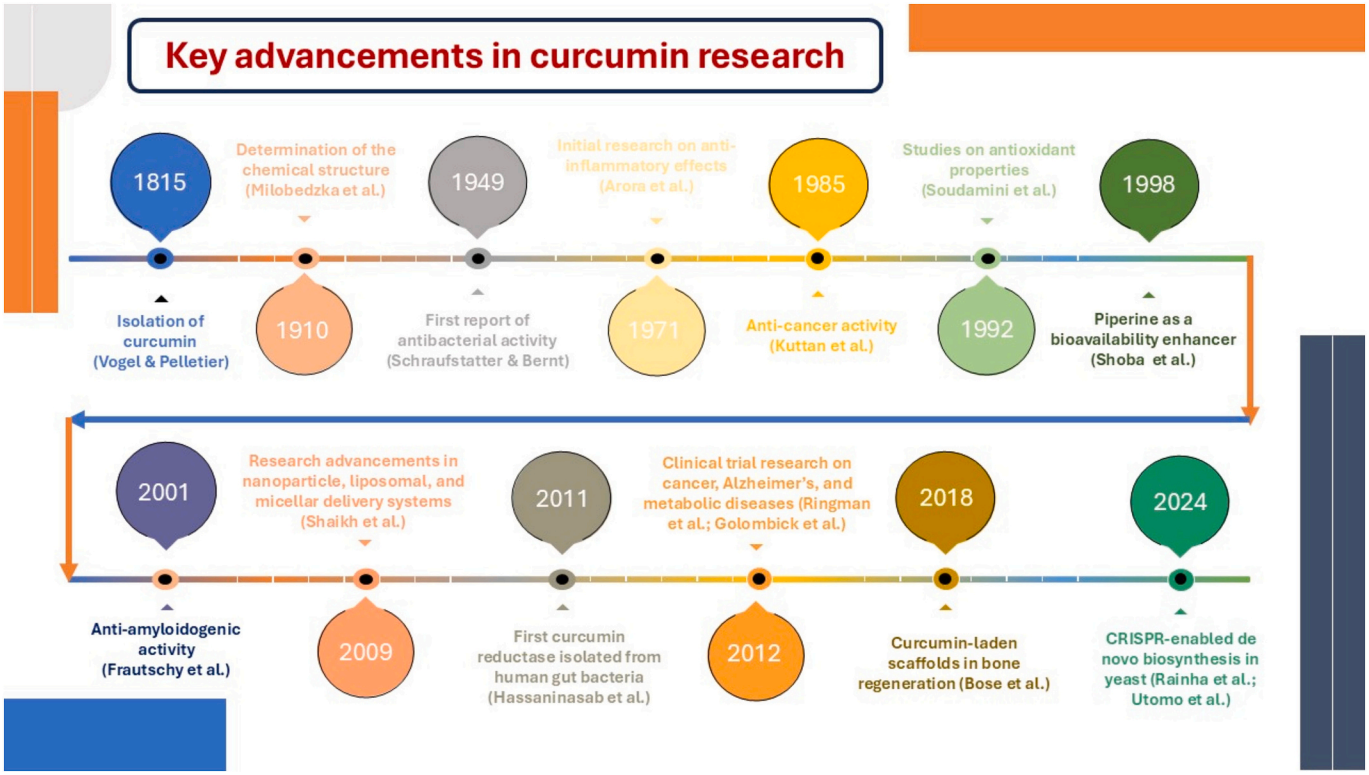

Fig. 12. Timeline of key advancements in curcumin research and applications (Arora et al., 1971; Bose et al., 2018; Frautschy et al., 2001; Golombick et al., 2012; Hassaninasab et al., 2011; Kuttan et al., 1985; Miłobędzka et al., 1910; Rainha et al., 2024; Ringman et al., 2012; Schraufstatter and Bernt, 1949; Shaikh et al., 2009; Shoba et al., 1998; Soudamini et al., 1992; Utomo et al., 2024; Vogel and Pelletier, 1815).

administration has been shown to reduce cognitive, memory, and motor deficits in disease model animals. In accordance, some oral formulations of curcumin trialed in AD and PD patients, older adults, and individuals with cognitive impairments, have provided improvements in cognitive and behavioral symptoms, and reductions in the accumulation of neurotoxic proteins. Furthermore, curcumin has shown beneficial effects on cholesterol levels and endothelial function, potentially countering neurodegenerative processes. RCT demonstrated curcumin's inhibition of NF-kB and antioxidant activity, but independently of Nrf2. Curcumin is generally well tolerated with doses below 4 g/day (Cheng et al., 2001; Lagoa et al., 2022; Ringman et al., 2012), but vigilant monitoring is advisable for older or frail subjects, even at lower doses. Of particular interest, therapeutic effects have been observed with curcumin doses up to 1 g/day, with cognitive improvements reported at doses below 200 mg (section 5).

Curcumin's bioavailability and pharmacological activity are strongly affected by metabolism, which encourages novel strategies involving manipulation of metabolic steps or use of metabolites to potentiate pharmacological applications. Evidence from human and animal studies identifies tetrahydrocurcumin as curcumin's principal active metabolite, possibly responsible (alongside hexahydrocurcumin) for the observed neuroprotective effects. Notably, tetrahydrocurcumin reaches higher levels in the blood, whereas curcumin itself is absent in CSF samples. While tetrahydrocurcumin's anti-inflammatory activity is established, further research is needed to clarify its effects on Aβ processing, dopamine regulation, and lifespan extension, as well as its potential influence on neurogenesis, tau and α-synuclein pathology, and other neuroprotective actions attributed to curcumin. As discussed in section 6, additional curcumin metabolites also demonstrated anti-inflammatory activity, and undiscovered bioactive metabolites may exist. Further research into the neuroprotective mechanisms of tetrahydrocurcumin and other metabolites, particularly at therapeutically relevant low micromolar and sub-micromolar concentrations observed in human plasma and CSF, is warranted.

Curcumin's pharmacological profile, like many phytochemicals, involves multiple low-potency yet interconnected mechanisms of action. Our systems biology approach has identified novel potential targets of curcumin relevant to neurodegeneration, extending beyond previously established targets such as NF-kB and STAT3. It was found that curcumin, by regulating microRNAs implicated in neurodegenerative diseases, might modulate the expression of genes involved in LTP like phospholipase C and calcineurin subunits. Moreover, emerging neuropathology models are beginning to reveal curcumin's capacity to modulate cellular senescence markers and influence neuronal differentiation. Interestingly, hippocampal neurogenesis may be enhanced specifically by low doses of curcumin (Kim et al., 2008). These novel mechanisms and targets are not being followed in human trials and merit further investigation with curcumin and its metabolites at clinically relevant dosages.

These targets hold promise as molecular biomarkers of curcumin's effects in clinical trials involving subjects with neurodegenerative diseases or age-related cognitive decline. Although current clinical trials are largely in the initial stages, long-term studies with larger cohorts and provided with specific biomarkers of response are essential to generate more informative and conclusive findings. Biomarkers closely related to LTP and synaptic functions, namely neurogranin and BDNF, can inform of the effect of curcumin treatments on critical targets. Neurogranin is a postsynaptic protein involved in memory consolidation and LTP signaling, and increased levels in CSF are measured in subjects with mild cognitive decline and AD, being used to monitor synaptic degeneration in AD patients (Ye et al., 2019). The major CNS neurotrophin BDNF is known to affect LTP, and neuronal plasticity and density in the hippocampus. Blood levels of BDNF correlated with mental state scores in AD and have been used as biomarkers of response to antidepressants (Li et al., 2023a; Medeiros et al., 2022).

Drug delivery, bioavailability, and NPs have emerged as key topics in

curcumin research in the last decade (Yeung et al., 2019). Successfully, innovative delivery systems and formulations have proven the possibility of increasing the oral bioavailability of curcumin in animals and humans. Meanwhile, advanced bioengineering approaches started being employed to develop targeted curcumin therapies for cancer and other diseases. Among the curcumin nanocarriers designed for CNS delivery, polymersomes, micellar and liposome-derived systems have demonstrated therapeutic efficacy. It is noteworthy that the BBB changes associated with aging and neurodegenerative disorders, which involve barrier leakiness and reversible neural dysfunction (Senatorov et al., 2019), could facilitate the neuroprotective actions of curcumin and improve the brain targeting of these delivery systems.

It should be mentioned that no registered clinical trials for tetrahydrocurcumin were identified, and specialized delivery systems for the metabolite are scarce (Elbanna et al., 2023). Given the increasing availability of chemically and biotechnologically produced tetrahydrocurcumin, along with its neuroprotective potential, the future development of delivery systems tailored for this metabolite is a logical and promising direction.

Finally, dermal delivery of curcumin offers a compelling alternative for its therapeutic application against inflammation and other conditions. One of turmeric's traditional uses involves topical application as poultice or paste, suggesting that curcumin may be absorbed through the skin at therapeutic doses. While curcumin's dermal permeability is lower than that of standard anti-inflammatory drugs, novel delivery systems reviewed here enhanced its transdermal absorption and pharmacological activity in various *in vivo* models. Engineered dermal formulations, and devices such as microneedle patches, represent a valuable alternative to oral administration for extended treatments of older patients with neuroprotective low doses or for addressing skin and musculoskeletal inflammation.

Despite the questions that remain open, the use of curcuminoids in neurodegenerative diseases and other inflammatory and age-related disorders may be a reality in the short term, now that biotechnological innovation has demonstrated the ability to improve delivery capacity and therapeutic efficiency. Additionally, recent bioengineering advancements are enabling the sustainable production of curcumin and novel medical applications like multi-action tissue scaffolds (Fig. 12).

To conclude, advancing curcumin research requires a multi-faceted approach integrating biotechnological, pharmacological, and regulatory strategies. A crucial priority is the optimization of scalable production methods, including biotechnological synthesis and nanomedicine manufacturing, to enhance the bioavailability and therapeutic potential of curcumin and its active metabolites, such as tetrahydrocurcumin. Given its promising neuroprotective properties, further research should explore the mechanistic basis of tetrahydrocurcumin's effects on synaptic plasticity, oxidative stress modulation, and neuroinflammation, particularly in models of neurodegenerative diseases.

Clinical trials should be designed to assess the long-term cognitive benefits of curcumin and tetrahydrocurcumin, employing rigorous pharmacokinetic evaluations and incorporating comprehensive biomarkers beyond traditional amyloid metrics. These studies should align with regulatory standards to facilitate potential drug approval, emphasizing robust cohort selection and well-defined clinical endpoints.

Furthermore, novel fabrication technologies, such as 3D printing, offer a pathway to personalized curcumin-based therapeutic delivery systems. These approaches could support the production of customized solid oral dosage forms, transdermal patches, and tissue-engineering scaffolds for regenerative medicine applications.

To accelerate progress in curcumin-based therapies, bioinformatics and systems biology should play a pivotal role in identifying molecular targets and optimizing therapeutic formulations. Network pharmacology and computational modeling can help elucidate curcumin's multi-target interactions, supporting the design of precision medicine strategies tailored to individual patient profiles.

Finally, overcoming regulatory and commercial barriers is essential to translating curcumin research into viable clinical applications. Establishing clear regulatory guidelines, improving standardization of curcumin formulations, and fostering collaborations between academia, industry, and regulatory bodies will be key to achieving widespread clinical adoption of curcumin-based therapeutics.

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Ricardo Lagoa: Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing. **Logesh Rajan:** Investigation, Writing – original draft. **Cristiana Violante:** Investigation, Writing – original draft. **Smith B. Babiaka:** Investigation, Writing – original draft. **Dorinda Marques-da-Silva:** Investigation, Writing – original draft, Writing – review & editing. **Bhupinder Kapoor:** Investigation, Writing – original draft. **Flávio Reis:** Validation, Writing – review & editing. **Atanas G. Atanasov:** Conceptualization, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ricardo Lagoa reports financial support was provided by Foundation for Science and Technology. Dorinda Marques-da-Silva reports financial support was provided by Foundation for Science and Technology. Flávio Reis reports financial support was provided by Foundation for Science and Technology and European Union's Horizon Europe program. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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