Mini Review

Dietary curcumin: a potent natural polyphenol for neurodegenerative diseases therapy

Abstract

Aggregation of misfolded amyloid proteins is a key factor for synaptic damage and impairment of neuronal communication in several neurodegenerative diseases. Since last few decayed several synthesized compounds, small molecules, drugs have been used to target against these misfolded proteins, but ultimately failed to prevent the misfolded protein aggregations and neurotoxicity effectively. Therefore, therapies for these diseases are elusive and under active investigation. As a potent anti-amyloid activity and its Pleotropic actions, recently curcumin has been used for treatment of several neurodegenerative diseases. It is the main ingredients of turmeric powder of the herb *Curcuma longa*. Its preferential binding properties with misfolded amyloid proteins attracted researchers to use as a potential therapy to prevent neurodegeneration. Importantly, curcumin is also a safe, inexpensive, easily available Polyphenol and it can cross blood brain barrier. Therefore, it is considered one of the promising natural Polyphenol for therapy of age related protein misfolding diseases, including several neurodegenerative disorders. In this mini review article we provided conceptual information about the multiple potentials of curcumin for prevention and/or treatment of neurodegenerative diseases.

Keywords: neurodegenerative diseases, amyloidosis, curcumin, neuroinflammation, anti-amyloid

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Abbreviations: Cc, cur-curcumin; Aβ, amyloid beta protein; NFTs, neuro fibrillary tangle; NF-κB, nuclear factor kappa beta; COX, cyclooxygenase; LOX, lipoxygenase; TNF, tumor necrosis factor; IL, interleukin; ROS, reactive oxygen species; RONS, reactive nitrogen species; HSP, heat shock proteins

Introduction

Neurodegenerative diseases are age related, multifactorial, and complicated disorders of nervous system, which has no successful treatment or cure.[1] Most of these diseases may onset with accumulation of misfolded proteins even more than decays before its clinical symptoms arise.[1] Multifactors are involved to initiate these disease progressions, including neuro-inflammation, oxidative damage and accumulation of misfolded amyloid proteins.[2–4] These events may work either independently, or together and ultimately impairs neuronal communications by damaging the neurons, which results a long term cognitive and motor dysfunction.[5] Therefore, to restore normal brain functions and to delay onset or progression of diseases, it is necessary to start therapy before disease start to progress.[6,7] Although several efforts have been implicated to attenuated disease progression using anti-amyloid, anti-inflammatory agents, small molecules and drugs, but none of them are in satisfactory level. Recently, as a safe, inexpensive, anti-amyloid Polyphenol, curcumin (Cur) draw a special attention to the researchers to use as a promising drug of choice to combat against several complicated neurodegenerative diseases.[7,8] It is and the principal yellow pigment (almost 77%) present in the turmeric root of *Curcuma longa*, and structurally diarylheptanoid in nature. Other two important component of turmeric powder are desmethoxycurcumin and bis-desmethoxycurcumin (Figure 1). Because of its anti-inflammatory properties, since more than five thousand years, curcumin has been used in Indian and Southeast Asian traditional Ayurveda medicine.[9] However, last few years scientist discovered its promising anti-amyloidogenic properties and started using as therapy for neurodegenerative diseases.[6,7] It can not only bind and inhibits the amyloid beta protein aggregation,[10–13] but also binds with Alfa synuclein,[14] huntingtin,[15] and prion proteins.[16] Therefore, based on its potent anti-amyloid activity, Cur is a promising natural compound to combat against neurodegenerative diseases caused by protein misfolding (Figure 1). This mini review provided some basic information about curcumin therapy and their potential impact on neurodegenerative diseases.

Neurodegenerative diseases

Neurodegenerative diseases are the age related brain disorders, which causes worsening of many of our normal body activities, including our daily movement, balance or motor coordination, speech ability, respiratory and cardiovascular functions.[3,17] In a simple word, this is a condition in which cells of the central nervous system are affected. Depending on the type of neurodegenerative disease and its affected area, the severity may vary. During the progression of these diseases, a massive demyelization takes place over time, lead to dysfunction and disabilities of many areas of brain, which normally control our normal body functions.[18] Since last few decades, almost 30-40 different neurodegenerative diseases have discovered which are listed below.

Linked between protein misfolding and neurodegeneration

Proteopathies or protein misfolding diseases area the class of diseases, which causes impairment of neuronal communication. Many of the neurodegenerative diseases (but not all) involved protein misfolding and their abnormal accumulation in intracellular and extracellular spaces.[8,19,20] For example, the most common age related neurodegenerative disease is Alzheimer's disease (AD), which causes early memory deficits, followed by gradual decline of cognitive and intellectual functions or dementia.[21] Aggregation of amyloid

beta protein (Aβ) as senile plaque in extracellular spaces,[22] and phosphorylated tau as neurofibrillary tangle (NFT) intracellularly[23] are the cardinal features of AD. Similarly, accumulation of other amyloid proteins, such as α-synuclein, huntingtin and prion proteins are noted in Parkinson's, Huntington and prion diseases respectively. Accumulation of all these misfolded proteins can cause impairment of synaptic communication, loss of synaptic integrity and impairment of daily brain function. These misfolded proteins can also impair cellular protein clearance pathways, including dysfunction of molecular chaperones, proteasome system and autophagy pathway.[8] Therefore, restoring of these essential pathways would be a good strategy to remove these misfolded aggregates from the cells, and to preserve their normal function. Although, several small molecules, drugs, natural Polyphenol have been investigated to inhibit these misfolded proteins in these diseases, but none of them are in satisfactory level or not able to halt their aggregation completely, therefore therapy is elusive. Whereas, we found "curcumin" as a natural anti-amyloid Polyphenol, which have potential role to inhibit misfolded protein aggregation, and also restore protein clearance pathways,[8,24] which are discuss further below.

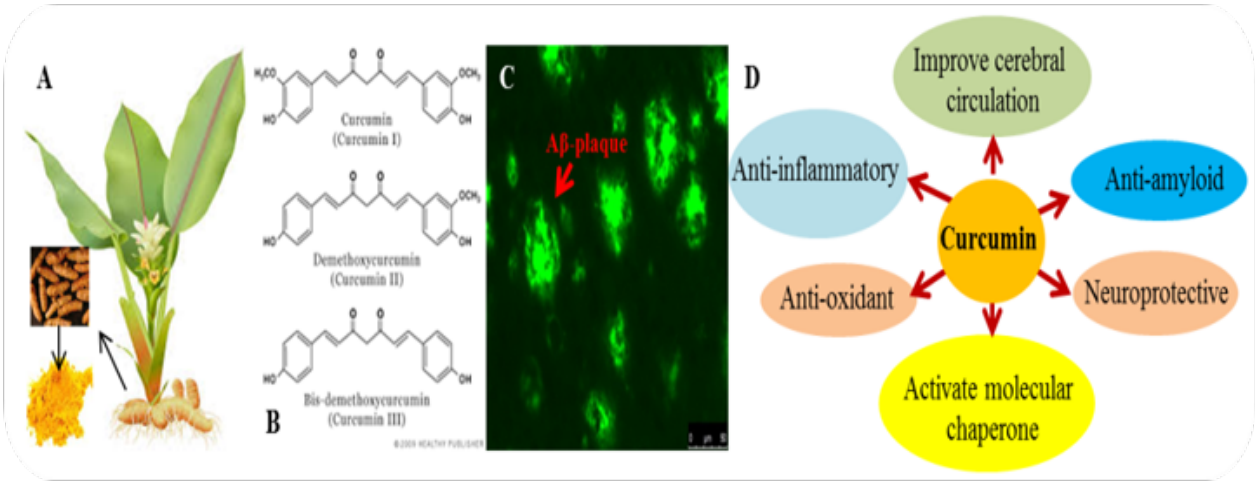

Figure 1 Curcumin- a natural Polyphenol, and an important health beneficiary component of the yellow powder of turmeric, which belongs to the roots of *Curcuma longa,* a herb from *Zingiberaceae* family.

A. The turmeric contains three active Polyphenol and Cur is the predominant (80%).

B. It is naturally fluorescent.

C. Show green fluorescence upon binding with Aβ-plaques (the principal misfolded protein in AD brain)

D. Pleotropic actions of curcumin on nervous system.

Relevance of curcumin therapy in neurodegenerative diseases

Curcumin has preferential binding to amyloid proteins and inhibits their further aggregation.[10,11] For example, it can strongly bind with Aβ (Figure 1C), the principal misfolded protein noted in AD. Not only that, Cur can also bind and inhibit the aggregation of tau,[24] α-synuclein,[14] huntingtin[15] and prion proteins[16] in tauopathies, PD, HD and prion diseases respectively. More recently, we found that Cur is able to restore the dysfunctions of molecular chaperones (heat shock proteins), which is essential for protein refolded and degradation of misfolded aggregates from the cell.[8] Though the exact mechanism how the Cur binds with these amyloid proteins and reduce the pathologies of these brain diseases is unclear, but it is established that it has Pleotropic action on nervous system (Figure 1D), which are summarized in the below Table 1–3.

Recommended doses of curcumin intake

Toxicological evaluation revealed that Cur is safe (up to 12g/day) as seen in animal studies and in phase-I clinical trial,[7,34] whereas, the major issues in successful Cur therapy are its absorption and stability in body fluids. Dietary Cur is very unstable in most of the body fluid, and poor water solubility and limited tissue bioavailability. For example, if deliver orally, it become Cur-gluocuronides and Cur-sulphates in the liver and eliminated rapidly from the body through urine. Whereas, if given intraperitoneally (i.p) or intravenously (i.v), it become catabolized to ferulic and dihydroferulic acid within few hours, therefore, exact dose of Cur requirement per day is practically difficult to measure.[7,27,34] It also depends on the way we take it, and also the exact formula of intake. As Cur is a hydrophobic in nature, therefore, it is readily dissolved in fat or oil. It has been revealed that Cur has very short half-life in plasma, whereas more stable in brain, because it is lipophilic and brain contain high fat compare to blood. Therefore, Cur mixed with oil would be better to absorb in our digestive system. Experimental animal results showed that 600nM is sufficient to reduce pathology in mouse model of AD.[7,27] Extrapolation of animal studies to clinical trial revealed that an oral supplementation of Cur in the range of 80-500mg/day are recommended to get its beneficial effect in human, whereas, intake of raw turmeric may be 2-4gram/day.[7,27] Several formulas are available to enhance tissue availability of Cur are:

i. Pairing Cur with black pepper (piperine), which can increase its stability in body fluids by inhibiting its glucuronidation

ii. Cur phytosomes complexed with phosphatidylcholine (Meriva or BCM-95);

iii. Cur nanoparticles (Theracurcumin) formula

iv. water-soluble Cur (polyvinyl pyrrolidone)

v. Solid lipid nanoparticles Cur formula (Longvida).[7,27]

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Table 1 List of common neurodegenerative diseases

Alzheimer's disease
Parkinson's disease
Huntington's disease
Prion disease
Creutzfeldt-Jakob disease
Lewy body dementia
HIV-associated dementia
Cerebral palsy
Pick's disease
Corticobasal degeneration
Progressive suprauclear palsy Amyotrophic lateral sclerosis
Multiple sclerosis
Ataxia telangiectasia
Spino cerebellar ataxia Narcolepsy
Spinal muscular atrophy
Adrenal leukodystrophy
Batten disease
Bovine spongiform encephalopathy
Familial fatal insomnia,
Fronto temporal lobar degeneration
Multiple system atrophy
Primary alcoholism lateral sclerosis
Schilder's disease
Subacute combined degeneration of spinal cord
Spielmeyer-Vogt-Sjogren-Batten disease
Toxic encephalopathy
Refsum's disease
Sandhoff 's disease
Alexander's disease
Alper's disease
Canavan disease
Cockayne syndrome
Kennedy's disease
Krabbe's disease
Neuroborreliosis
Machado-Joseph disease
Niemann Pick disease
Pelizaeus-Merzbacher disease Steele-Richardson-Olszewski disease
Tabes dorsalis

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However, researcher found a range of 4-8 capsules of 500mg of each Longvida (125mg of curcumin) per day may be efficacious.[7,27,34] Another study showed that much less, even 80mg/day of solid lipid nanoparticles-Cur formula (Longvida) may be sufficient to prevent of delay further neurodegeneration.[34]

Table 2 Misfolded protein aggregation involved in most common neurodegenerative diseases

Diseases	Proteins	Pathology	Affected area	Complications
Alzheimer's	Aβ, Tau	Extracellular plaque, neurofibrillary tangle	Hippocampus, amygdale, frontal, entorihnal cortex	Memory loss, personality change, worried, depressed
Parkinson's	α- Synuclein	Lewy body	Substantia nigra, striatum, PFC	Abnormal muscle movement, memory loss
Huntington's	Huntington	Inclusion bodies in cytoplasm, nucleus	striatum	Uncontrolled movements, clumsiness, memory loss
Prion	Prion protein (PRPN)	Prion plaques	Whole CNS	Memory loss, personality change, movement disorder

Table 3 Pleotropic actions of curcumin to treat neurodegenerative diseases

Actions	Mechanisms	References
Anti-amyloid properties	Binds with Aβ and prevent its oligomerization & fibril formation	10,11,25
Inhibition of Aβ production	Inhibit activities of β-secretase (BACE), inhibiting amyloid precursor protein (APP) processing pathway	13,24
Aβ clearance:	Stimulate phagocytosis, thus decrease Aβ-plaques	11,26,27
Inhibition of NFTs	Bind with NFTs and inhibits tau phosphorylation (pTau)	28
Inhibition of other amyloid	Bind with α-synuclein in PD, huntingtin in HD and prion aggregates in prion disease	14,29
Potent Antioxidant:	Scavenges ROS/RONS, increase antioxidant levels, decrease lipid peroxidation, chelate toxic metals.	26,27,30
Anti-inflammatory activity:	Down regulate NF-κB, COX-2, 5-LOX, TNF, IL-1, IL-6.	26,27
Regulate activity of molecular chaperones	Restore levels of heat shock proteins (HSP90, 70, 60, 60, HSC70), protease system.	8
Enhance NGF, BDNF, GDNF, neurogenesis & synaptogenesis	Increase expression of BDNF, NGF, GDNF and can promote neurogenesis, synaptogenesis	27,31
Improving cerebral circulation:	Inhibits inflammation of brain vasculature leading to improvement of overall blood supply, reduce platelets adhesion in brain microvascular endothelial cell.	32,33

Discussion

Aggregation of misfolded amyloid proteins in the central nervous system is a leading cause of synaptic loss, neurodegeneration, and cognitive and behavioral impairment in several neurodegenerative diseases,[1] which have no cure. Finding effective molecule, drug is vital to prevent or delay their further progression. As a potent anti-amyloid, anti-oxidant, anti-inflammatory Polyphenol, Cur has been widely investigated in the field of neurodegenerative diseases research.[7,8] Though since last five thousand years Cur has been widely used for wound healing in traditional Ayurvedic medicine of India, and other South East Asian countries, but its Pleotropic actions, including anti-amyloid properties has been discovered last decay only.[10,11]

However, because of its potential impact to prevent and treat a wide spectrum of incurable and chronic diseases, nowadays Cur is globally accepted as one of the wonder drug for future.[7] For example, recent research demonstrated that Cur can be used for Alzheimer's, Parkinson's, Huntington's, prion's diseases, multiple sclerosis, schizophrenia, depression, epilepsy, cerebral ischemia, and brain tumor.[7,8,11,14–16] It has been reported to reduce plaque burden and improve cognitive functions in mouse model of AD, and protected against Aβ-toxicity in vitro and *in vivo*.[7,11,24,27] Despite strong evidence supporting the roles of Cur in inhibition of amyloid pathology in different brain diseases, its drug target is unclear. Further, how Cur can reduce these protein aggregates is poorly understood. However, we know that as a potent antioxidant, it can reduce oxidative stress, one of the leading causes of neuronal cell death noted in different brain disease.[27] Similarly, neuro-inflammation plays a critical role

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in neurodegenerative disease pathogenesis, and as a potent anti-inflammatory agent, Cur can decline inflammation, thus prevent further pathogenesis.[27] Furthermore, its preferential binding towards amyloid proteins and inhibition of their further aggregation could be the principal mechanism for an effective therapeutics to prevent neurodegeneration.[10,11] Not only that, Cur also decreases tau protein aggregation; reduce soluble tau in human tau transgenic (HtauTg) mouse model.[24] Another promising mechanism recently we observed is that it can regulate a common endogenous protein clearance pathway, such as the molecular chaperones or heat shock protein (HSP).[8,24] Endogenous protein clearance pathway, such as HSPs have significant role in protein folding and maturation, and renaturation of misfolded proteins, thus play pivotal role to remove these aggregated proteins. This essential system is significantly down regulated in different brain diseases.[8,24] Therefore, activation and or restoration of dysfunctional protein clearance pathways in different brain diseases by Cur would be a great strategy to remove the misfolded amyloid protein aggregates, and prevent or delay further neuronal damage in several neurodegenerative diseases.[8]

Conclusion

Protein misfolding and their accumulation inside or outside of neurons are the key pathological feature in several neurodegenerative diseases including Alzheimer's, Parkinson's Huntington's and prion diseases. Several drugs, small molecules or natural compound have been investigated to inhibit these misfolded protein aggregations, but none of them are effective. Because of its strong amyloid binding capability, significant inhibitory effects of misfolded protein aggregation, and restoration of protein clearance pathways, Cur is considered one of the promising natural Polyphenol to combat against several neurodegenerative diseases. It is anticipated that the information provided through this mini review should help to researcher to get a conceptual detail about the Pleotropic actions of Cur for neurodegenerative diseases therapy

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Conflict of interest

Author declares that there is no conflict of interest.

References

1. Selkoe DJ. Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases. *Nat Cell Biol*. 2004;6(11):1054–1061.
2. Amor S, Puentes F, Baker D, et al. Inflammation in neurodegenerative diseases. *Immunology*. 2010;129(2):154–169.
3. Bredesen DE, Rao RV, Mehlen P. Cell death in the nervous system. *Nature*. 2006;443(7113):796–802.
4. Dias VE, Junn, Mouradian MM. The role of oxidative stress in Parkinson's disease. *J Parkinsons Dis*. 2013;3(4):461–491.
5. Caballol N, Marti MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. *Mov Disord*. 2007;17:S358–S366.
6. Frautschy SA, Cole GM. Why pleiotropic interventions are needed for Alzheimer's disease. *Mol Neurobiol*. 2010;41(2–3):392–409.
7. Hu S, Maiti P, Ma Q, et al. Clinical development of curcumin in neurodegenerative disease. *Expert Rev Neurother*. 2015;15(6):629–637.
8. Maiti P, Manna J, Veleri S, et al. Molecular chaperone dysfunction in neurodegenerative diseases and effects of curcumin. *Biomed Res Int*. 2014;2014:495091.
9. Prasad S, Aggarwal BB. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: Benzie IFF, Wachtel-Galor S, editors. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd ed. Boca Raton (FL): CRC Press; 2011.
10. Ono K, Hasegawa K, Naiki H, et al. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils *in vitro*. *J Neurosci Res*. 2004;75(6):742–750.
11. Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. *J Biol Chem*. 2005;280(7):5892–5901.
12. Allen SJ, Watson JJ, Shoemark DK, et al. GDNF, NGF and BDNF as therapeutic options for neurodegeneration. *Pharmacol Ther*. 2013;138(2):155–175.
13. Garcia-Alloza M, Borrelli LA, Rozkalne A, et al. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. *J Neurochem*. 2007;102(4):1095–1104.
14. Singh PK, Kotia V, Ghosh D, et al. Curcumin modulates alpha-synuclein aggregation and toxicity. *ACS Chem Neurosci*. 2013;4(3):393–407.
15. Hickey MA, Zhu C, Medvedeva V, et al. Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease. *Mol Neurodegener*. 2012;7:12.
16. Hafner-Bratkovic I, Gaspersic J, Smid LM, et al. Curcumin binds to the alpha-helical intermediate and to the amyloid form of prion protein - a new mechanism for the inhibition of PrP(Sc) accumulation. *J Neurochem*. 2008;104(6):1553–1564.
17. Thompson LM. Neurodegeneration: a question of balance. *Nature*. 2008;452(7188):707–708.
18. Cannon JR, Greenamyre JT. The role of environmental exposures in neurodegeneration and neurodegenerative diseases. *Toxicol Sci*. 2011;124(2):225–250.
19. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. *Nat Rev Neurosci*. 2003;4(1):49–60.
20. Cardinale AR, Chiesa R, Sierks M. Protein misfolding and neurodegenerative diseases. *Int J Cell Biol*. 2014;2014:217371.
21. Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. *Neurol Clin*. 2007;25(3):577–609.
22. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol*. 2007;8(2):101–112.
23. Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron*. 2014;82(4):756–771.
24. Ma QL, Zuo X, Yang F, et al. Curcumin suppresses soluble tau dimers and corrects molecular chaperone, synaptic, and behavioral deficits in aged human tau transgenic mice. *J Biol Chem*. 2013;288(6):4056–4065.
25. Ryu EK, Choe YS, Lee KH, et al. Curcumin and dehydrozingerone derivatives: synthesis, radiolabeling, and evaluation for beta-amyloid plaque imaging. *J Med Chem*. 2006;49(20):6111–6119.
26. Lim GP, Chu T, Yang F, et al. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci*. 2001;21(21):8370–8377.
27. Begum AN, Jones MR, Lim GP, et al. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *J Pharmacol Exp Ther*. 2008;326(1):196–208.
28. Mutsuga M, Chambers JK, Uchida K, et al. Binding of curcumin to senile plaques and cerebral amyloid angiopathy in the aged brain of various animals and to neurofibrillary tangles in Alzheimer's brain. *J Vet Med Sci*. 2012;74(1):51–57.

29. Caughey B, Raymond LD, Raymond GJ, et al. Inhibition of protease-resistant prion protein accumulation in vitro by curcumin. *J Virol.* 2003;77(9):5499–5502.

30. Anand P, Thomas SG, Kunnumakkara AB, et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochem Pharmacol.* 2008;76(11):1590–1611.

31. Gibson SA, Gao GD, McDonagh K, et al. Progress on stem cell research towards the treatment of Parkinson's disease. *Stem Cell Res Ther.* 2012;3(2):11.

32. Avci G, Kadioglu H, Sehirli AO, et al. Curcumin protects against ischemia/reperfusion injury in rat skeletal muscle. *J Surg Res.* 2012;172(1):e39–e46.

33. dos Santos Jaques JA, Ruchel JB, Schlemmer KB, et al. Effects of curcumin on the activities of the enzymes that hydrolyse adenine nucleotides in platelets from cigarette smoke-exposed rats. *Cell Biochem Funct*. 2011;29(8):630–635.

34. Di Silvestro RA, Joseph E, Zhao S, et al. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr J*. 2012;11:79.

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