About OMICS Group

OMICS Group is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Apolipoprotein E4 Mediated Targeting of Blood Brain Barrier Using Nano-Micellar Metal Chelators for Treatment of Alzheimer's Disease

Assist. Prof. Dr. Fatemeh Bahadori

What is Alzheimer's disease (AD)?

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills.

Although the risk of developing AD increases with age – in most people with AD, symptoms first appear after age 60 – AD is not a part of normal aging. It is caused by a fatal disease that affects the brain.

Alzheimer's Disease

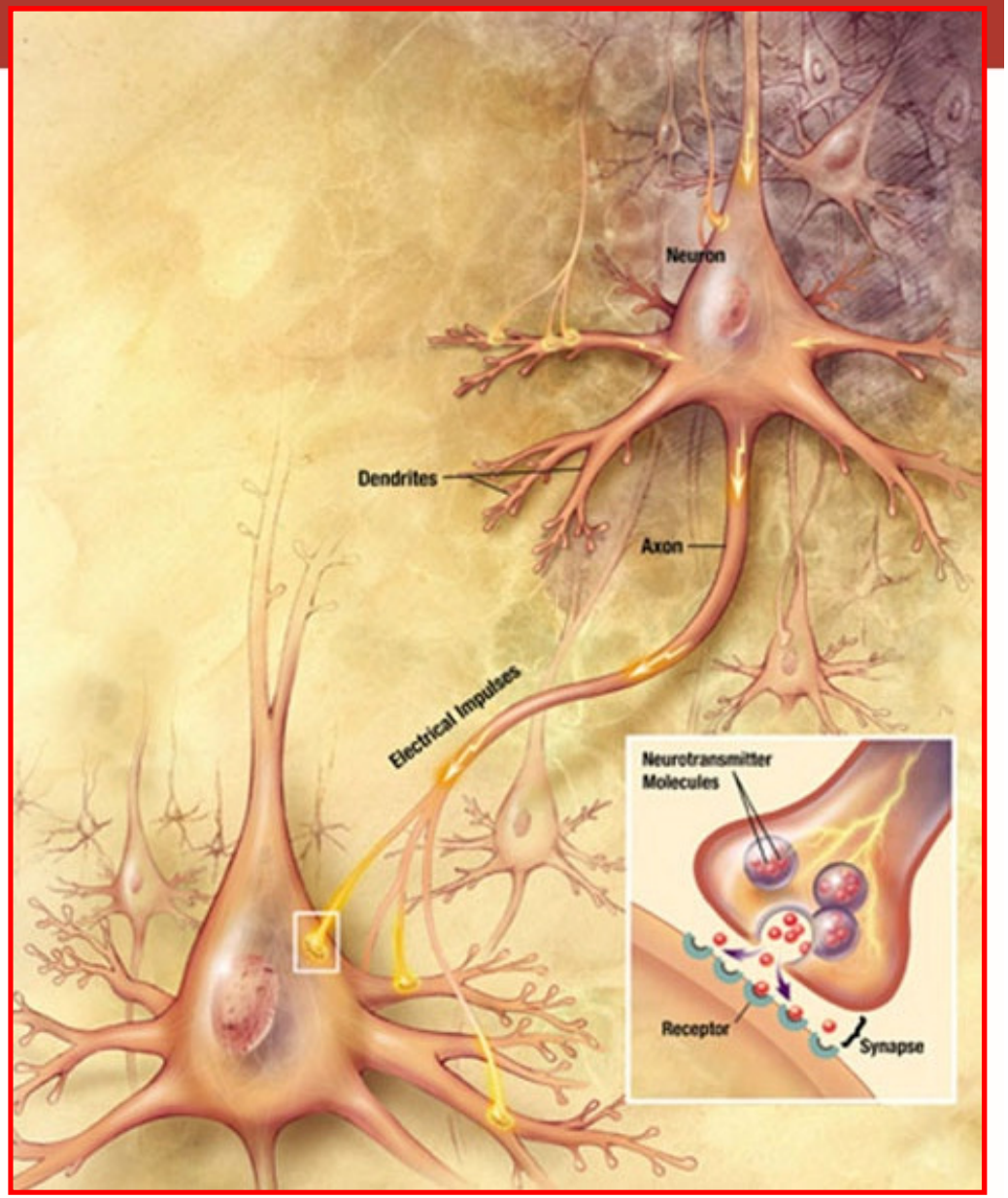
- AD is the most common cause of dementia among people age 65 and older.
- Scientists estimate that around 4.5 million people now have AD.
- For every 5-year age group beyond 65, the percentage of people with AD doubles.

- By 2050, 13.2 million older people are expected to have AD if the current numbers hold and no preventive treatments become available.

Inside the Human Brain

Neurons

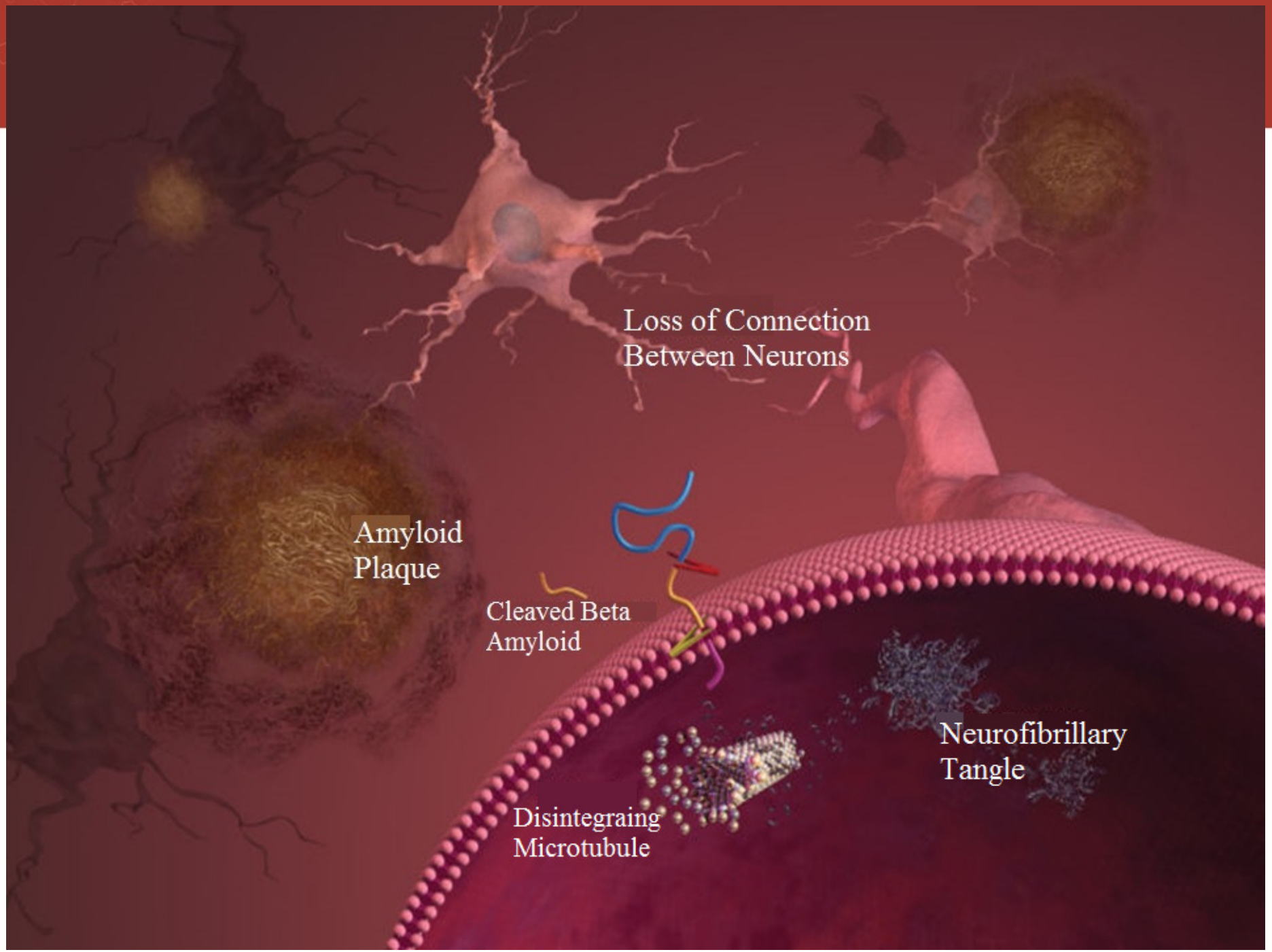
- The brain has billions of neurons, each with an axon and many dendrites.
- To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.



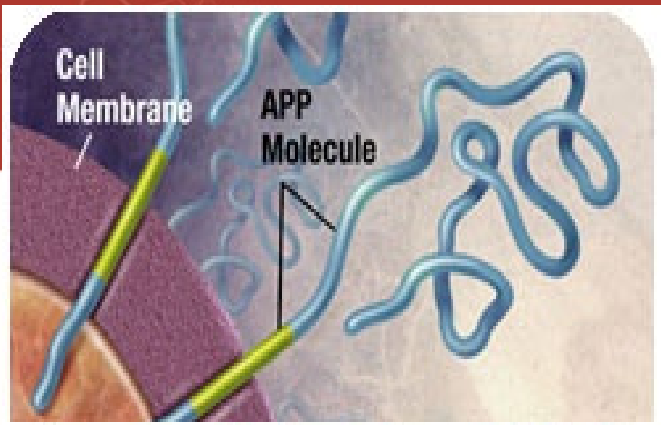
Plaques and Tangles: The Hallmarks of AD

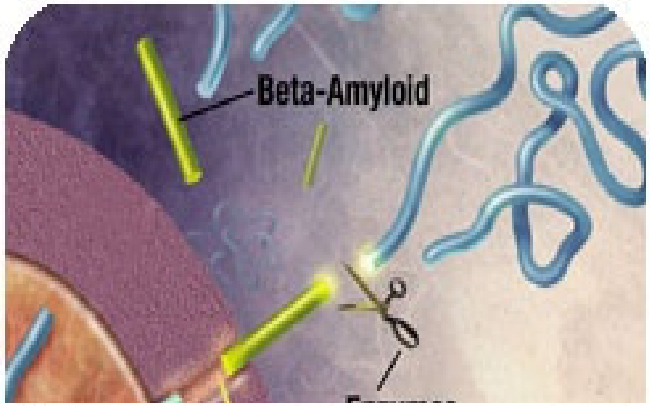
The brains of people with AD have an abundance of two abnormal structures:

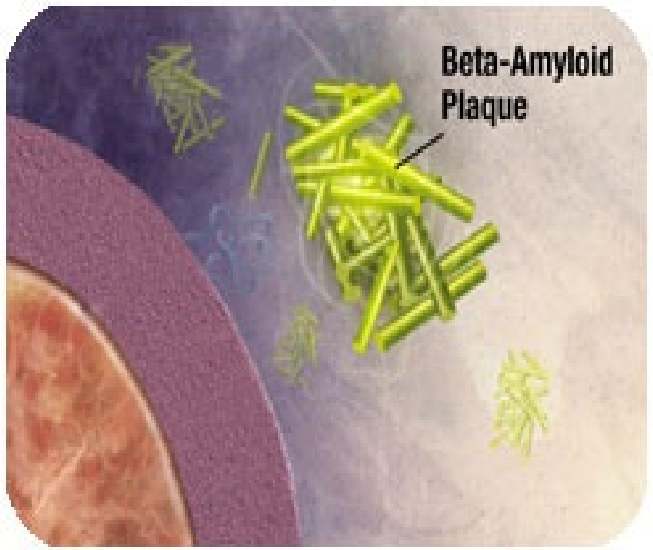
- beta-amyloid plaques, which are dense deposits of protein and cellular material that accumulate outside and around nerve cells
- neurofibrillary tangles, which are twisted fibers that build up inside the nerve cell


Loss of Connection
Between Neurons
Amyloid
Plaque
Cleaved Beta
Amyloid
Neurofibrillary
Tangle
Disintegraing
Microtubule

Beta-amyloid Plaques





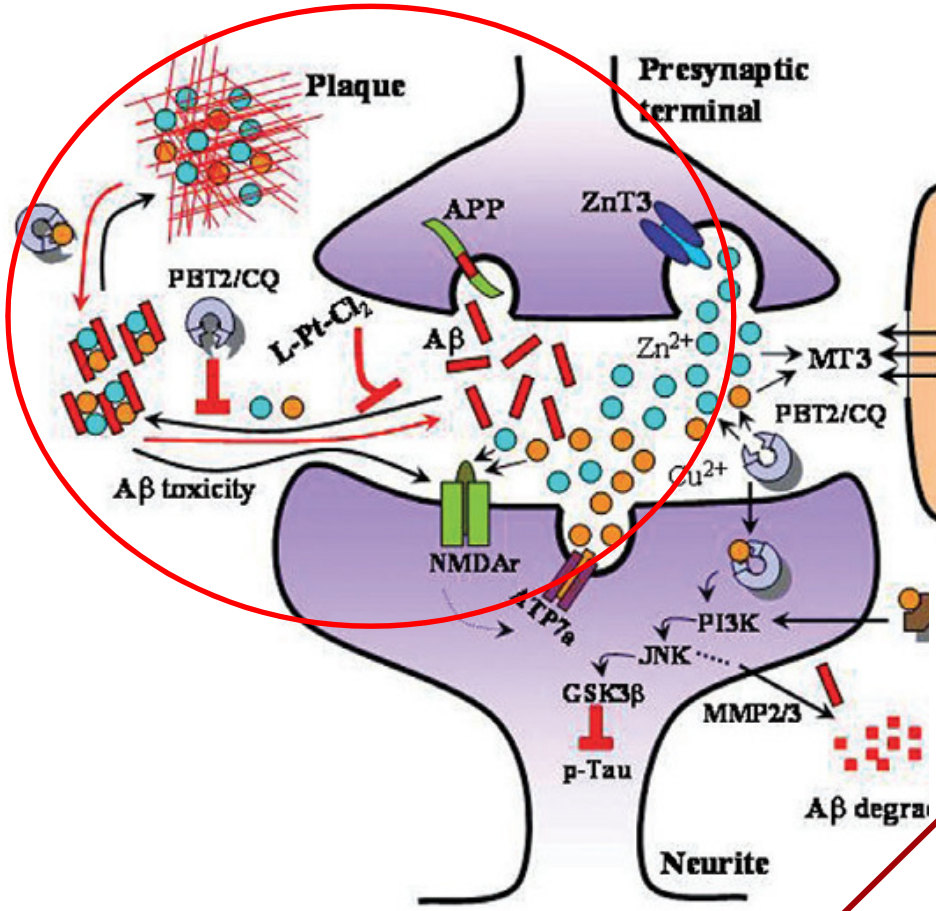


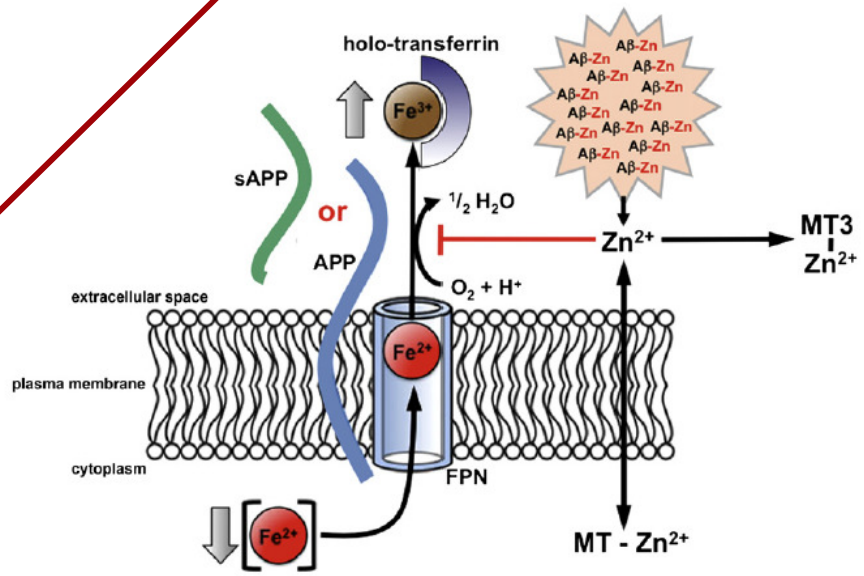
Amyloid precursor protein (APP) is the precursor to amyloid plaque.

1. APP sticks through the neuron membrane.
2. Enzymes cut the APP into fragments of protein, including beta-amyloid.
3. Beta-amyloid fragments come together in clumps to form plaques.

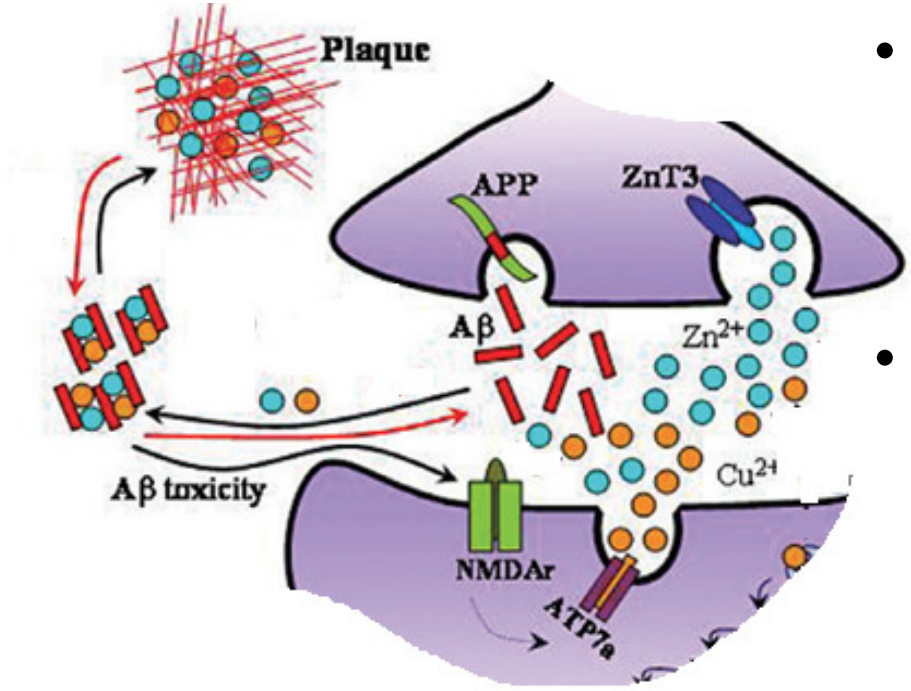
In AD, many of these clumps form, disrupting the work of neurons. This affects the hippocampus and other areas of the cerebral cortex.

Alzheimer's Disease





Aβ is a bi valent metal depot



- Zn at concentrations of 300 nM can rapidly destabilize Aβ and lead to fibril formation
- Free Cu is extremely efficient in the generation of free radicals and has been shown to induce partial aggregation of Aβ
- The increase of Fe in this micro-environment possibly could catalyze further free radical generation, thus leading to an increase in Aβ fibril

Cu (~400 μM)
Zn (~1 mM)
Fe (~1 mM)

There are two logic ways to prevent binding of metals to proteins

- **First of which is to find a compound that has more affinity to proteins than metals. However in practice it is impossible to design such compounds since Aβ is shapeless in the absence of metals.**
- **The second way is to find compounds with affinity to metals.**

Second solution is actually to use the metal chelators in treatment of AD.

- ❑ Although there are number of metal chelators which are used in the treatment of metal deposition disease since long years ago approved by FDA, non of them is suitable to use in the treatment of AD due to their neurotoxicity effect.

- ❑ The more important, all of known metal chelators are hydrophilic which means they are not able to cross Blood Brain Barrier (BBB).

There is currently no cure for most forms of dementia including AD.

Pharmacotherapy is focussed on symptomatic benefit and slowing disease progression, but a number of possible disease modifying and preventive strategies based on current understanding of AD pathophysiology are under investigation.

Curcuma longa

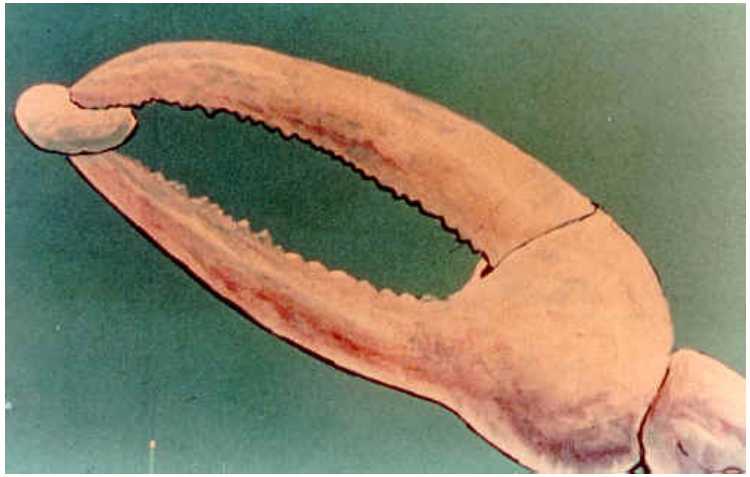
Rosemarinus officanalis

Before the development of modern medicine people relied on a large arsenal of natural remedies for the treatment of CNS related maladies. In western societies, here has been increasing interest in herbal medicines, which are often perceived as a more ‘natural’ and ‘soft’ treatments compared to synthetic drugs.

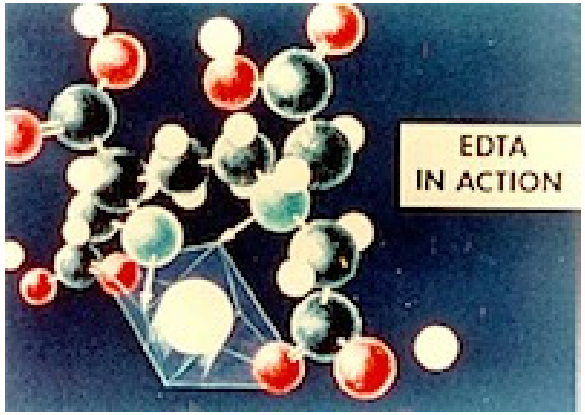
There are very few reports on natural metal chelators and this is where synthetic metal chelators are neurotoxic.

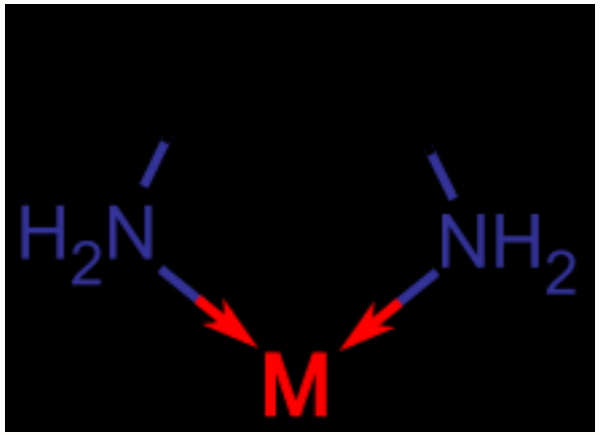
Although there are quit much reports on metal chelating activity of natural sources, almost all of them are based on only chelating Fe^{+2} and very few of them report the chelating activity against all divalent metals: Fe^{+2}, Cu^{+2} and. Zn^{+2}. However latter metal ions are more important in treatment of AD.

The word chelation is derived from Greek χηλή, *chēlē*, meaning "claw"

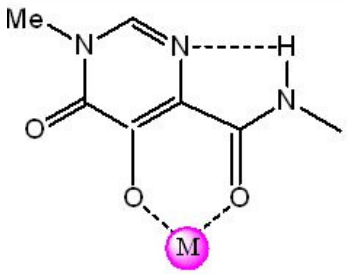


Chemically, the chelating agent is claw shaped and attacks a positively charged metal and surrounds it making it inactive and eventually removes it from the body.

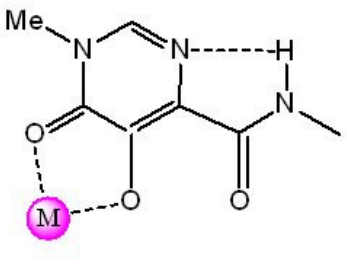




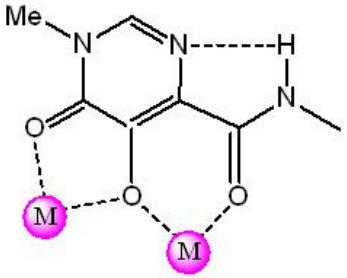
Both synthetic and natural product studies on metal chelators done since now, gave us very precious data about structure-activity relationship of these compounds.



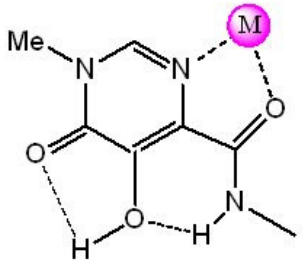
1-a



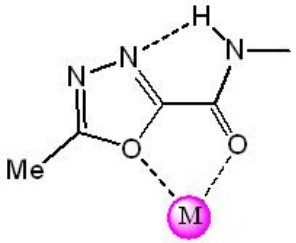
1-b



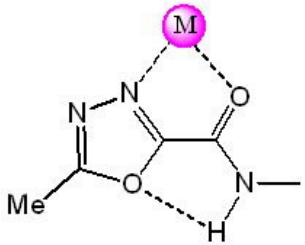
2-a



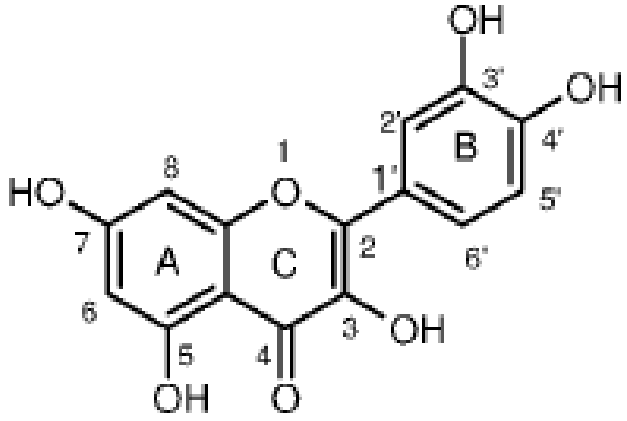
2-b



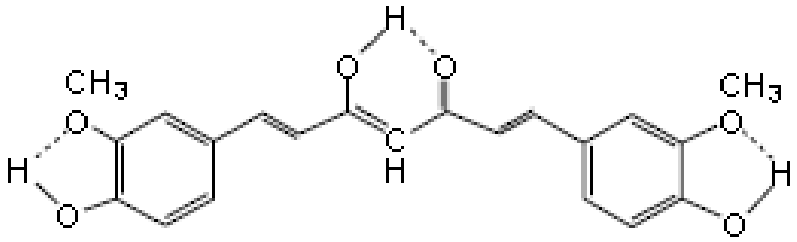
2-c



2-d

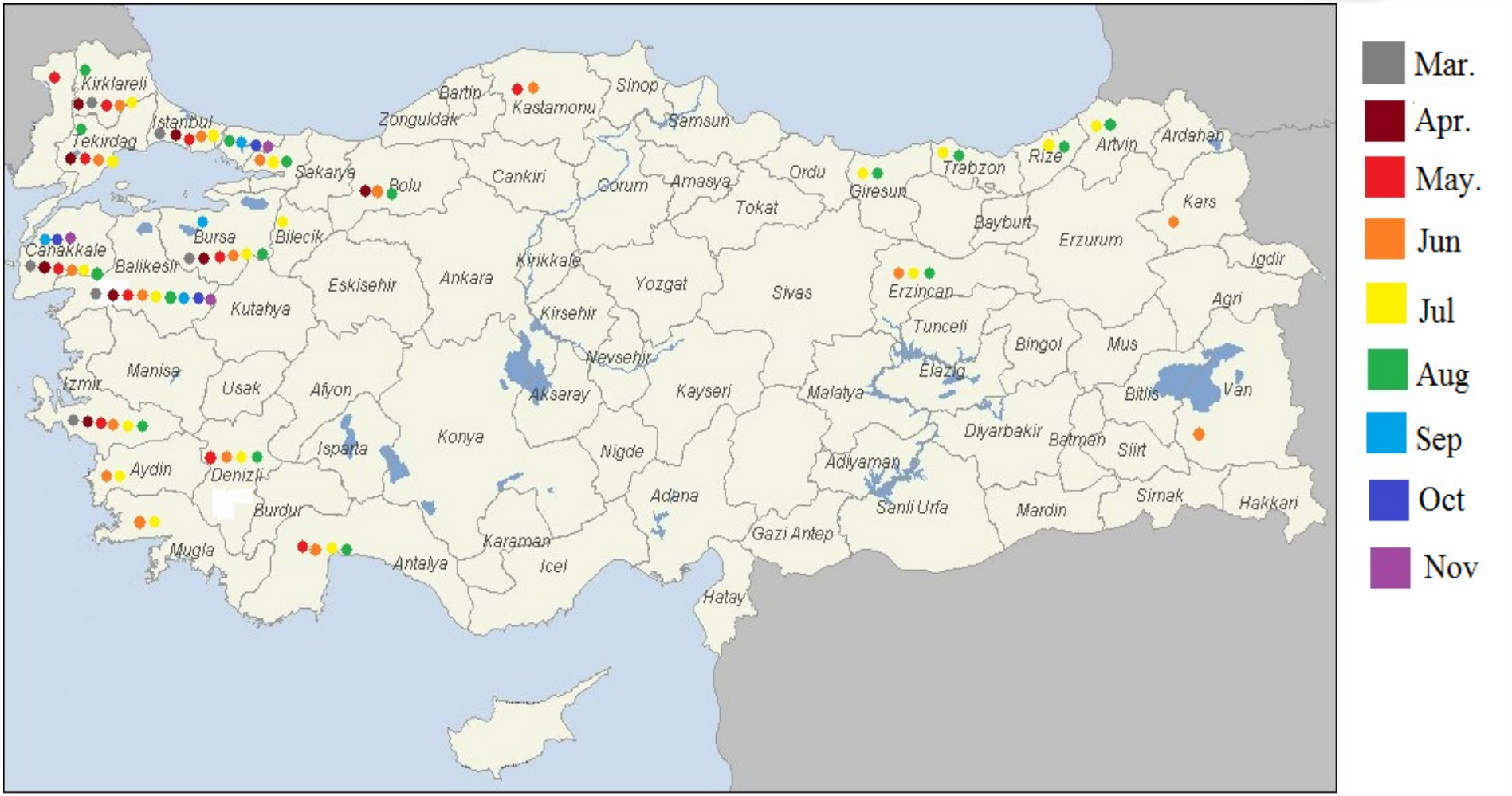


Quercetin



Curcumin

Assist. Prof. Dr. Abdulselam Ertaş (Dicle University, Diyarbakır)



	Extracts	Total Phenolic	Total Flavonoid
Astragalus leporinus	PE:800mg	92	16
	AC:1.3g	92	20
	ME:10g	90	16
	WATER:..	90	11
Astragalus schizopterus	PE:600mg	68	48
	AC:800mg	17	61
	ME:9.1g	46	45
	WATER:...	83	51
Astragalus dissmutus	PE:530mg	110	10
	AC:300mg	110	16
	ME:5g	84	12
	WATER:...	74	10
Centaurea lycopifolia	PE:800mg	125	14
	AC:2.6g	115	17
	ME:9.1g	96	12
	WATER:...	127	12
Centaurea balsamita	PE:650mg	112	11
	AC:5.2g	117	14
	ME:12g	151	15
	WATER:...	205	18
Verbascum pinetorum	PE:500mg	151	28
	AC:1g	586	31
	ME:5g	304	16
	WATER:..	350	25
	U:çokvar	67	11
Verbascum flavidum	PE:290mg	146	47
	AC:450mg	128	66
	ME:5g	232	50
	WATER:...	97	51
Veronica thymodies pseudocier	PE:1.4g	93	46
	AC:1.1g	19	52
	ME:4.3g	248	47
	WATER:...	360	51
Stachys thirkei	PE:9g	146	47
	AC:1.1g	95	56
	ME:3.8g	167	50
	WATER:...	106	53
melissa oficinalis waterbsp altisima	PE:850mg	112	47
	AC:1.4g	118	50
	ME:2.1g	390	48
	WATER:...	317	59
Calystegia silvatica	PE:1.1g	191	14
	AC:1.1g	151	16
	ME1.7g	133	13
	WATER:...	173	24
Hypericum capitatum	PE:4.2g	112	44
	AC:2.1g	65	47
	ME:6g	215	53
	WATER:....	189	50
	U:var		
Sedum sediforme	PE:9g	137	11
	AC:1.1g	254	23
	ME:7.2g	336	17
	WATER:....	185	16
Carderia draba waterbsp draba	PE:700mg	83	47
	AC:700mg	144	61
	ME:1.8g	67	50
	WATER:...	61	50
	U:var		
Carlina corymbosa	PE:2.8g	200	46
	AC:1.1g	88	49
	ME:6g	98	49
	WATER:...	133	52
	U:var		
Onopordum polycephalum	PE:1.8g	148	13
	AC:2.1g	142	18
	ME:4g	117	13
	WATER:...	101	12
	U:var		
Onopordum carduchorum	PE:2.7g	132	11
	AC:1.9g	110	12
	ME:2g	108	11
	WATER:...	146	14
	U:var	67	12
Carduus **pyncephalus waterbsp. abidus**	PE:7.2g	154	11
	AC:3.4g	110	19
	ME:30g	103	12
	WATER:....	562	11
	U:var	65	11
Gundelia tournefortii L. var. *tournefortii*	PE:2g	144	10
	AC:1.8g	202	18
	ME:2.4g	148	16
	WATER:...	153	18
	U:var		
Trifolium angustifolium waterbsp angustifoliu	PE:670mg	123	50
	AC:330mg	114	65
	ME:4.5mg	71	48
	WATER:...	102	49
	U:var		
Scolymus haspanicum	PE:2.4mg	137	11
	AC:1g	105	17
	ME:4.1g	225	14
	WATER:..	144	17
	U:var		
Alcea pallida	PE:1.5g	132	14
	AC:2.1g	175	20
	ME:10g	107	13
	WATER:...	153	12
	U:var		
Alcea apterocarpa	PE:3.5g	125	11
	AC:1g	144	21
	ME:	96	11
	WATER:...	110	11
	U:var		
Alcea setosa	PE:1.2g	149	53
	AC:1.2g	80	46
	ME:2.5g	61	49
	WATER:...	79	49
	U:var		
Alcea hohencharkei	PE:1g	135	50
	AC:800mg	32	65
	ME:3.7g	106	46
	WATER:...	63	46
	U:var		
Malva neglecta **örnek-33**	PE:300mg	90	15
	AC:400mg	91	20
	ME:	68	16
	WATER:...	65	12
	U:var		
Capsela bursa-postaris	PE:1.2g	129	16
	AC:800mg	90	20
	ME:	71	16
	WATER:..	76	14
	U:var		
Achillea cappadocica	PE:800mg	90	47
	AC:1.1g	98	48
	ME:2.8g	102	49
	WATER:..	92	50
	U:yok		
Sideritis libanotica Labill. waterbsp. *Linearis*	PE:600mg	75	46
	AC:	149	56
	ME:3.8g	112	50
	WATER:...	131	49
	U:var		
Anchusa arvensis waterbsp *Orientalis*	PE:800mg	117	18
	AC:300mg	105	28
	ME:2.6g	116	16
	WATER:...	125	13
	U:var		
Tropogon latifolius waterbsp angustifolius	PE:1.5g	153	49
	AC:1.5g	106	49
	ME:2.5g	84	49
	WATER:...	92	47
	U:var		
Achillea wilhemsi	PE:700mg	102	15
	AC:1.7g	85	14
	ME:4.5g	116	18
	WATER:..	126	16
	U:yok		
Silene Compacta	PE:1g	94	48
	AC:1.1g	120	47
	ME:8g	61	46
	WATER:...	77	47
	U:var		
Pulicaria dysenterica	PE:1.2g	137	48
	AC:	123	56
	ME:6g	370	52
	WATER:..	120	49
	U:var		
Ballota nigra waterbsp. Anatolia	PE:250mg	131	16
	AC:1g	114	32
	ME:	96	26
	WATER:...	113	13
	U:var		
Malvella sharardiana	PE:500mg	116	16
	AC:600mg	96	21
	ME:	87	16
	WATER:...	85	12
	U:var		

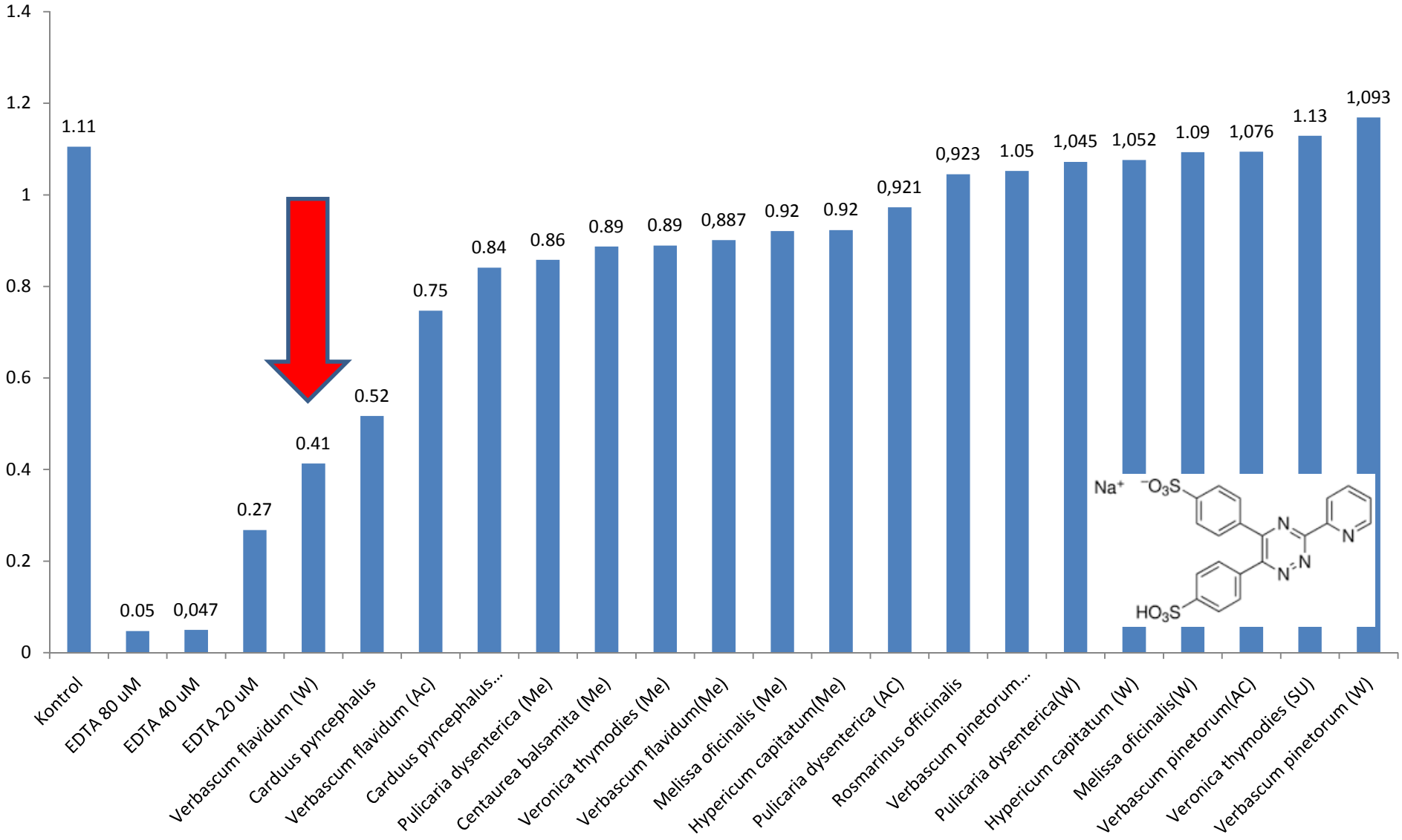
Studied plants consisted of

- *Astragalus leporinus,*
- *Astragalus schizopterus,*
- *Astragalus distinctissimus,*
- *Centaurea lycopifolia,*
- *Centaurea balsamita,*
- *Centaurea Iberica,*
- *Centaurea diffusa,*
- *Centaurea urvillei* subsp. *urvillei,*
- *Verbascum flavidum,*
- *Stachys thirkei,*
- *Melissa officinalis* subsp. *officiinalis,*

,

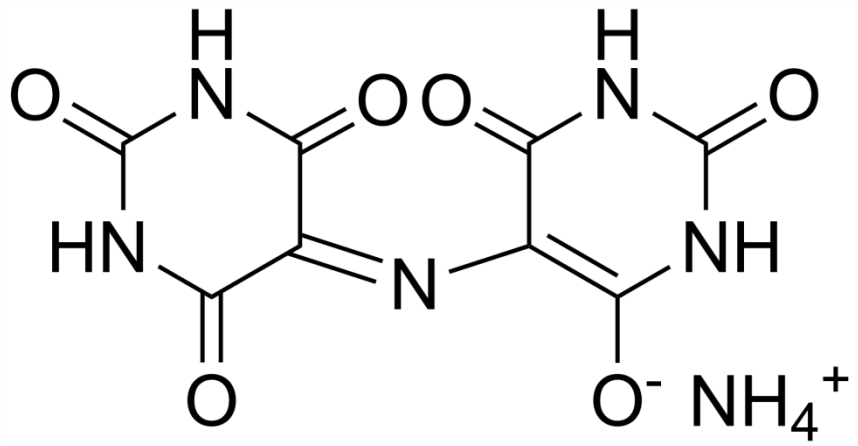
- *Calystegia silvatica,*
- *Hypericum capitatum,*
- *Hypericum triquetrifolium,*
- *Sedum sediforme,*
- *Cardaria draba* subsp. *draba,*
- *Carlina corymbosa,*
- *Pulicaria dysenterica,*
- *Onopordum polycephalum,*
- *Onopordum carduchorum*
- *Gundelia tournefortii L. var. tournefortii,*
- *Scolymus hispanicus,*
- *Rosmarinus officinalis*

Fe^{+2} Chelating was measured using Decker and Welch (1990)'s method with basic modifications to correct the deviations raised from extract's colour



The extracts were added to a solution of 2 mM FeCl2 (100 lL). The reaction was initiated by the addition of 5 mM ferrozine (200 lL). The mixture was shaken vigorously and left standing at room temperature for 10 min. After the mixture reached equilibrium, the absorbance was determined at 562 nm. EDTA was used as a reference compound.

Cu^{+2} and Zn^{+2} Chelating Activity



Murexide is used in analytical chemistry as a complexometric indicator for complexometric titrations and as a colorimetric reagent for measurement of calcium and rare earth metals

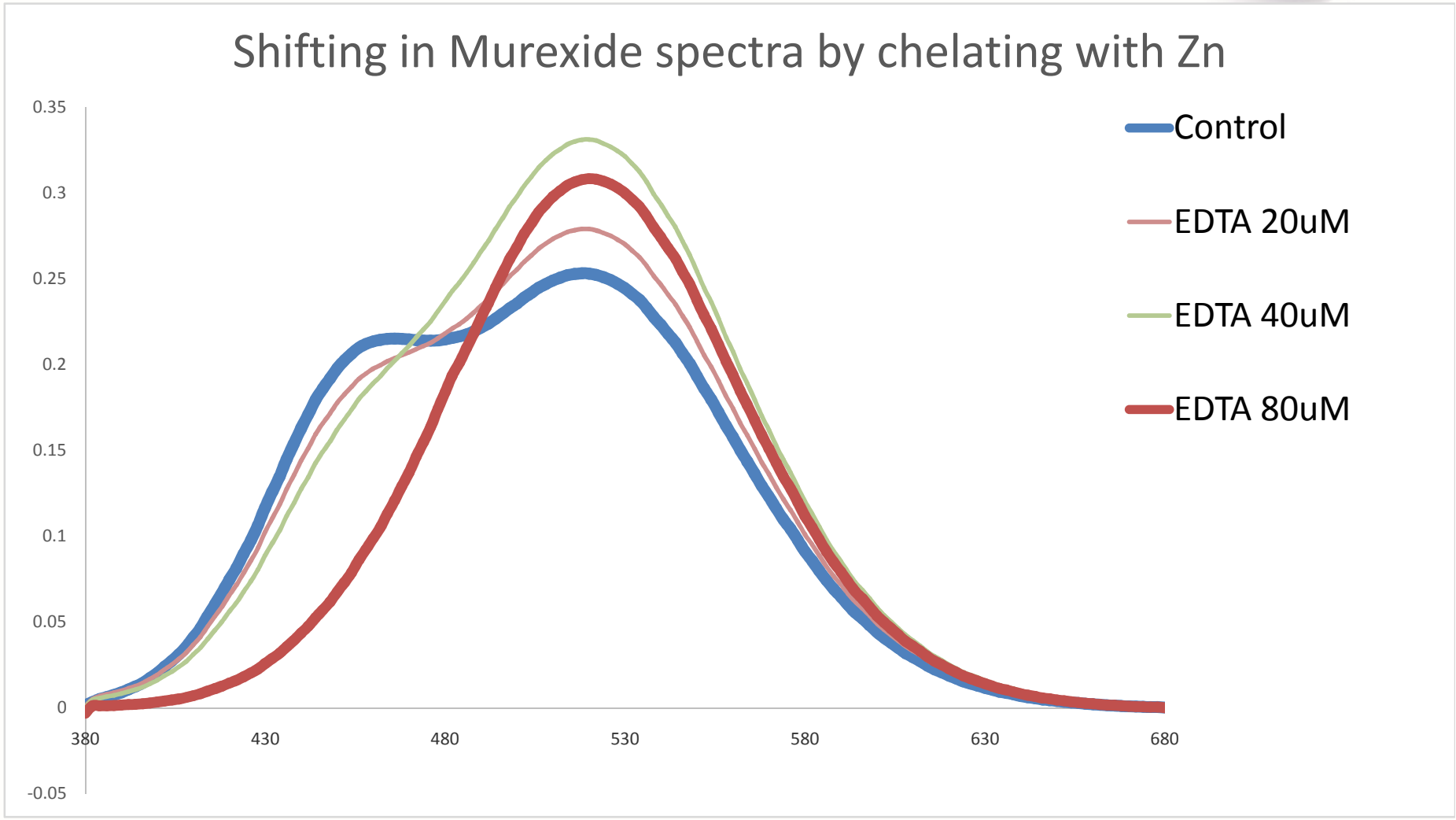
Cu^{+2} Chelating Activity

Rosemarinus officanalis

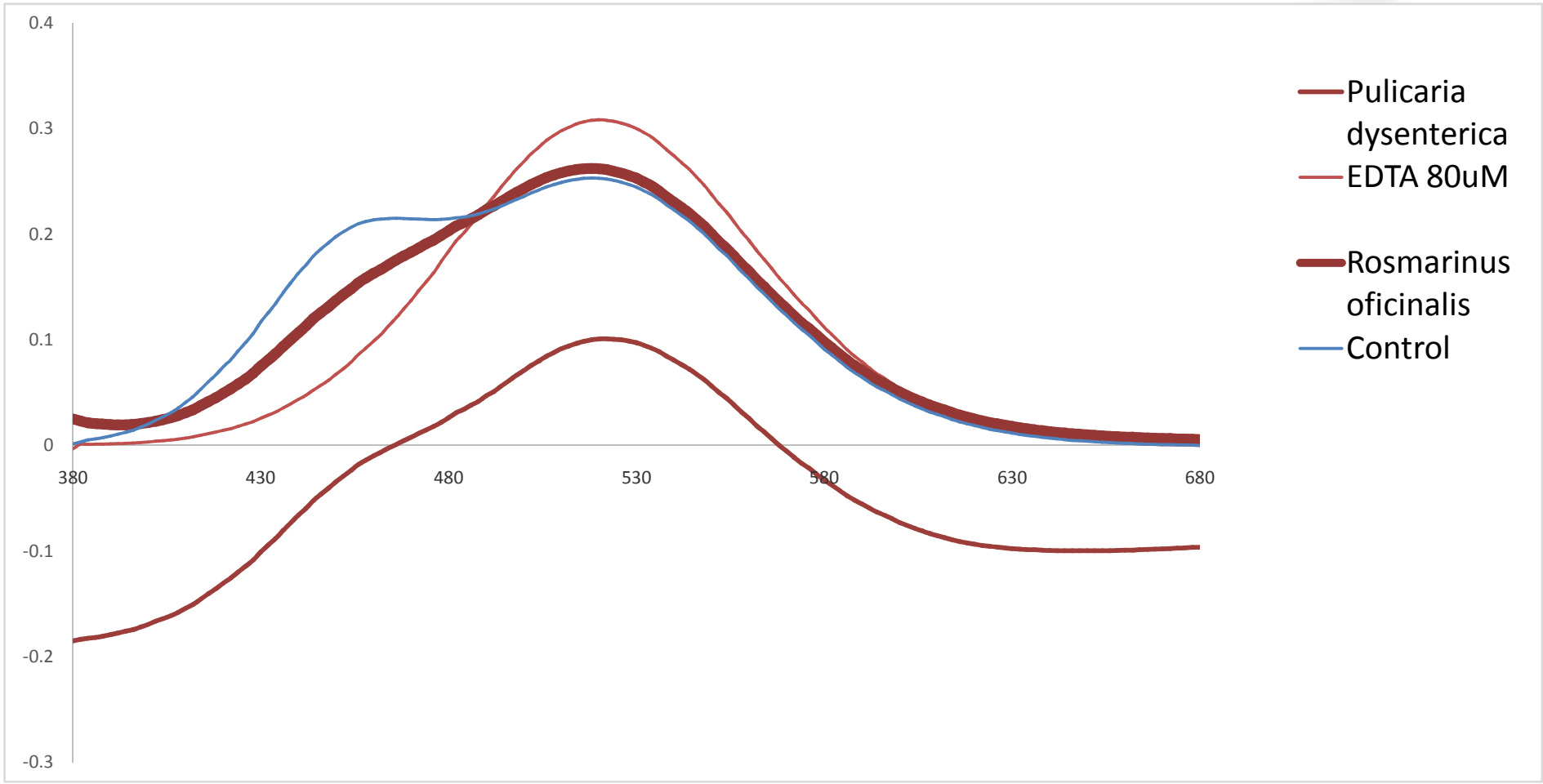
Shifting of murexide absorption peak from 522 to 475 nm upon chelating with Cu^{+2} ions.
A new method for evaluating metal chelating activity of plant extracts

Cu^{+2} Chelating Activity of *Verbascum flavidum*

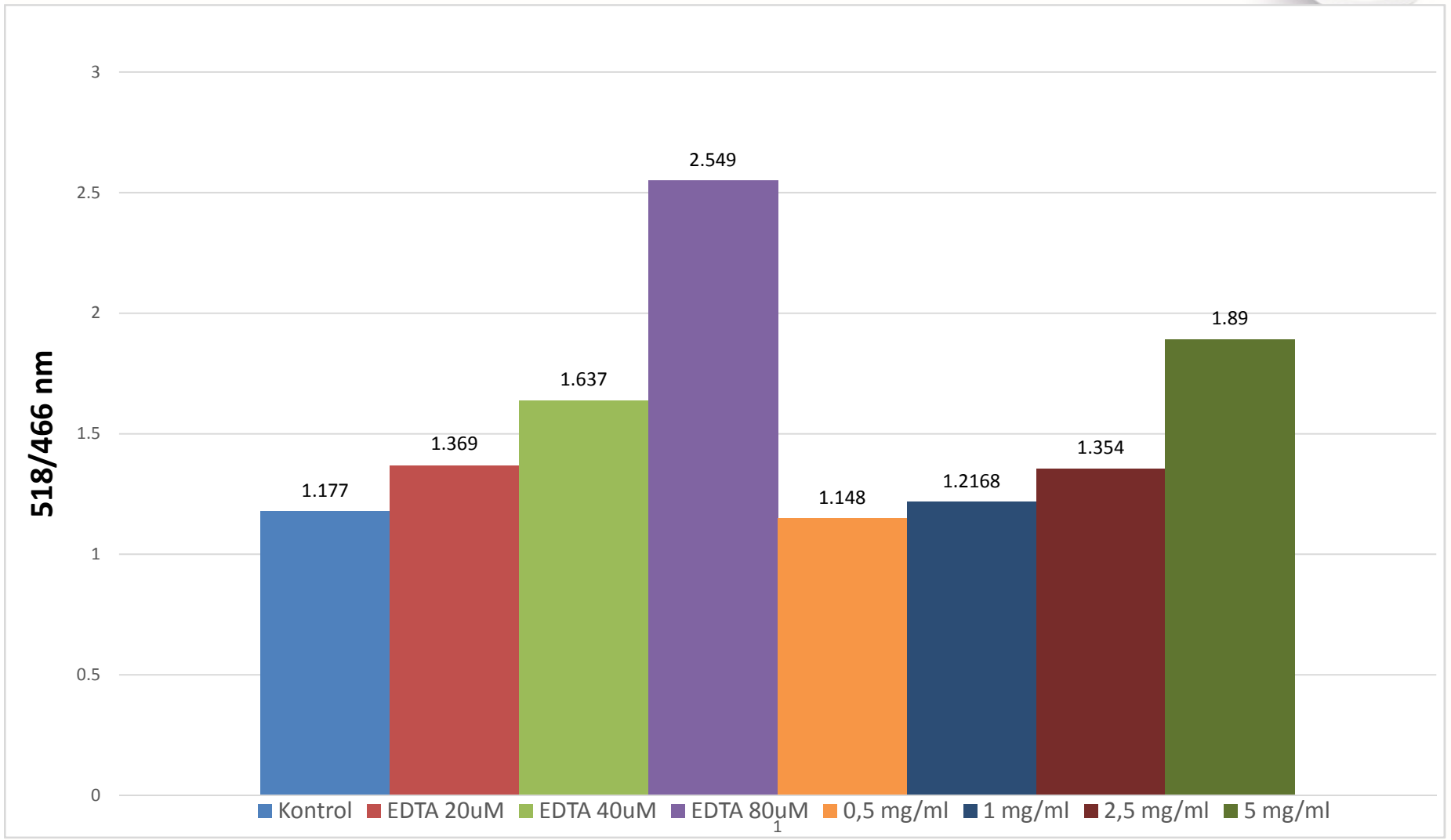
Measuring Zn+2 Chelating activity of plant extracts by calculating peak intensity at 518/466



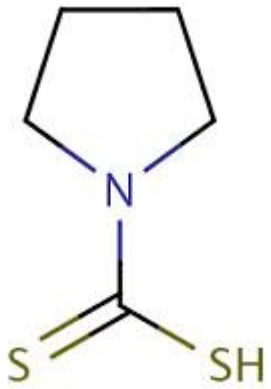
Zn^{+2} Chelating activity of plant extracts



Zn^{+2} Chelating Activity of *Verbascum flavidum*



PDTC and Alzheimer



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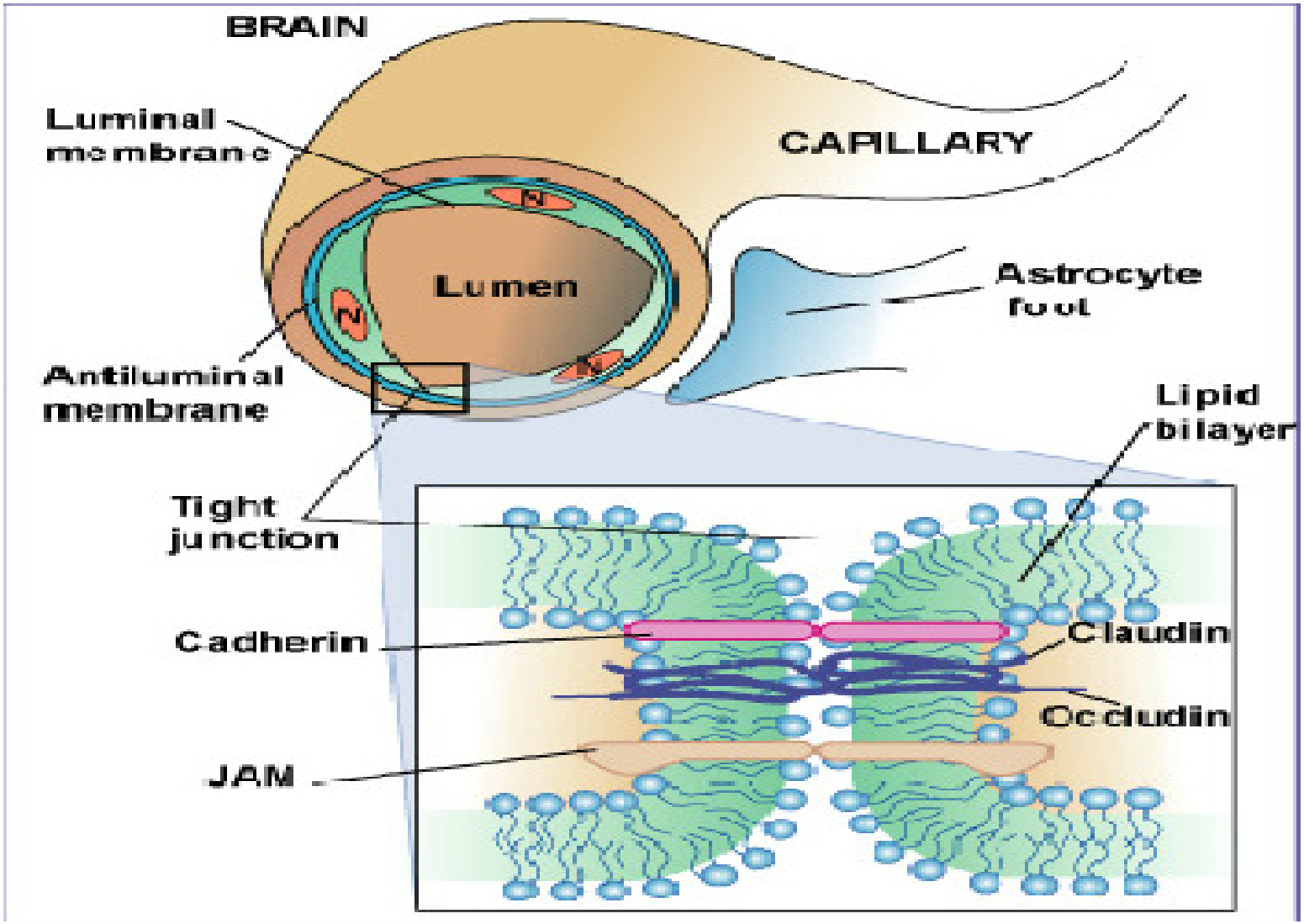
Neurobiology of Disease

Pyrrolidine Dithiocarbamate Activates Akt and Improves Spatial Learning in APP/PS1 Mice without Affecting β-Amyloid Burden

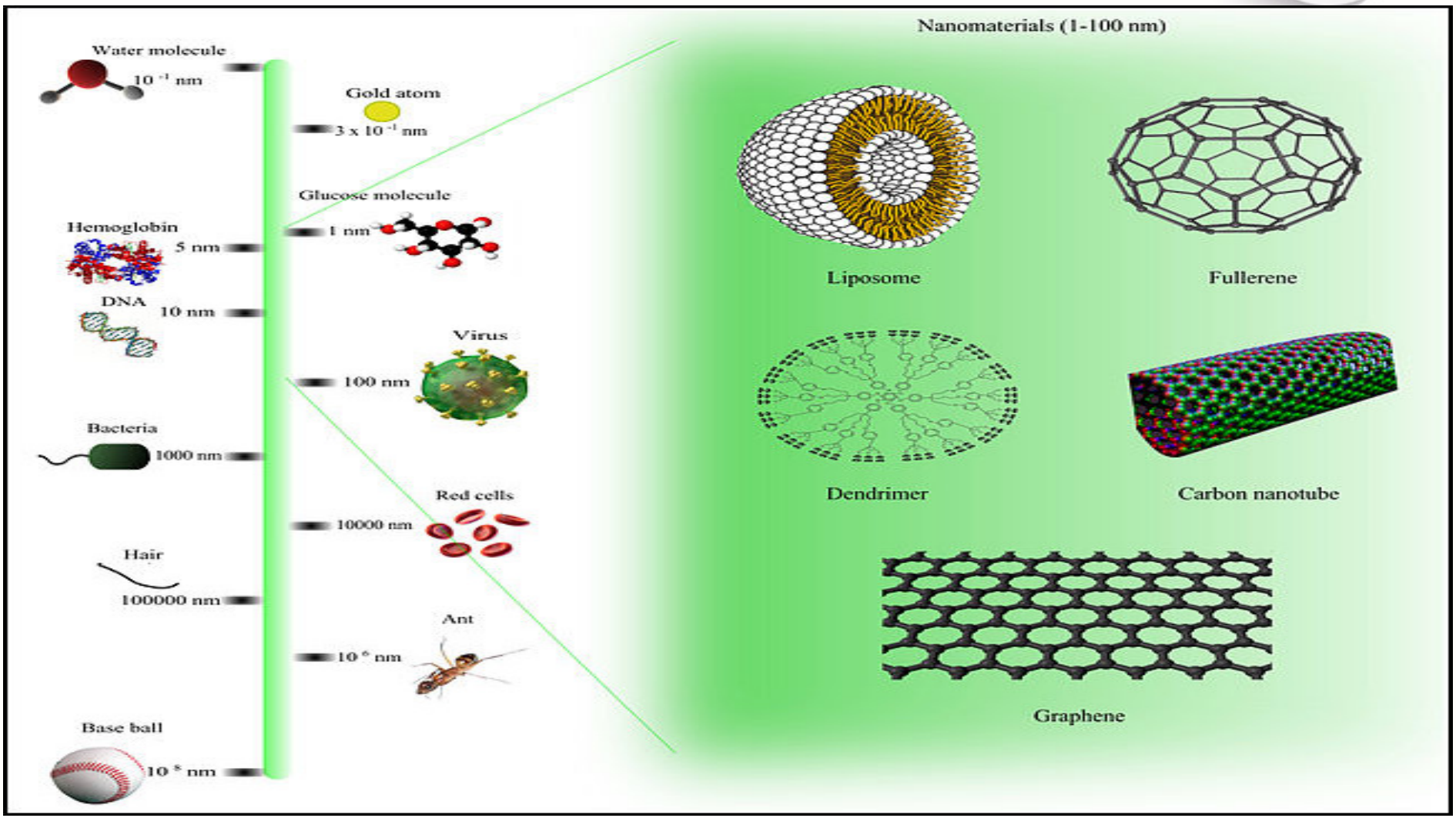
Tarja M. Malm,[1] Henna Iivonen,[1] Gundars Goldsteins,[1] Velta Keksa-Goldsteine,[1] Toni Ahtoniemi,[1] Katja Kanninen,[1] Antero Salminen,[2,4] Seppo Auriola,[3] Thomas Van Groen,[2] Heikki Tanila,[1,4] and Jari Koistinaho[1,5]

[1]A. I. Virtanen Institute for Molecular Sciences and Departments of [2]Neuroscience and Neurology and [3]Pharmaceutical Chemistry, University of Kuopio, and Departments of [4]Neurology and [5]Oncology, Kuopio University Hospital, FIN-70211 Kuopio, Finland

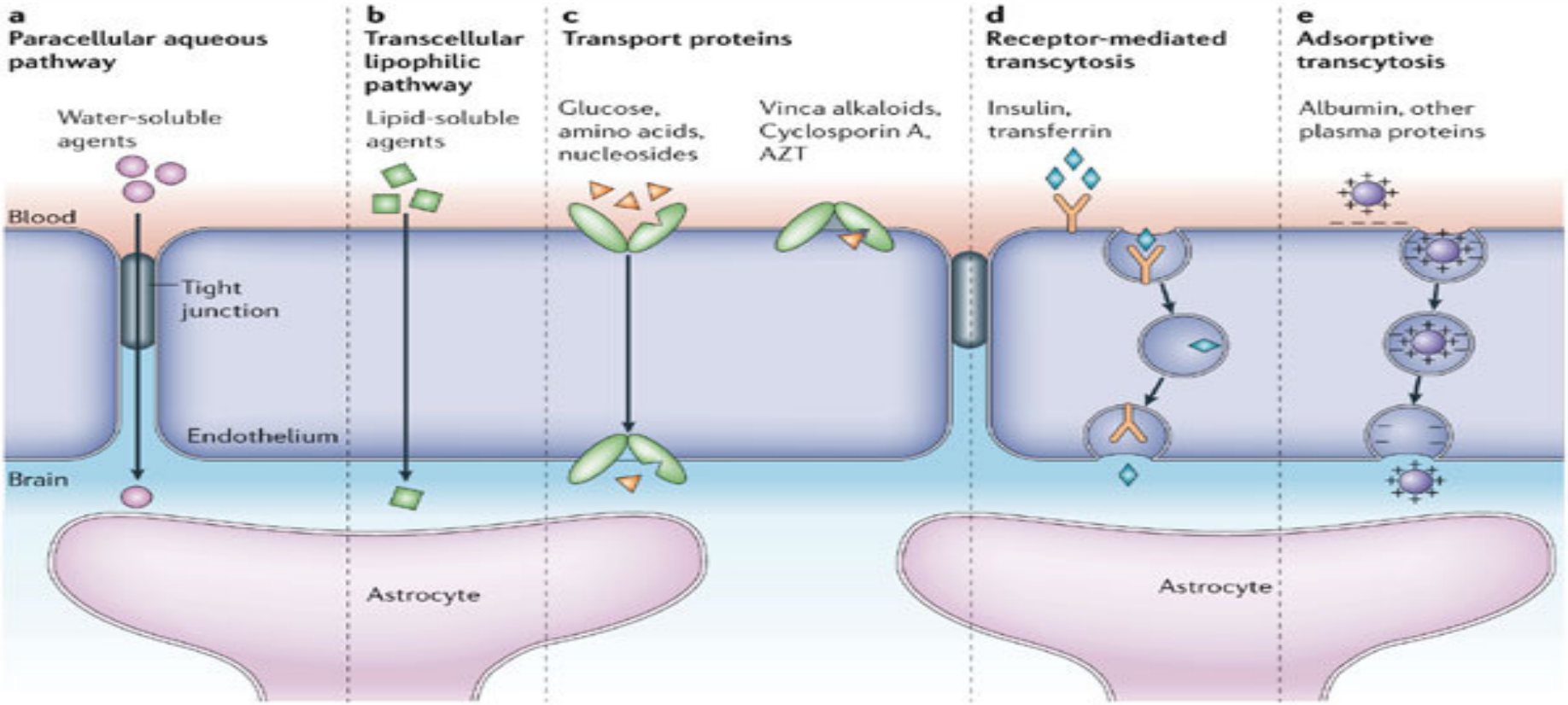
Tight Junctions in Blood Brain Barrier



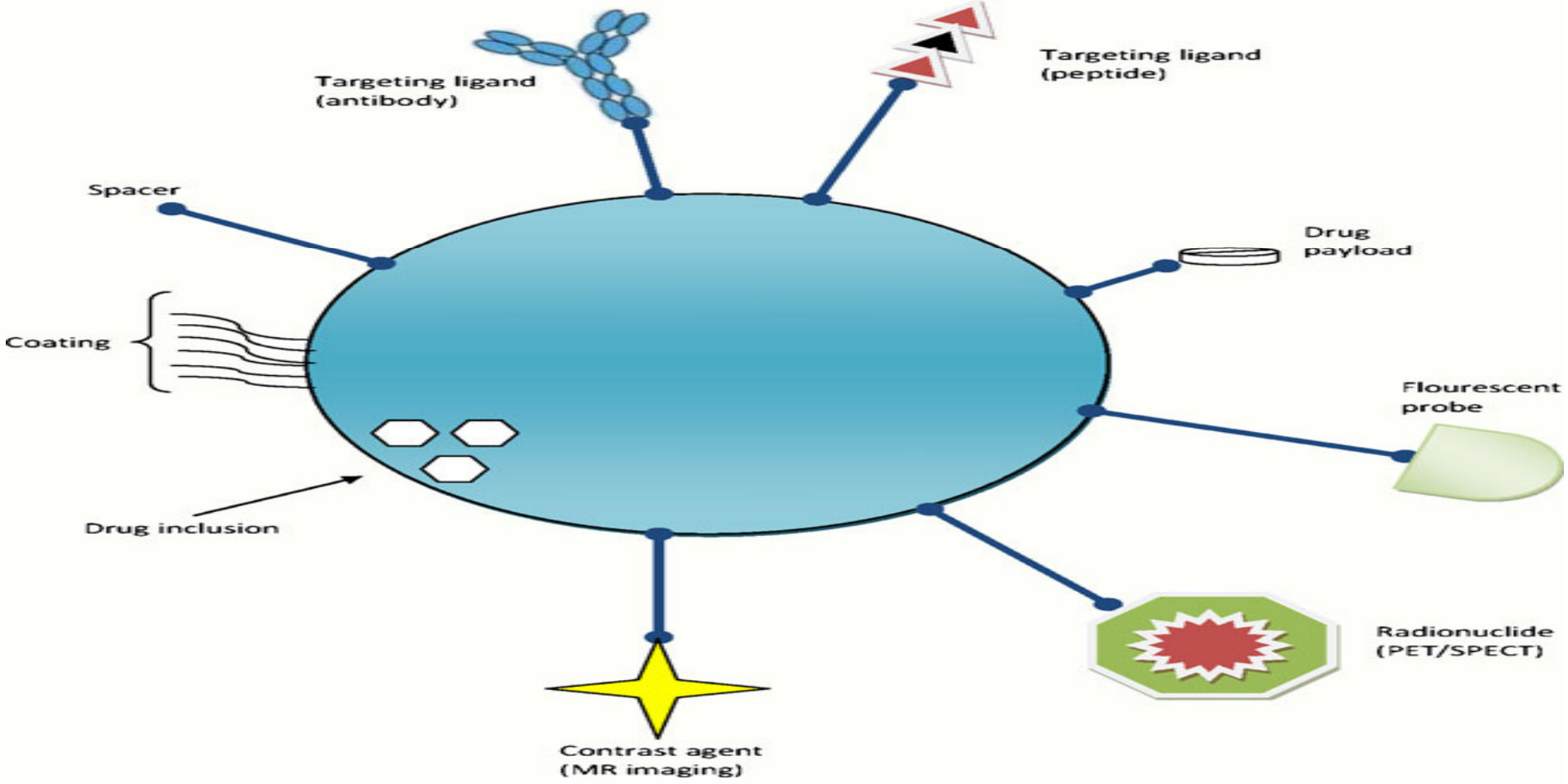
Nano Drug Delivery Systems



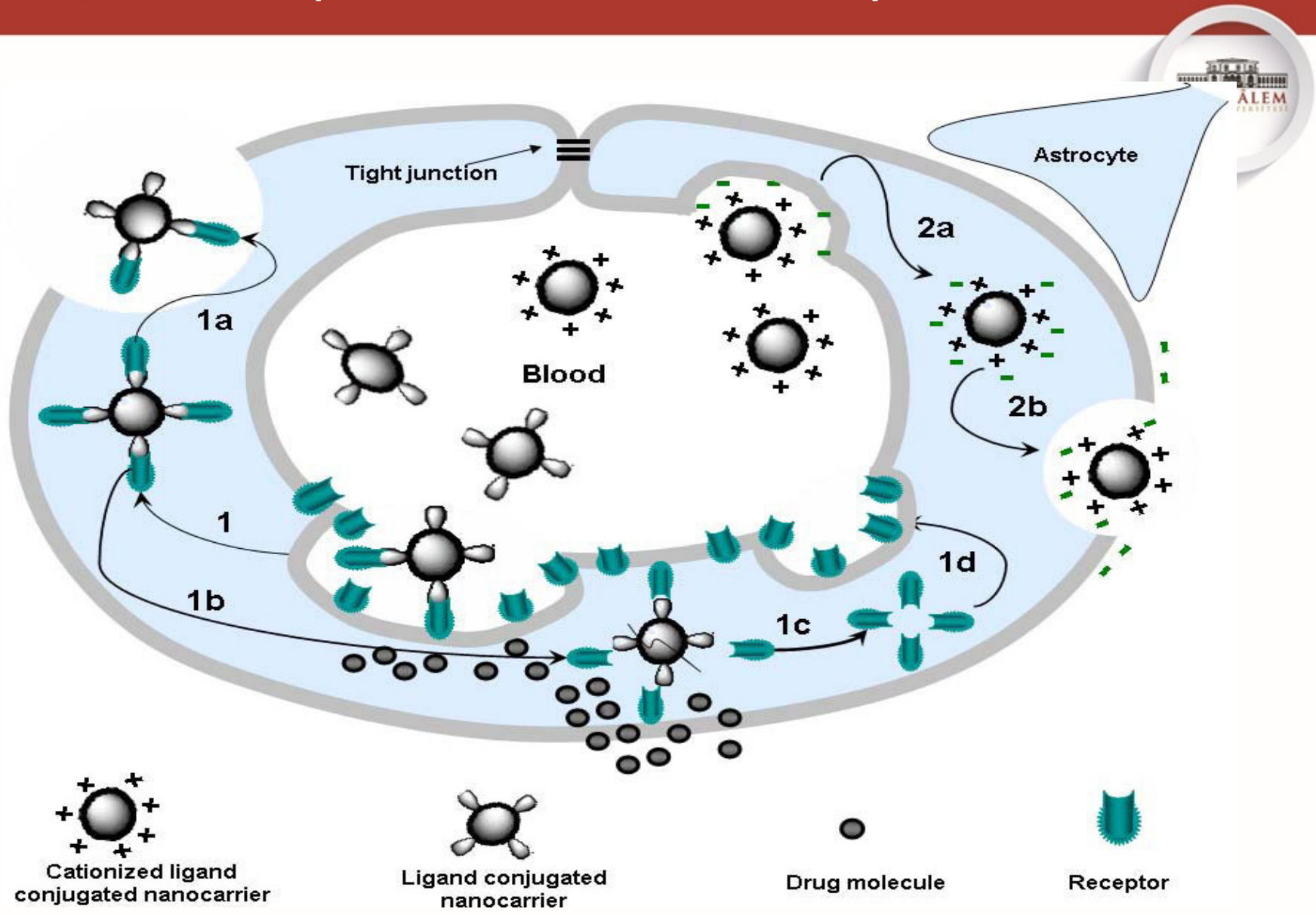
Passing Trough BBB



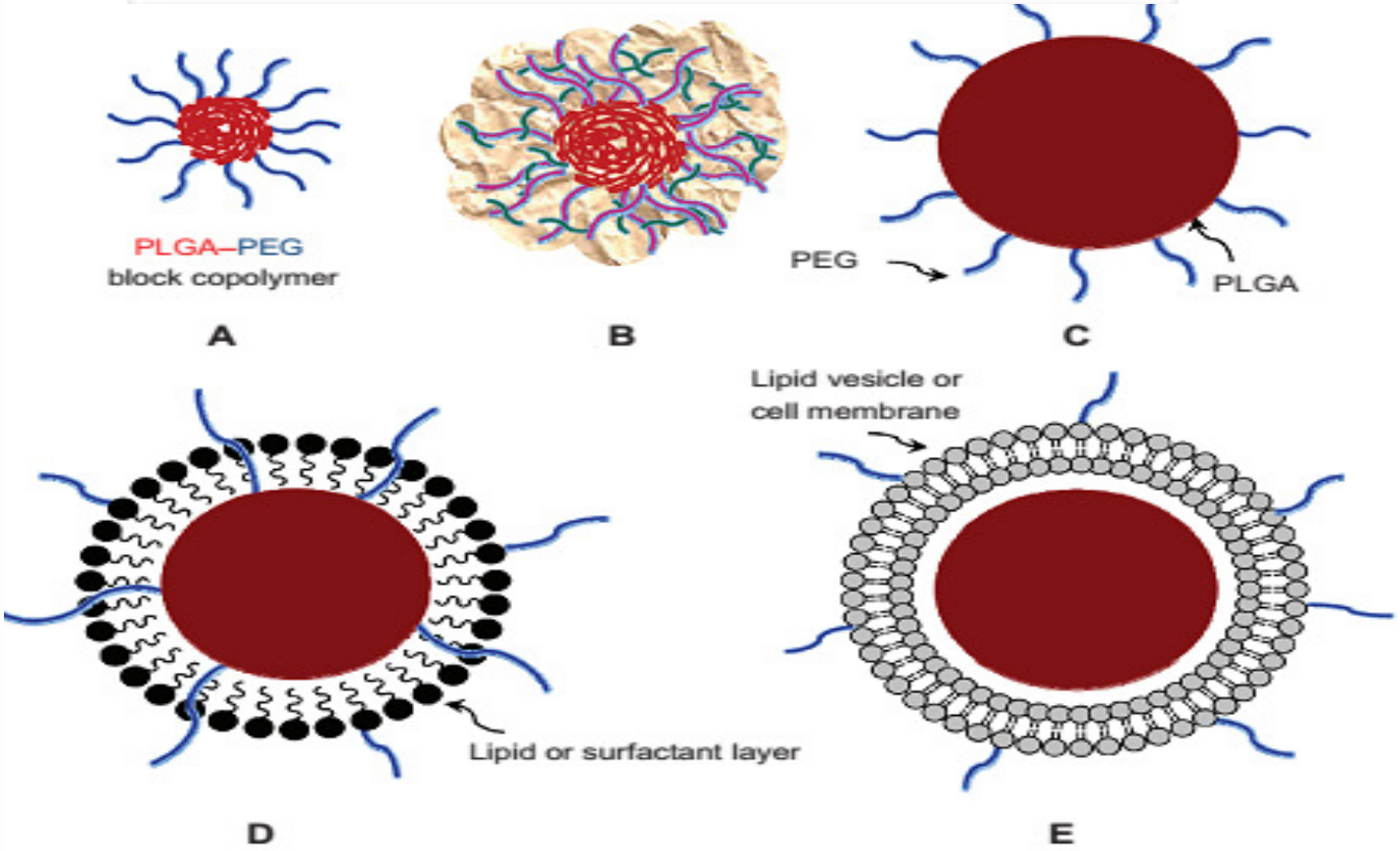
Surface modification of Nano Drug Delivery Systems



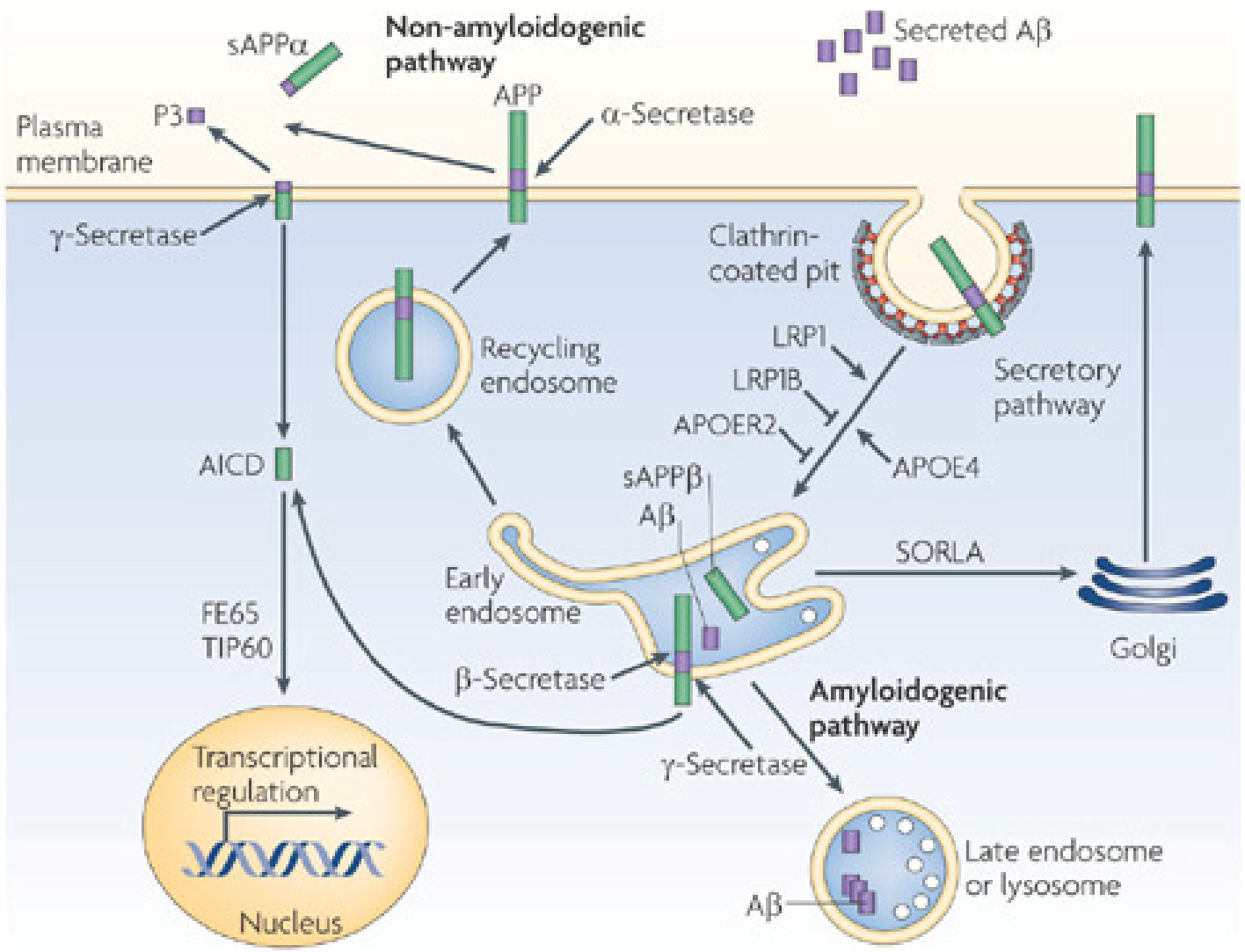
Receptor Mediated Endocytosis



Biodegradable Poly Lactide-co-Glycolide (PLGA, 50:50)



Apolipoprotein E-4 and its Role in Alzheimer's Disease



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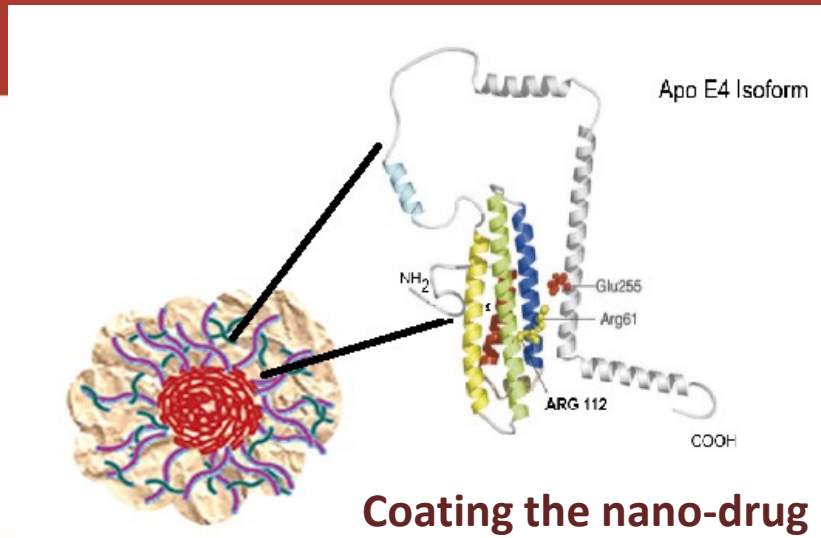
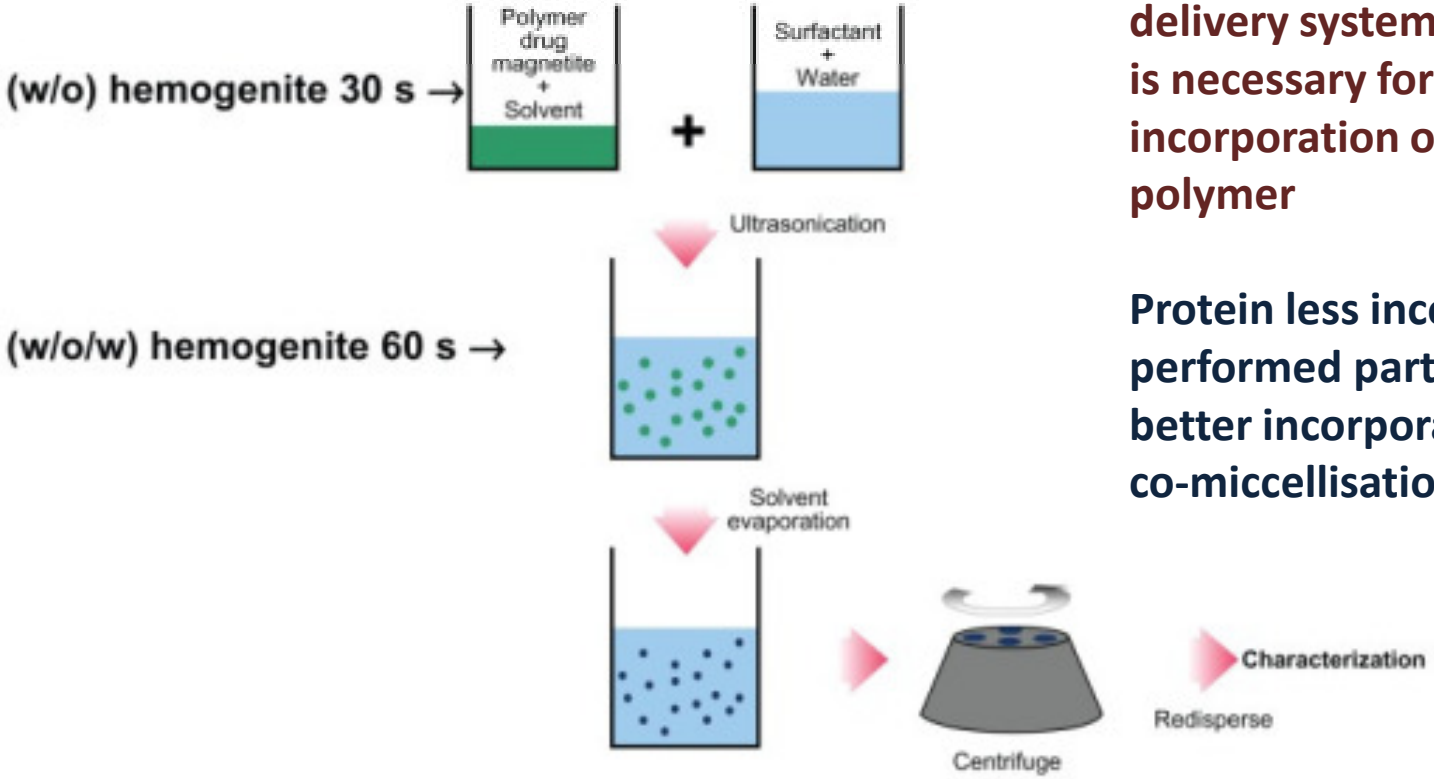
Drug Loading and Apo E-4 Incorporation





Coating the nano-drug delivery system with Tween 80 is necessary for better incorporation of protein with polymer

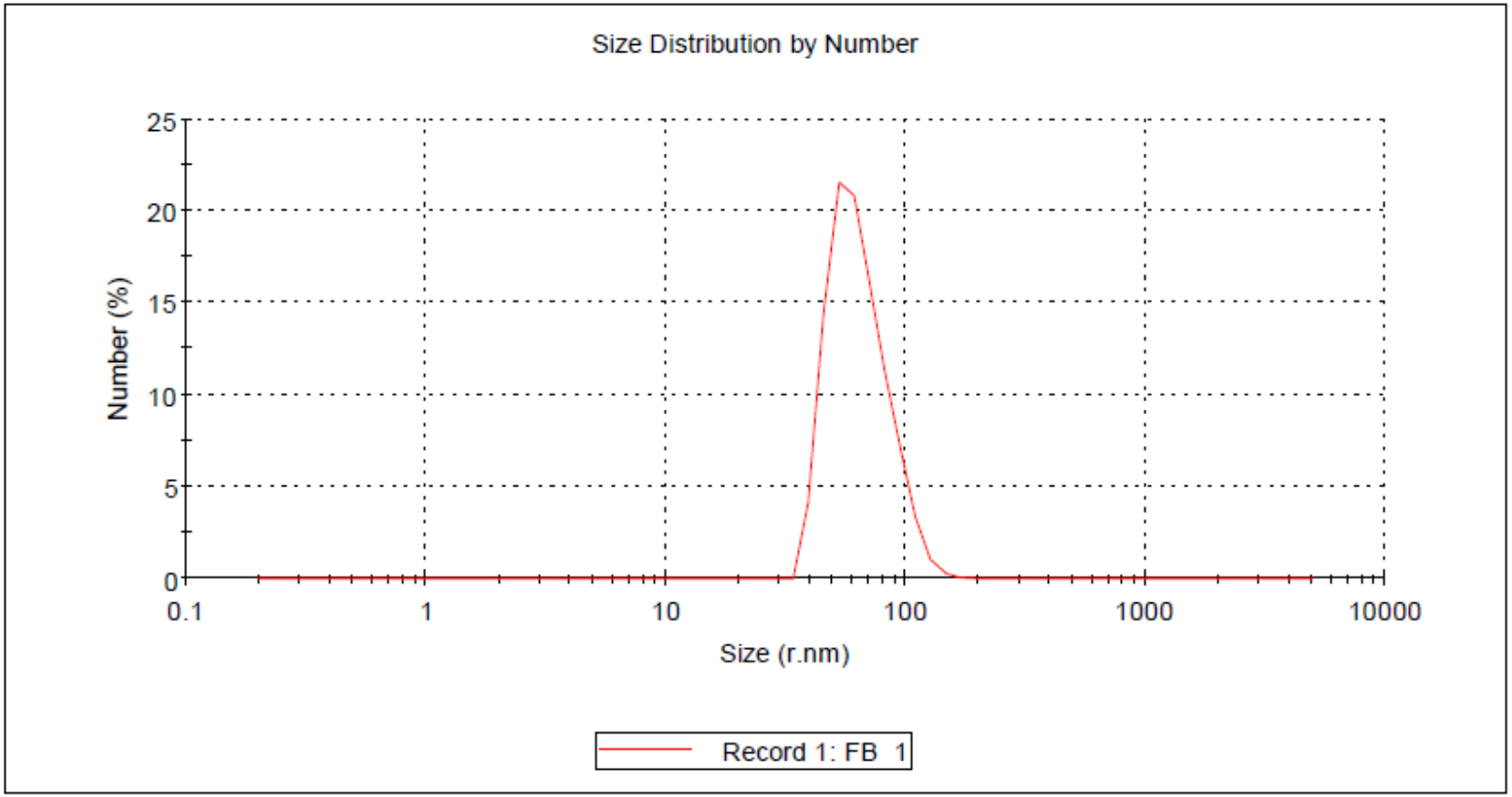
Protein less incorporates with performed particles and better incorporates with it in co-miccellisation method

Hydrodynamic Size of PLGA Particles

No significant changes happen upon loading plant extracts or synthetic compound

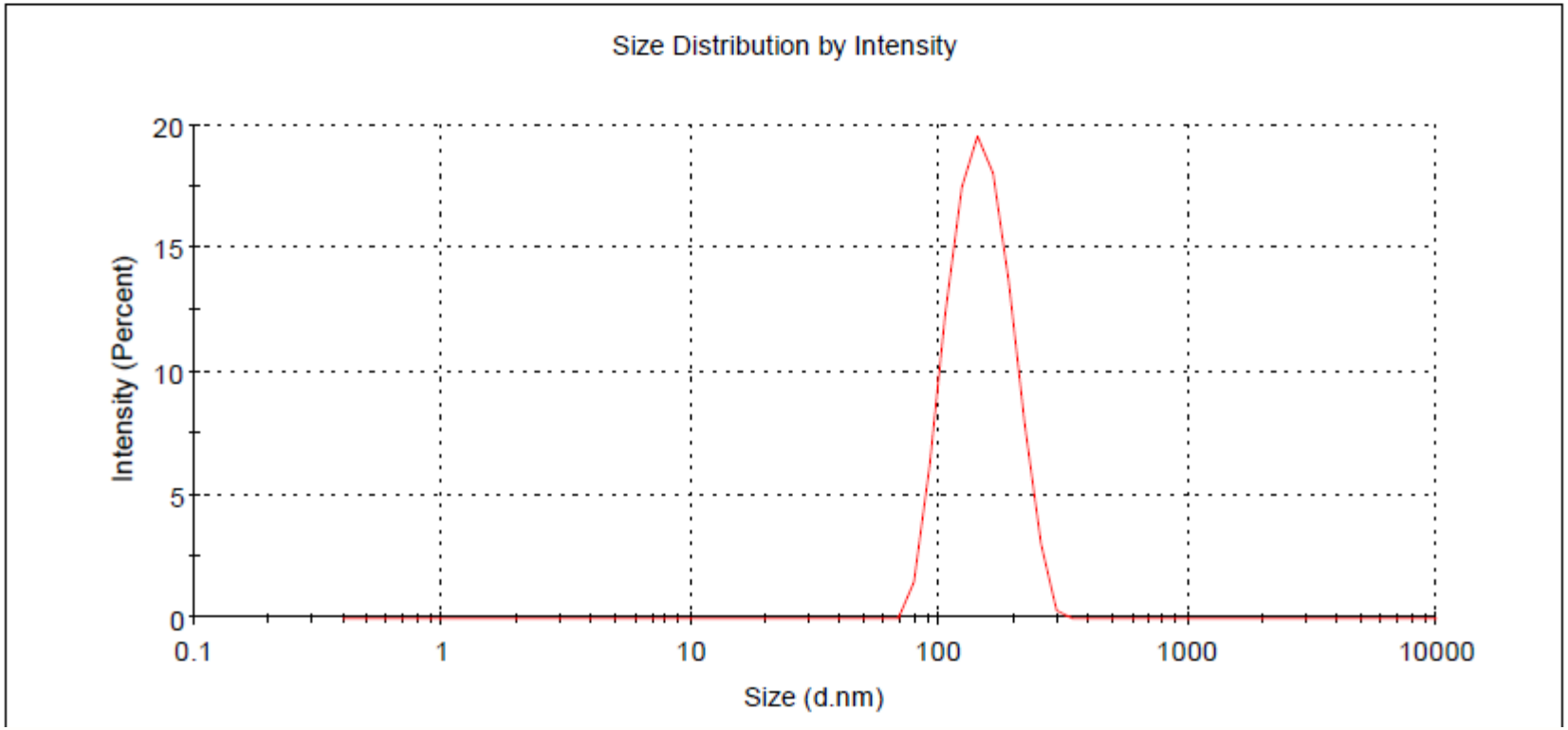
			Diam. (nm)	% Number	Width (nm)
Z-Average (r.nm):	79,27	**Peak 1:**	65,27	100,0	18,75
PdI:	0,072	**Peak 2:**	0,000	0,0	0,000
Intercept:	0,964	**Peak 3:**	0,000	0,0	0,000

Result quality Good

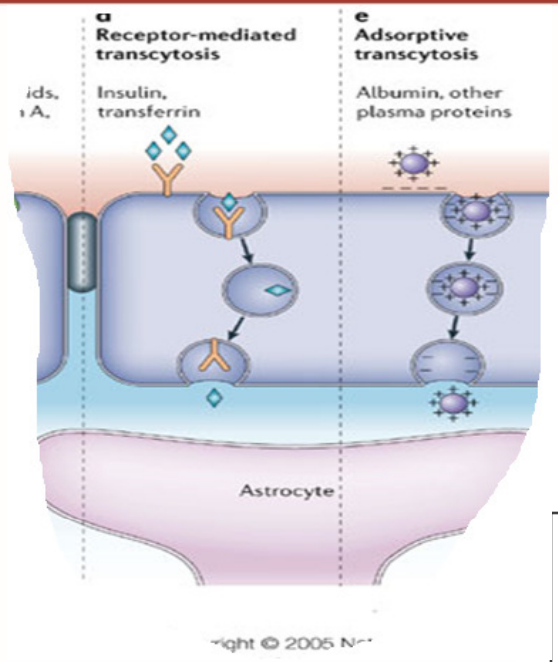


Apo E-4 incorporated PLGA Particles

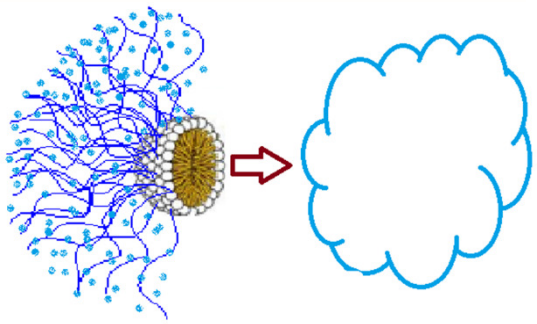
		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 139,8	**Peak 1:**	150,7	100,0	41,54
PdI: 0,074	**Peak 2:**	0,000	0,0	0,000
Intercept: 0,939	**Peak 3:**	0,000	0,0	0,000
Result quality Good				

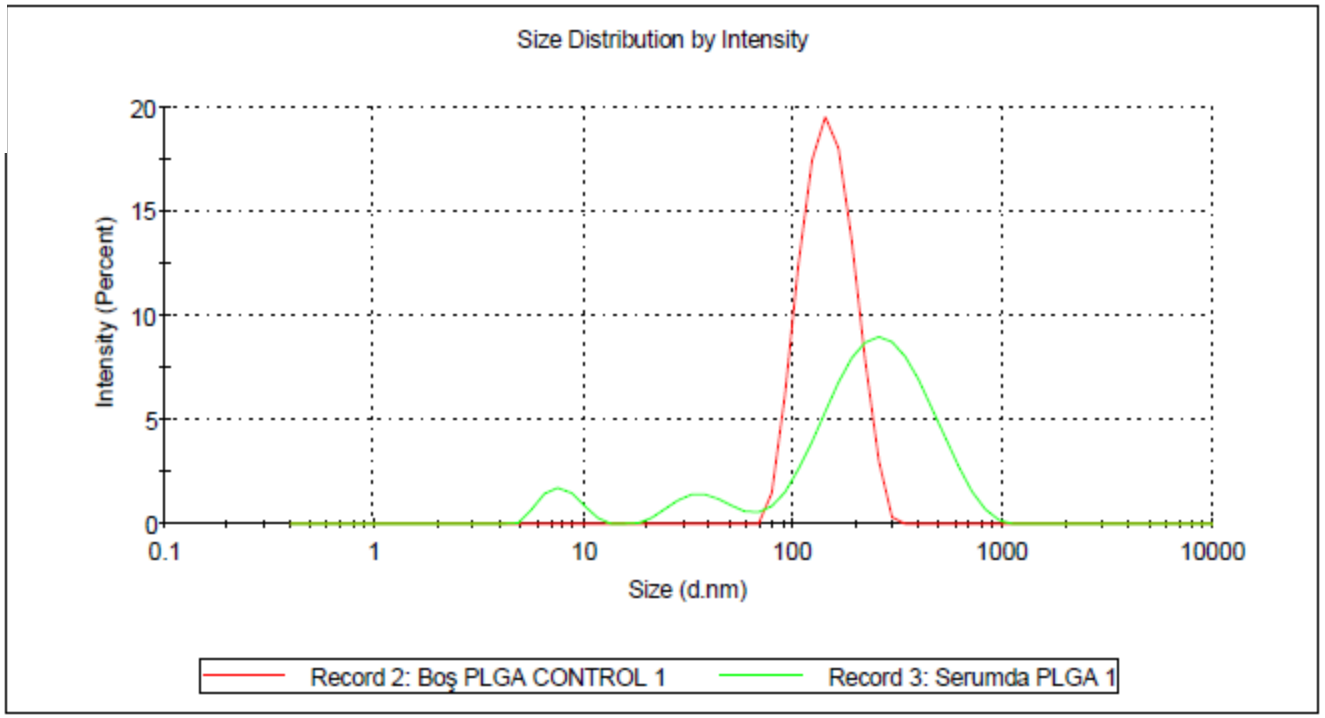


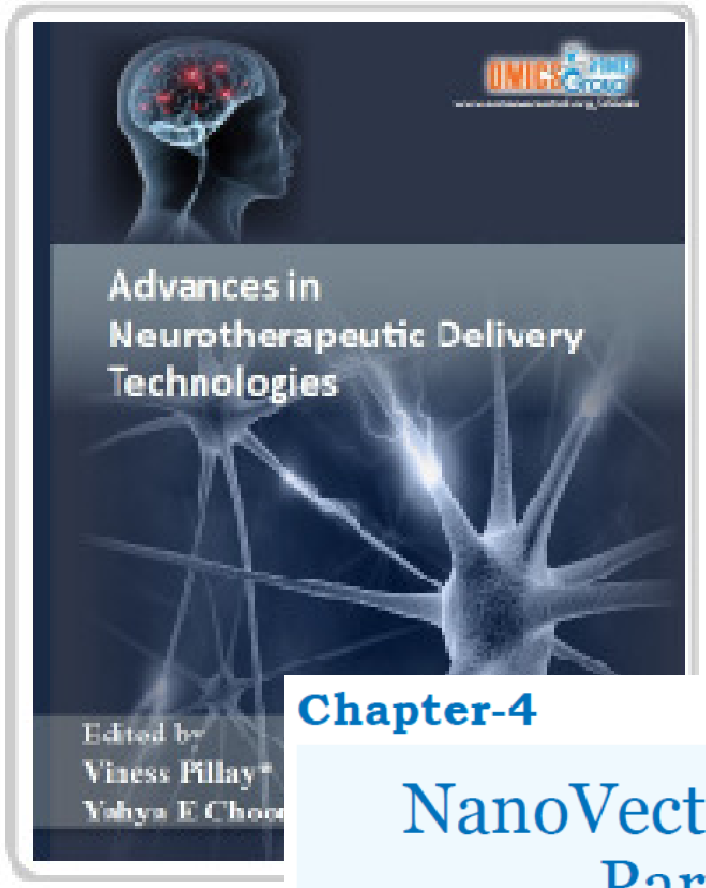
Stability of PLGA Nano-Particles



		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	139,8			
PdI:	0,074			
Intercept:	0,939	Peak 1:	150,7	100,0	41,54
		Peak 2:	0,000	0,0	0,000
		Peak 3:	0,000	0,0	0,000
Result quality	Good			







Chapter-4

NanoVectors for Neurotherapeutic Delivery Part I: Liposomes and Micelles

Tansel Comoglu[1*] and Fatemeh Bahadori[2]

[1]Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100, Tandogan, Ankara, Turkey
[2]Bezmialem Vakif University, Faculty of Pharmacy, Department of Pharmaceutical Biotechnology, 34093, Fatih, Istanbul, Turkey

Metal Protein Aattenuating Activty

A- Tris Base pH= 7.4

Aβ 1-42 + $CuCl_2$ → 1 H., 37°C→ Aggregation

Aggregates are visible under microscope

B-

Aβ 1-42 + $CuCl_2$ + EDTA→ 1 H., 37°C→ Aggregation
+ Verbascum flavidum extract
+ Rosmarinus officinalis extract
+ PDTC

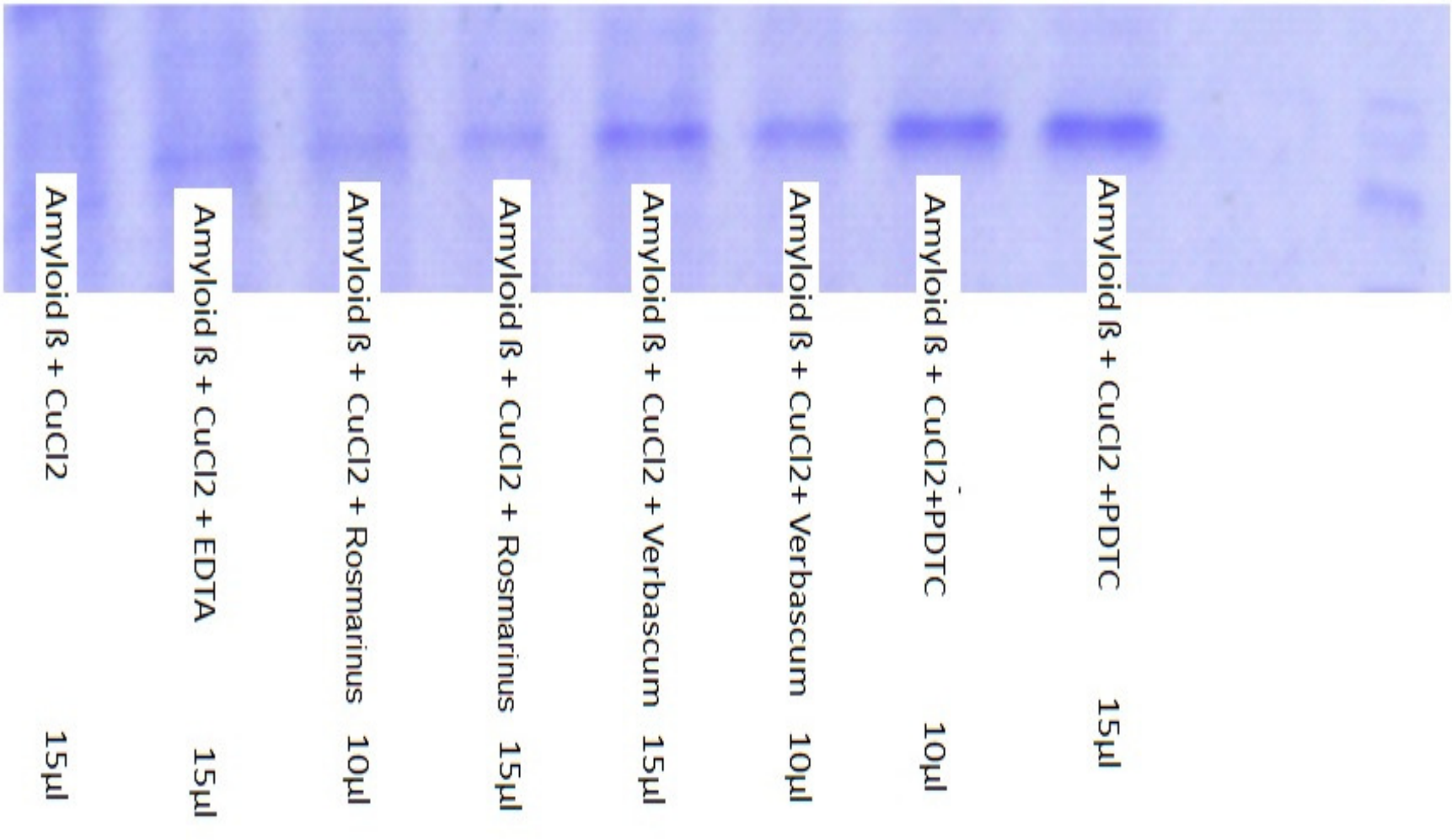
→ Centrifuge →measure the protein amount in supernatant usning SDS-PAGE

C- a) Aβ 1-42 + $CuCl_2$ → 1 H., 37°C→ Aggregation

b) +EDTA or +V.f or +Ro or +PDTC

→ Centrifuge →measure the protein amount in supernatant usning SDS-PAGE

Results of SDS-Page



Conclusion

- *Verbascum flavidum* and *Rosmarinus officinalis* are promisng Metal Chelators while *Ro* is the more trustable one because of its well known toxicity profile
- Pyrrolidine Dithiocarbamate (PDTC) is a very convenient compound to establish more investigagtions on it in the frame of Alzheimer's disease treatment
- Both natural and synthetic metal chelators show better activity in prevention of Alzheimer's disease than in treatment of it

THANKS

Ph.D. Candidate Burak Çelik
and
Grad. Student Fatma Kazdal

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