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.

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.

Doaa A. Ghareeb, Ph.D

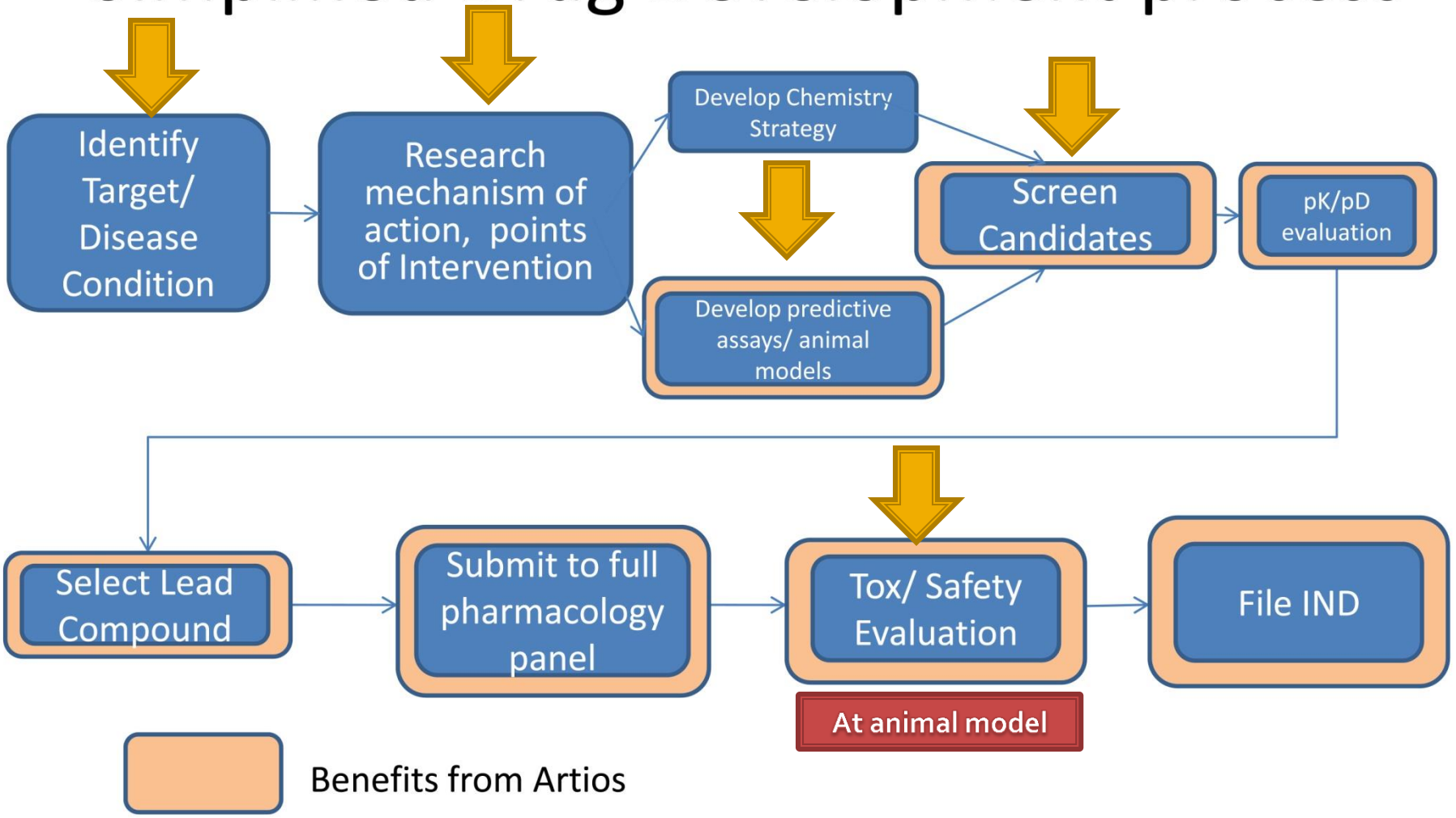
From Remedy to nanoparticles for AD treatment

Pharmacovigilance-2015

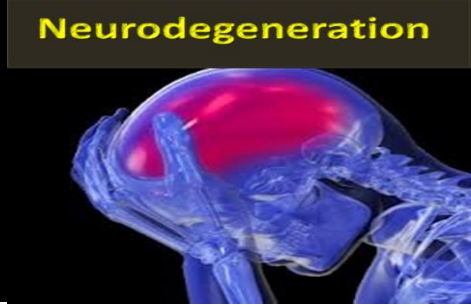
Outlines

- Introduction about AD
- Introduction about *Berberis vulgaris* and Berberine
- Disease induction by different mechanism
- Disease treatment with extract, active compound and NP
- Conclusion

Simplified Drug Development process



The target Alzheimer Disease

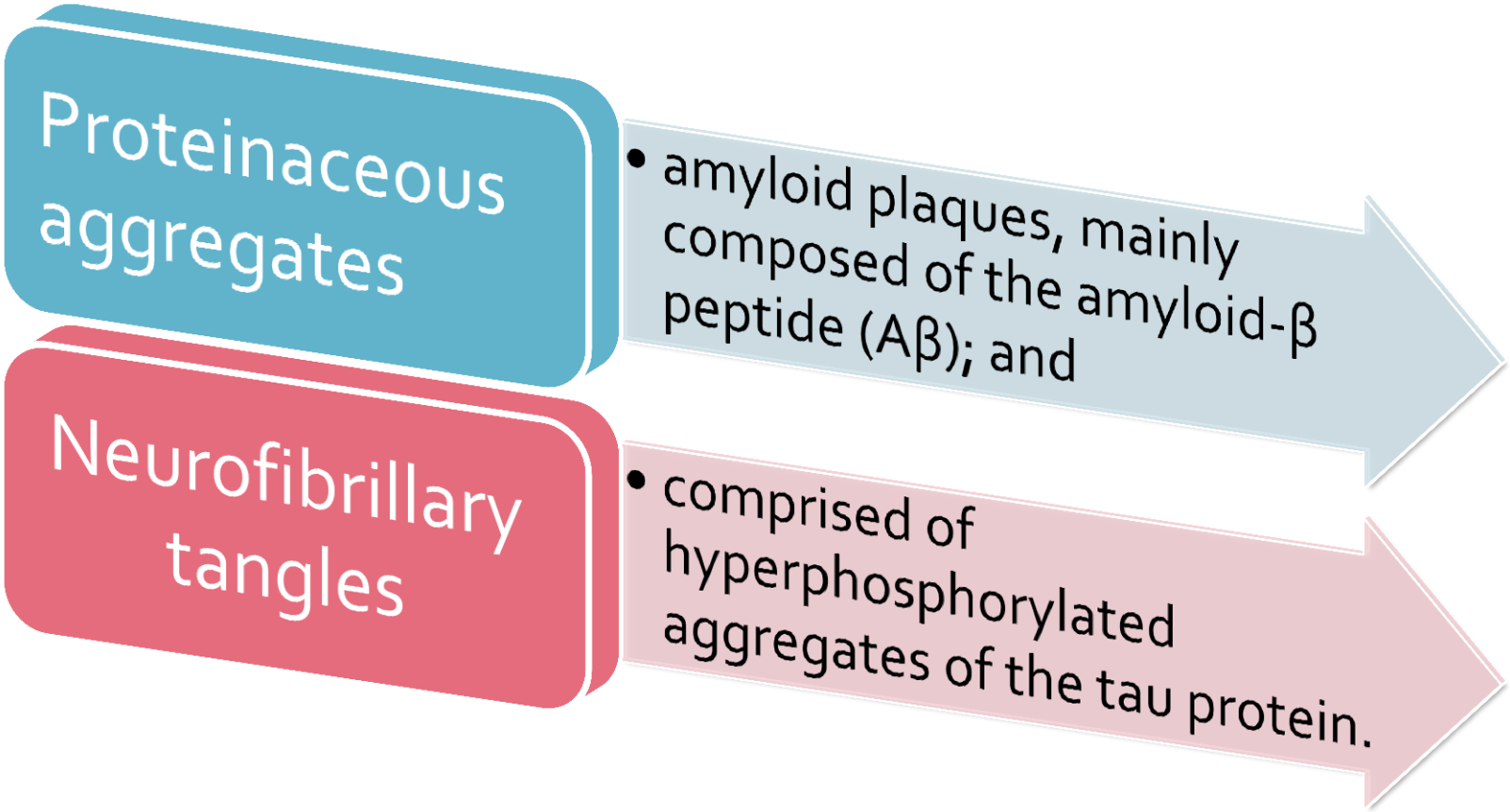


- Alzheimer's disease (AD) is a complex neurodegenerative condition which has become a major public health problem because of its increasing prevalence, long duration and high cost of care.
- AD is the fourth leading cause of death among 10% of 70 years aged people after myocardial infraction, stroke and cancer.
- It affects the middle-to old-aged individuals, approximately one in four individuals over the age of 85 and it is estimated that more than 25 million people worldwide are affected to some degree by AD.

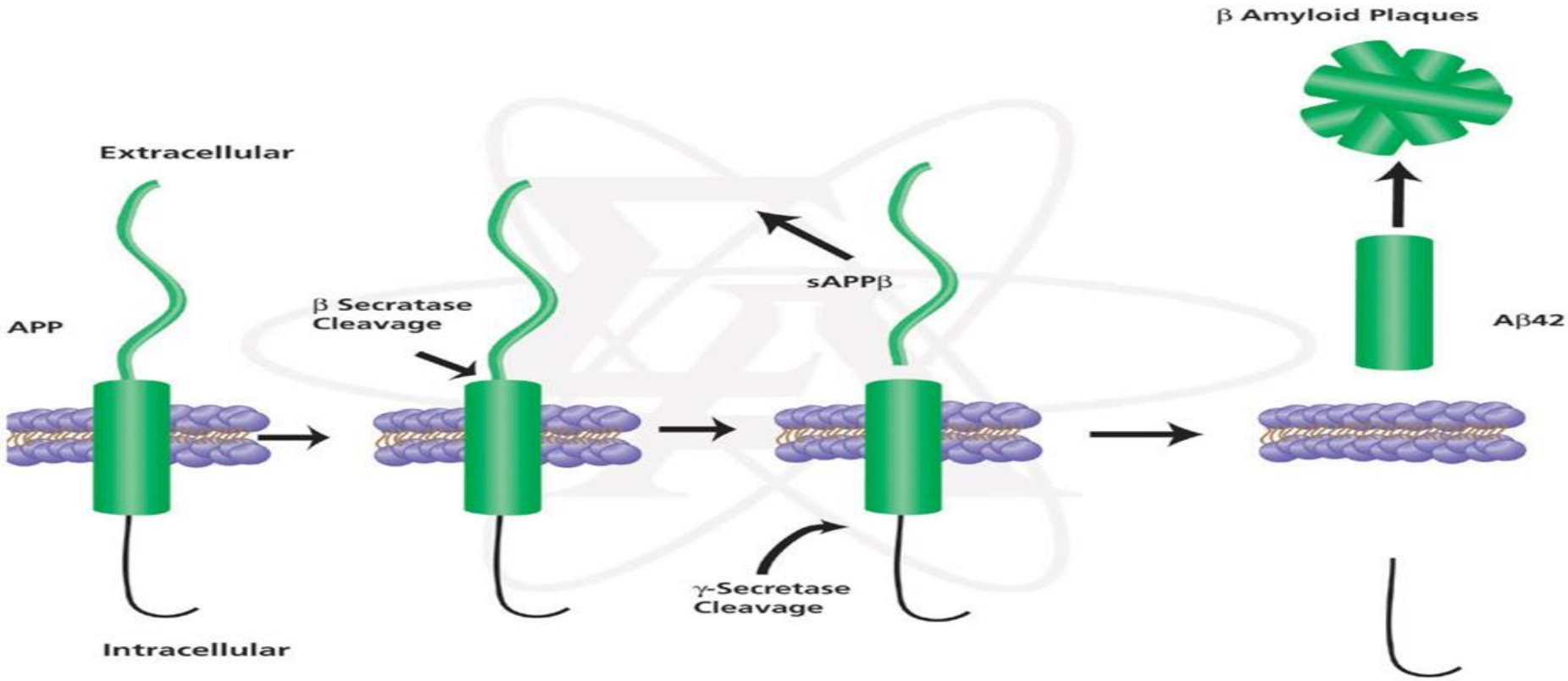
Research Mechanism of action Alzheimer's disease hallmarks

- AD is characterized by loss of short term memory, disorientation, and impairment of judgment and reasoning.

Neuropathologically, the AD brain is characterized by two hallmark



- β- amyloid accumulation:
- Aβ is produced from amyloid precursor protein (APP) by serial proteolytic reactions catalyzed by β-site of APP cleaving enzymes β-secretase and γ-secretase.



Risk factors for amyloid aggregation

- In Egypt, we have several factor lead to AD progression such as;
  - Water Pollution
  - Liver disease
  - Insulin resistance syndrome
  - Aging and oxidative stress related disorder.

Therefore,

We target different causes and/or mechanisms

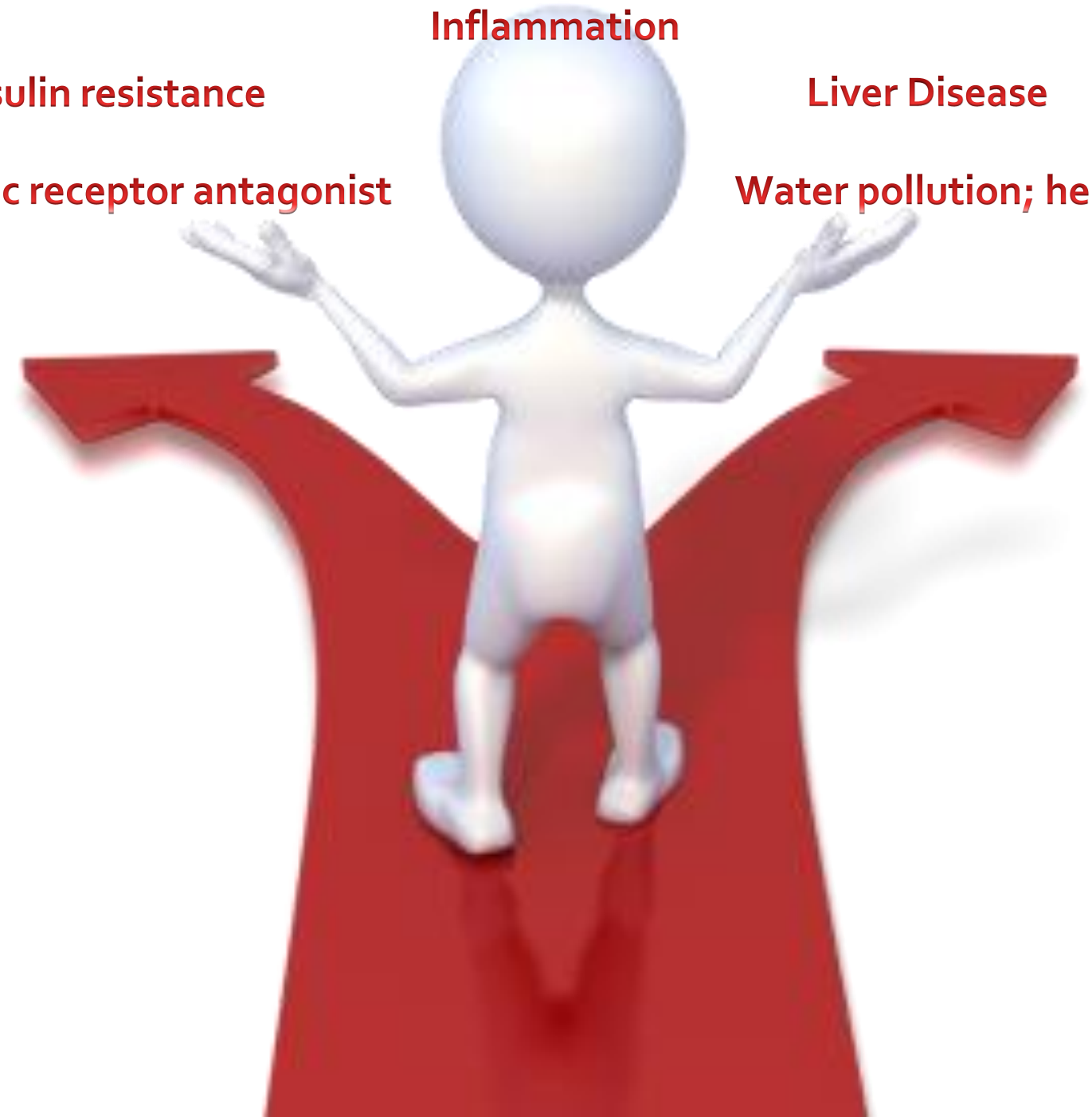
Inflammation

Insulin resistance

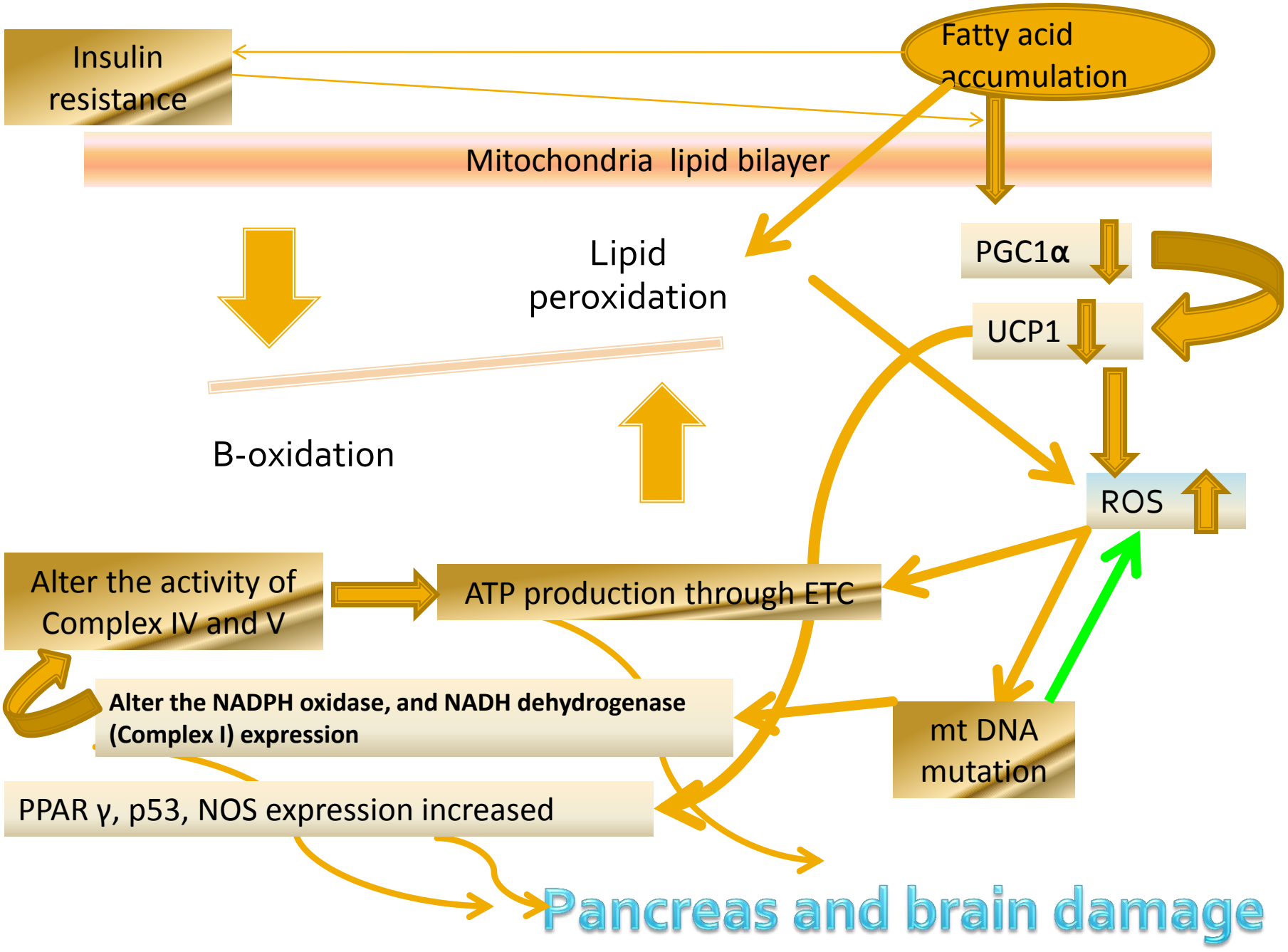
Liver Disease

Muscarinic receptor antagonist

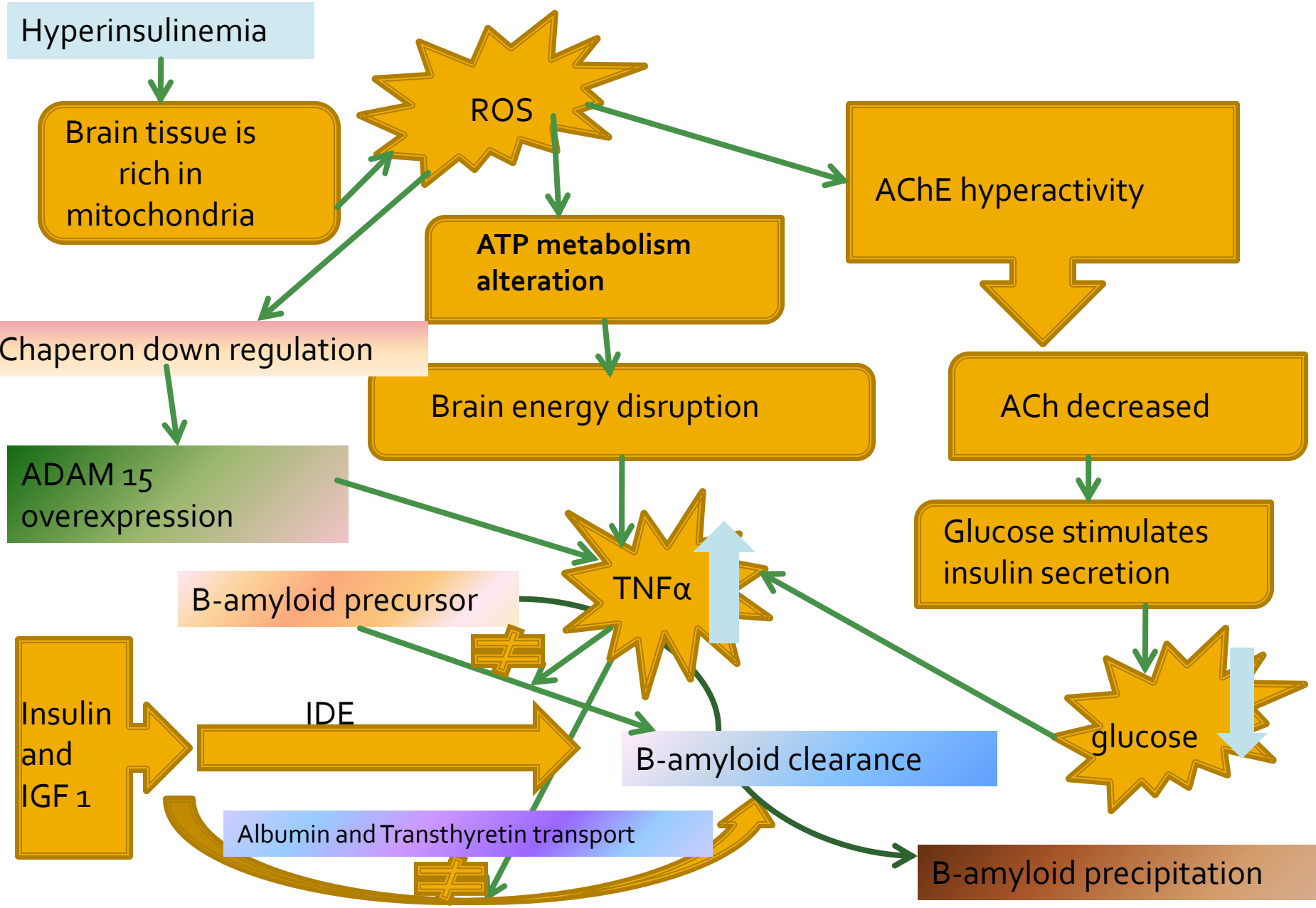
Water pollution; heavy metal

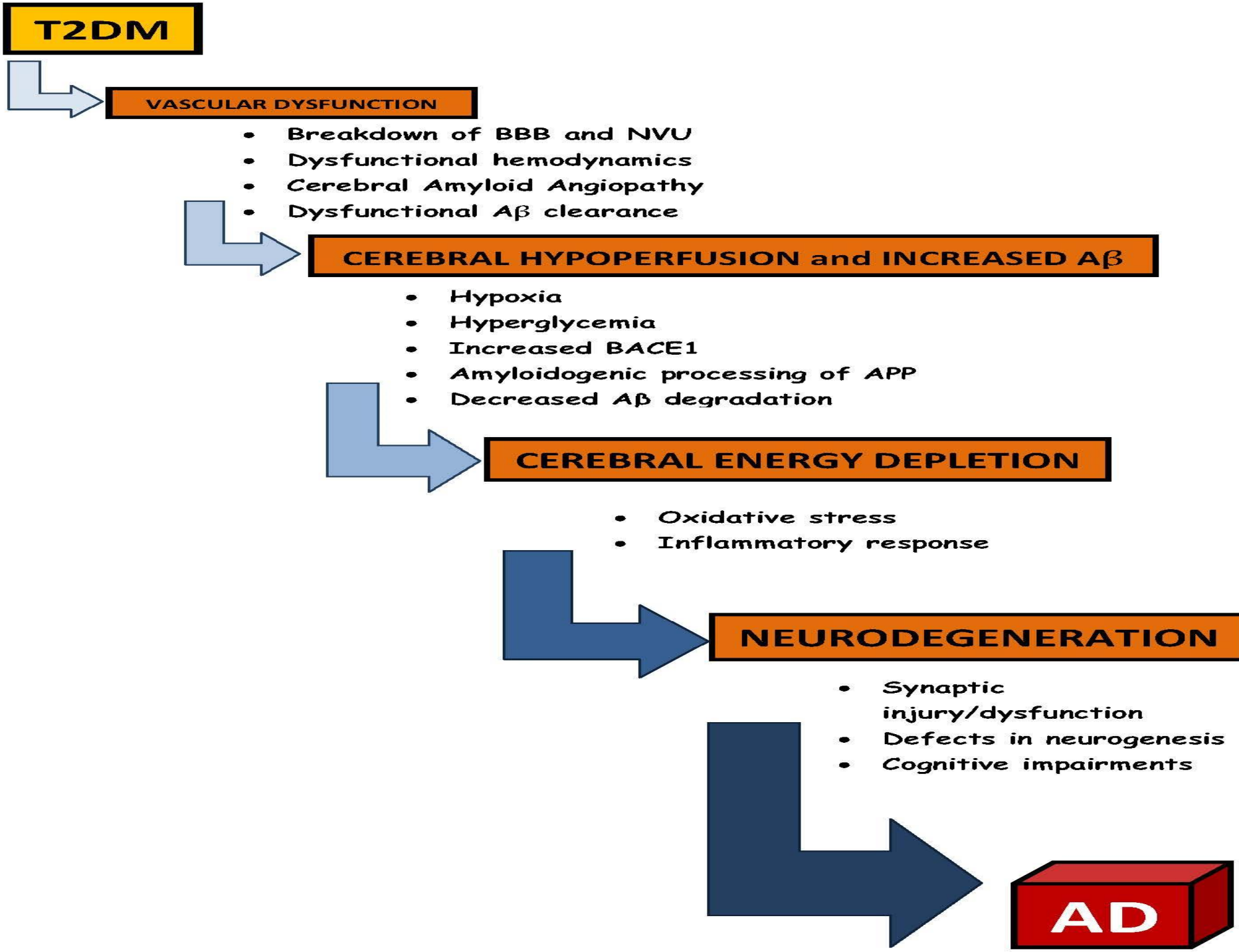


- brain insulin signaling has faced a novel and increased interest in neuroscience research, either in its signaling pathways and/or as a promising therapy against diabetes and age-relate neurodegenerative disorders.


Insulin resistance
Fatty acid accumulation
Mitochondria lipid bilayer
Lipid peroxidation
PGC1α
UCP1
B-oxidation
ROS
Alter the activity of Complex IV and V
ATP production through ETC
Alter the NADPH oxidase, and NADH dehydrogenase (Complex I) expression
mt DNA mutation
PPAR γ, p53, NOS expression increased
Pancreas and brain damage

Oxidative stress and brain tissue

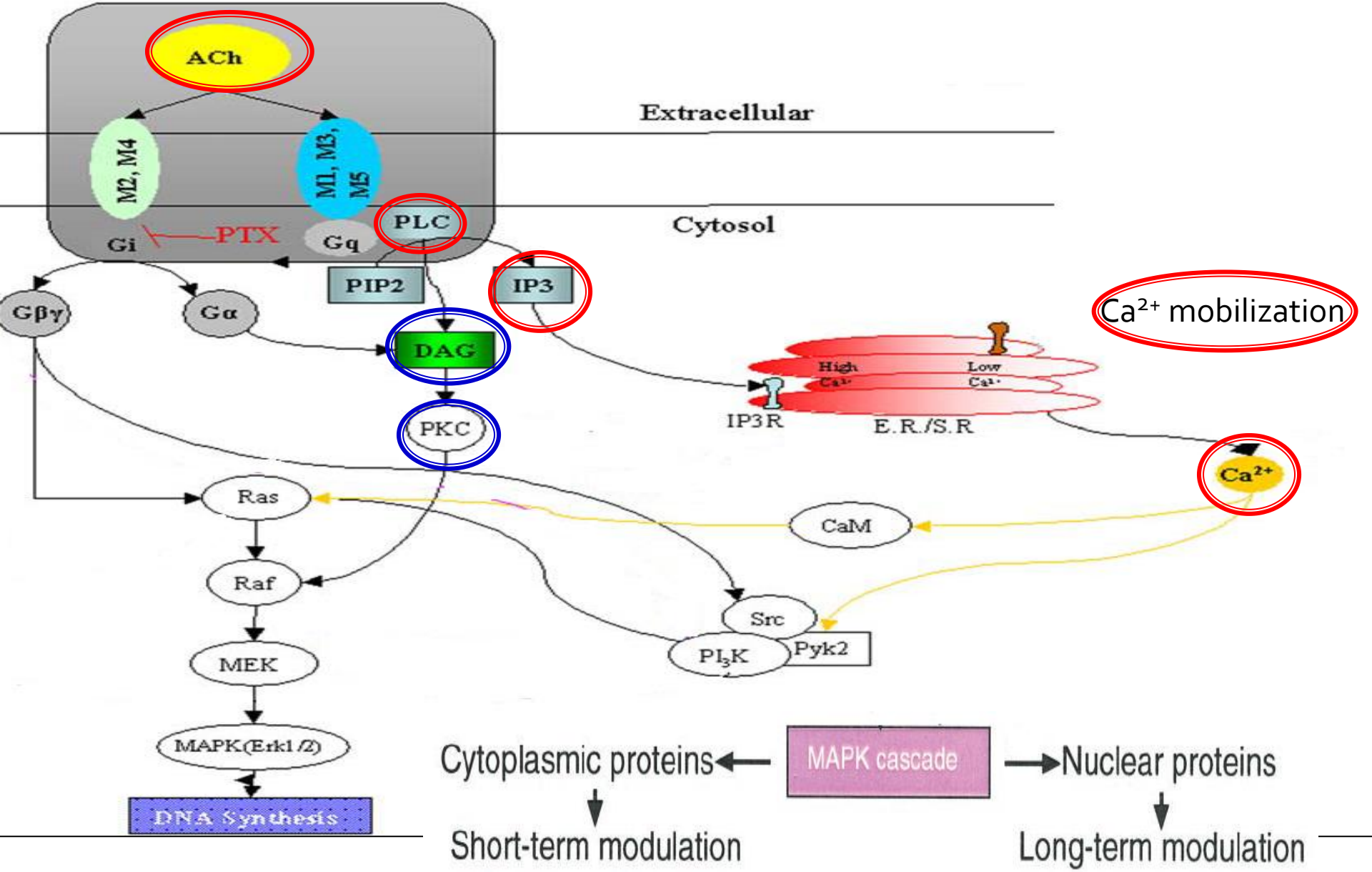



T2DM
VASCULAR DYSFUNCTION
Breakdown of BBB and NVU
Dysfunctional hemodynamics
Cerebral Amyloid Angiopathy
Dysfunctional Aβ clearance
CEREBRAL HYPOPERFUSION and INCREASED Aβ
Hypoxia
Hyperglycemia
Increased BACE1
Amyloidogenic processing of APP
Decreased Aβ degradation
CEREBRAL ENERGY DEPLETION
Oxidative stress
Inflammatory response
NEURODEGENERATION
Synaptic injury/dysfunction
Defects in neurogenesis
Cognitive impairments
AD

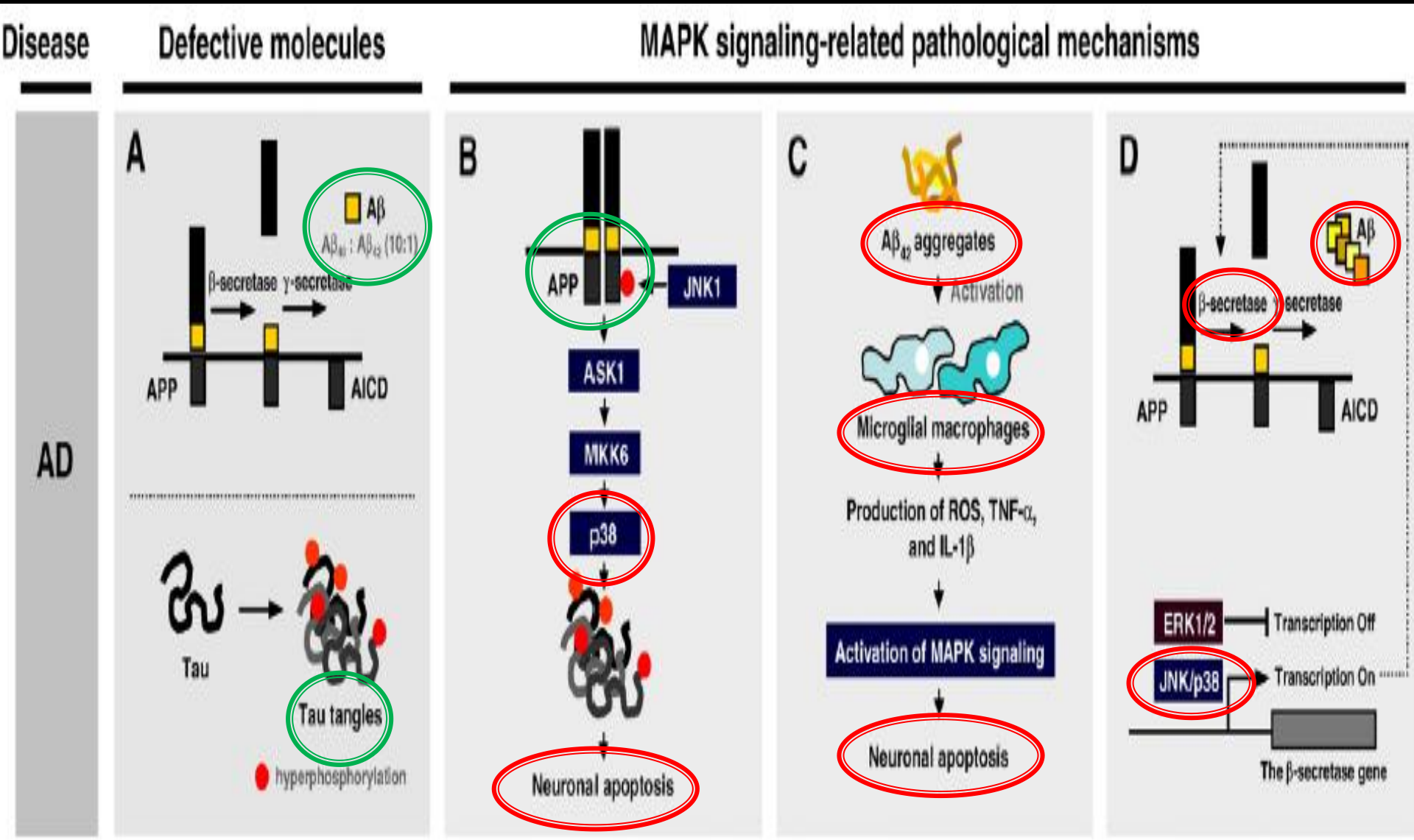
Muscarinic receptor antagonist

Insulin resistance

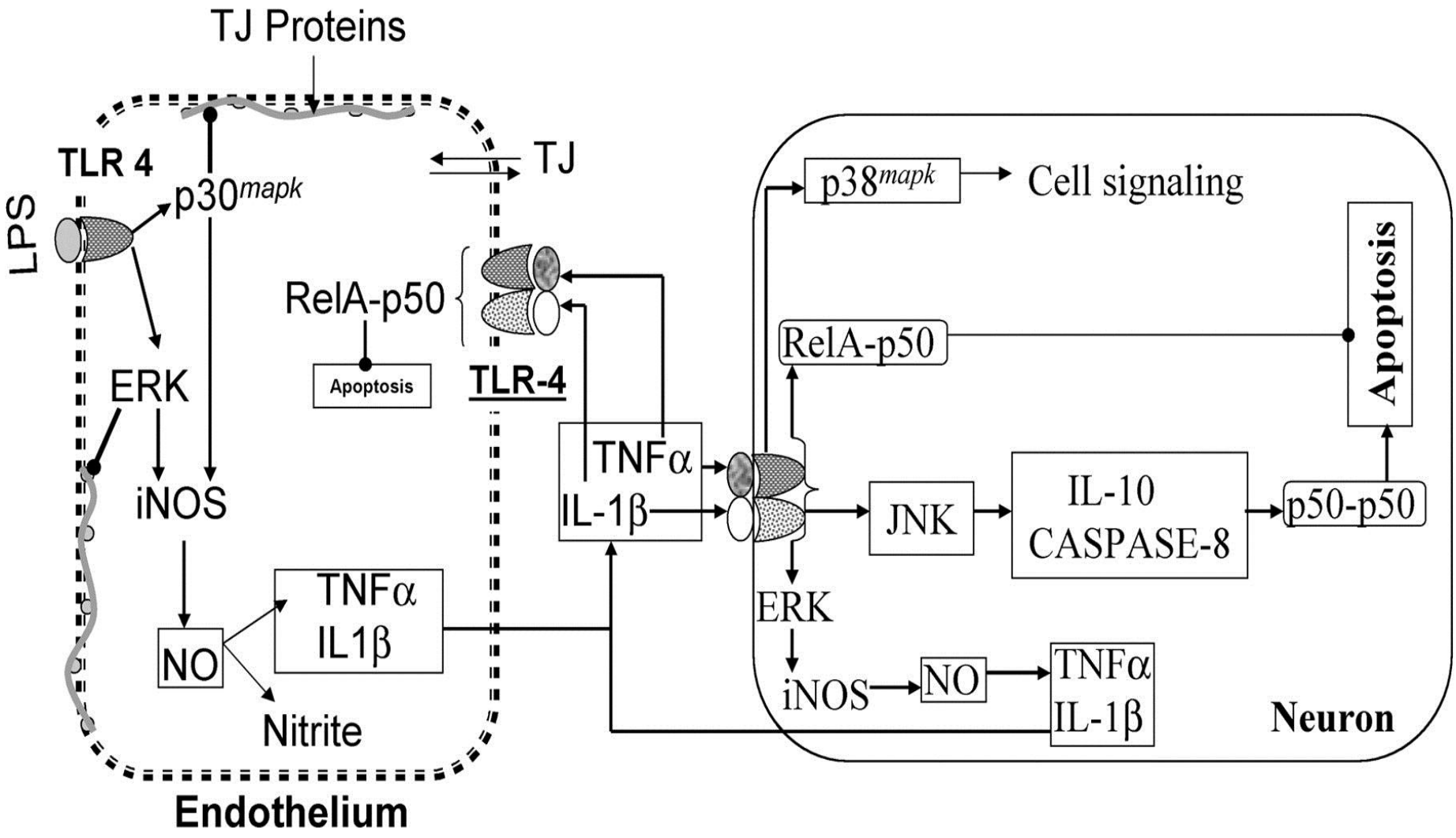
Muscarinic receptor-coupled signal transduction pathways



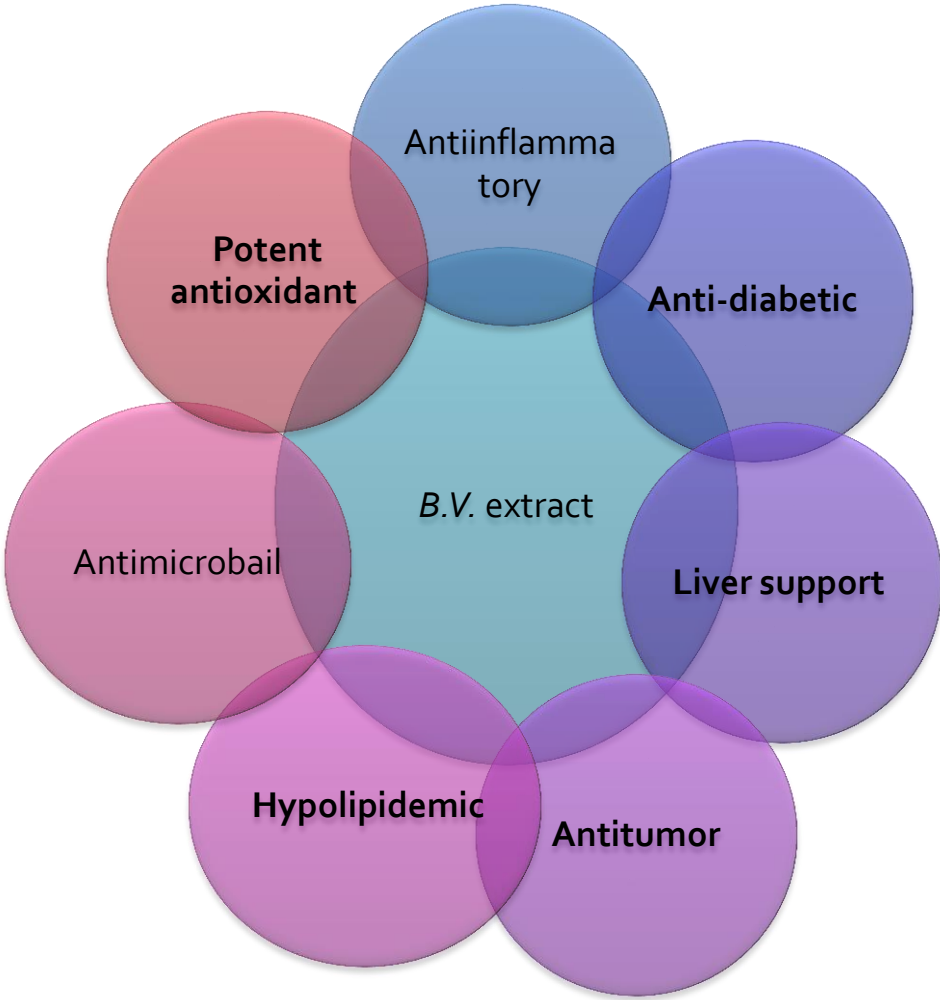
Roles of MAPK pathways in the pathogenesis of Alzheimer's disease

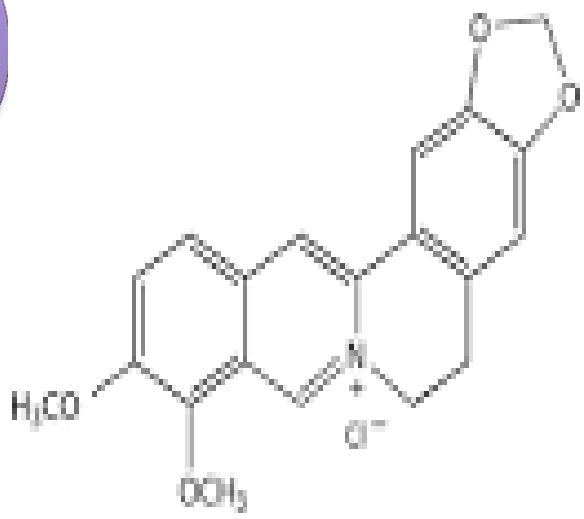


Neuroinflammation

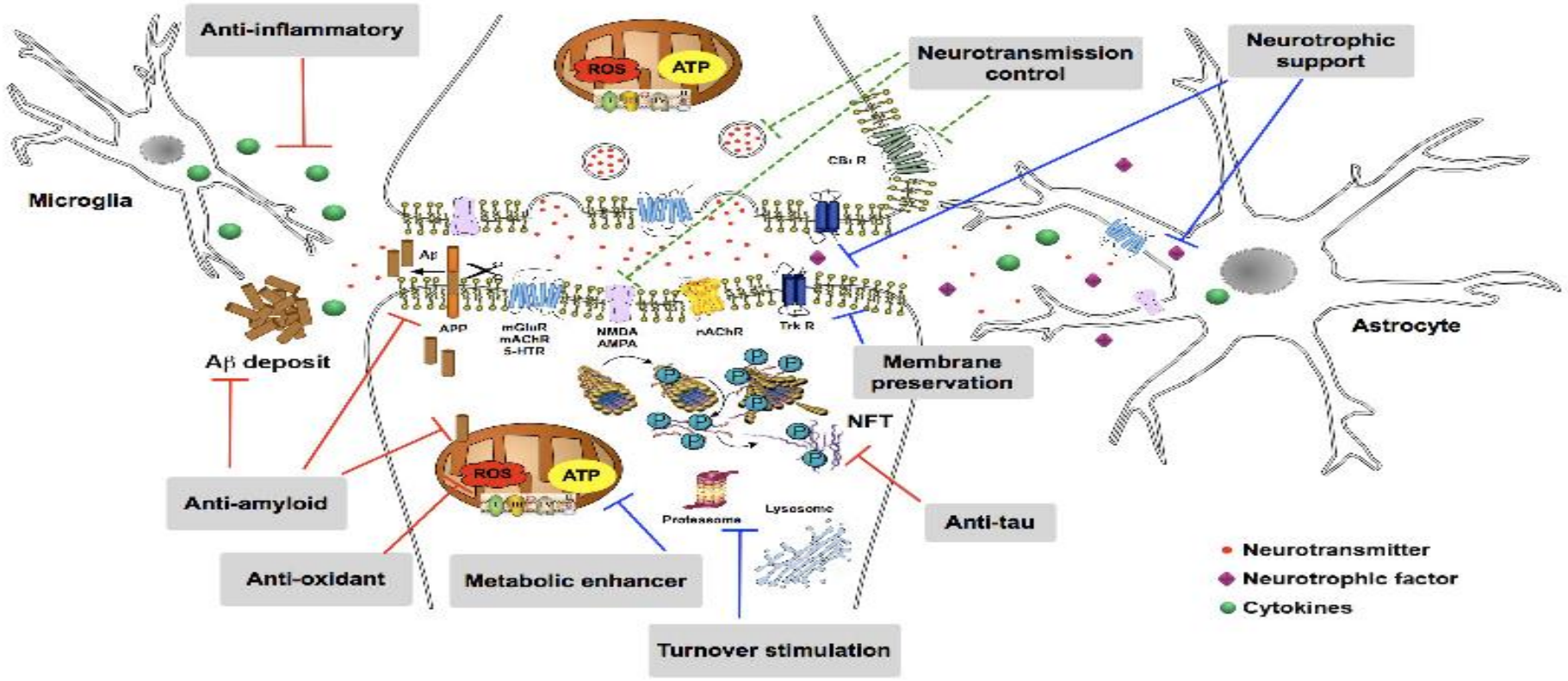


Identify lead
Berberise vulgaris L.





Main cellular targets that are currently under development to prevent or retard the progression of Alzheimer to disease states

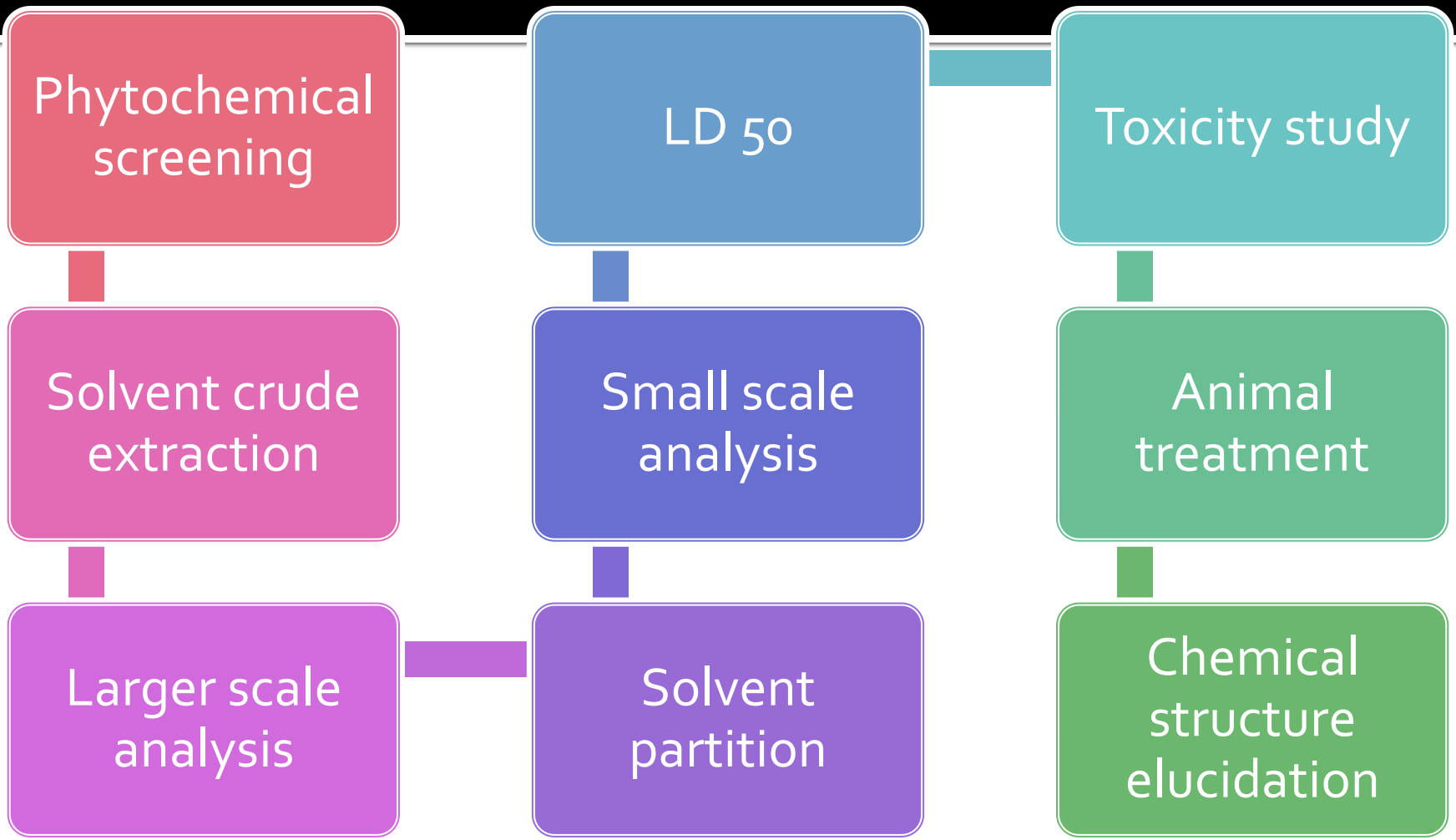


Neurotransmitter: ACh, DOPA. Neurotrophic factor: the neurotrophin BDNF (brain-derived neurotrophic factor). Membrane preservation and neuron plasticity: CREB (cAMP response element-binding protein). Metabolic enhancer: ATP, NADP. Glucose. Anti-inflammatory: TNF-alpha. Antioxidants: ROS, XO, ALD, TBARS

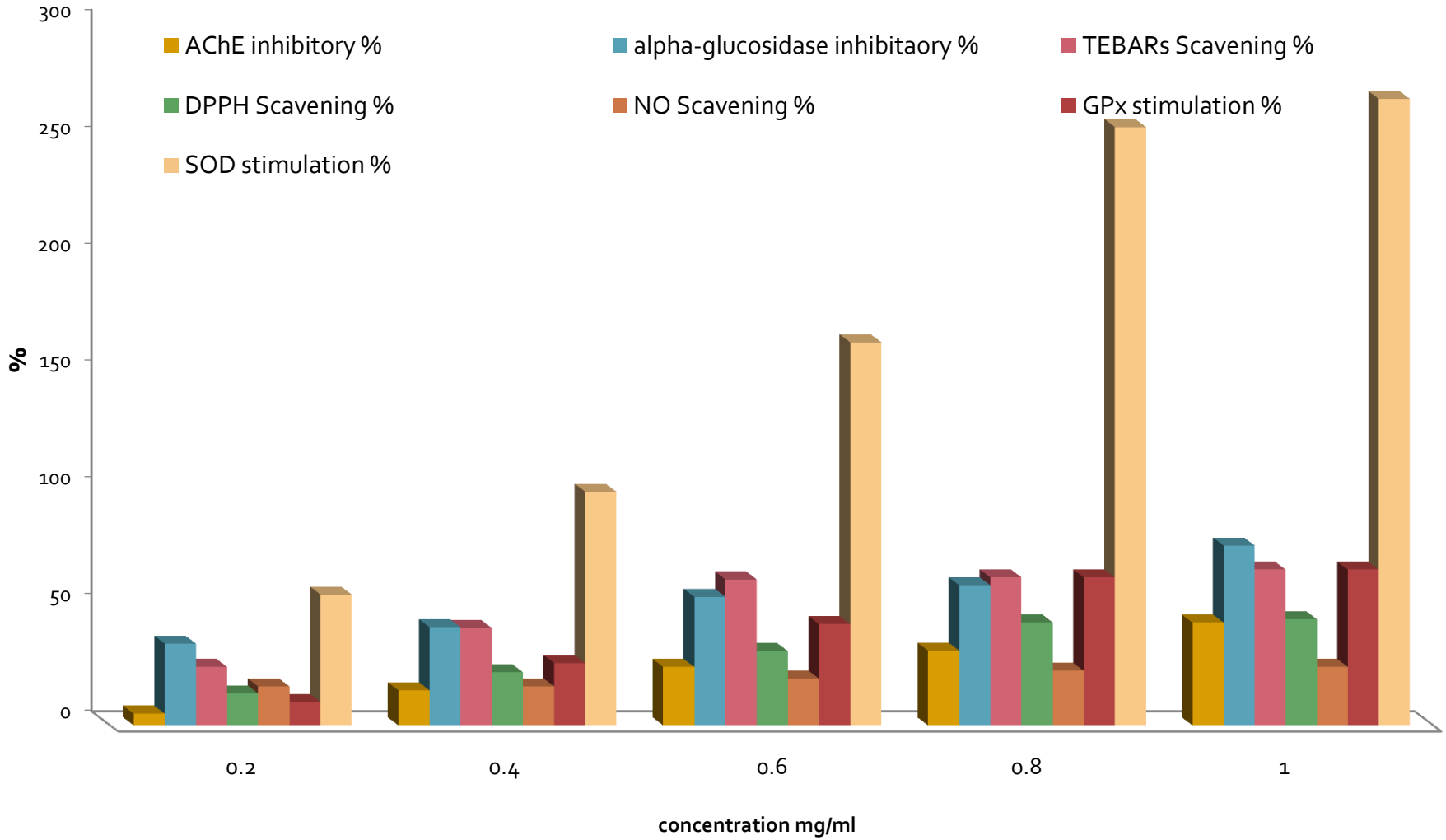
Assays and results

We are achieving the target

Assays

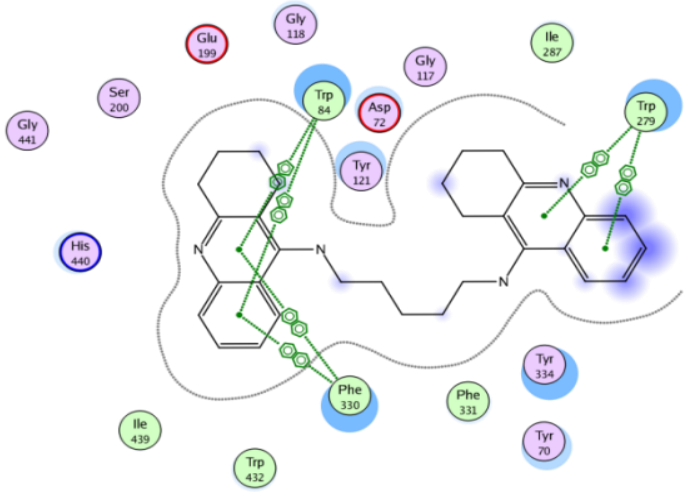

Phytochemical screening
Solvent crude extraction
Larger scale analysis
Solvent partition
Small scale analysis
LD 50
Toxicity study
Animal treatment
Chemical structure elucidation

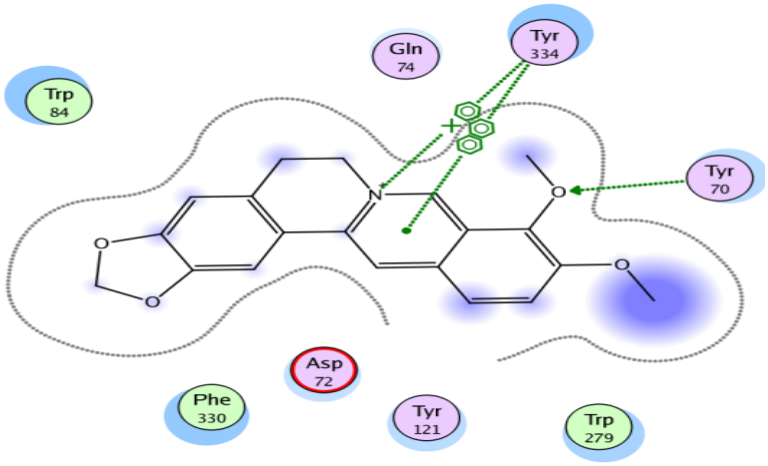
In vitro Inhibitory effect percentage of Berberine chloride and *Berberis vulgaris toward* AChE.



Molecular modeling analysis of berberine activity

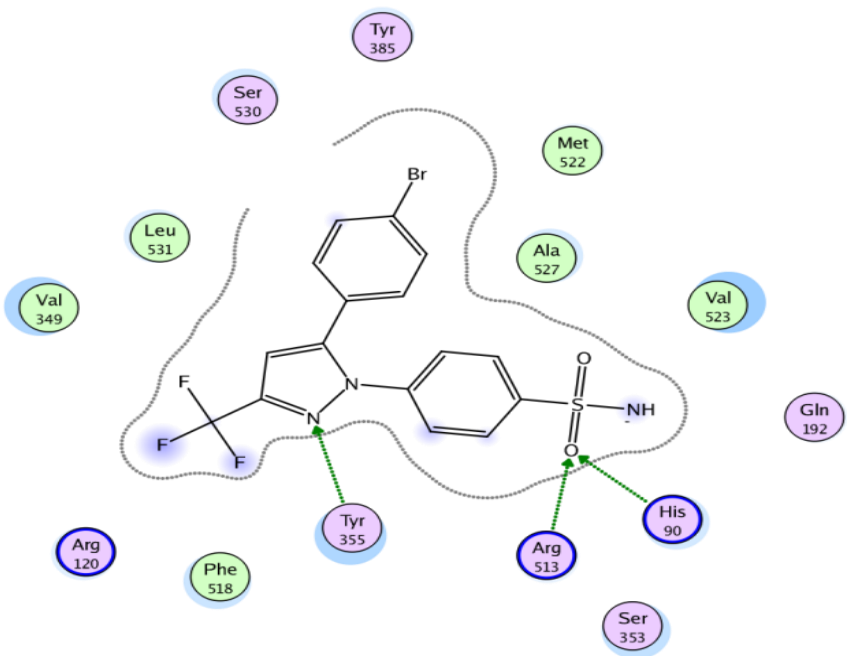
Docking models of the compound-enzyme acetylcholinesterase (AChE) complex

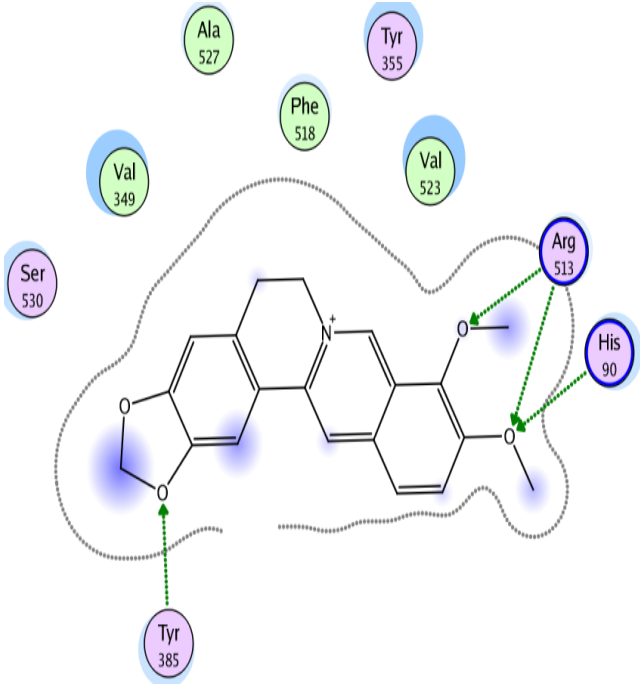




Molecular modeling analysis of berberine activity

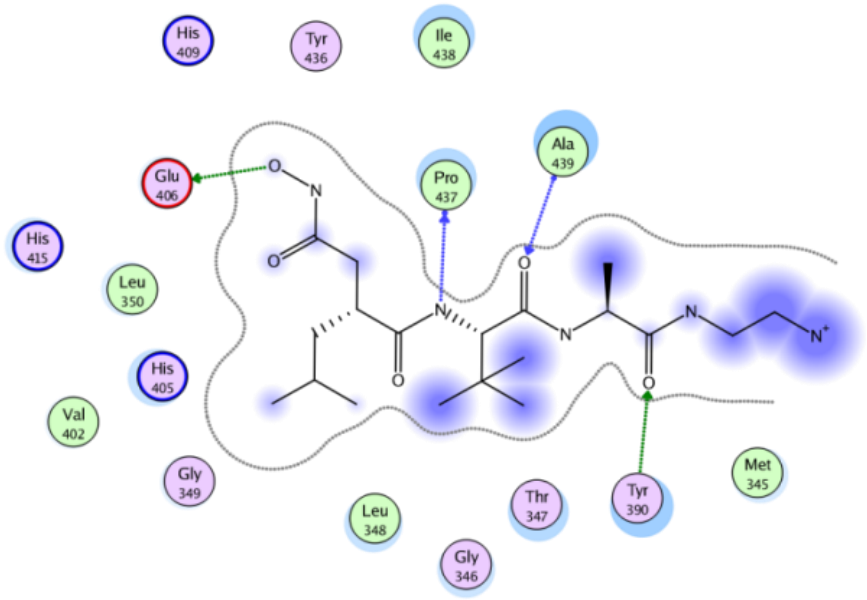
Docking models of the compound-enzyme Cyclooxygenase-2 (COX-II) complex.

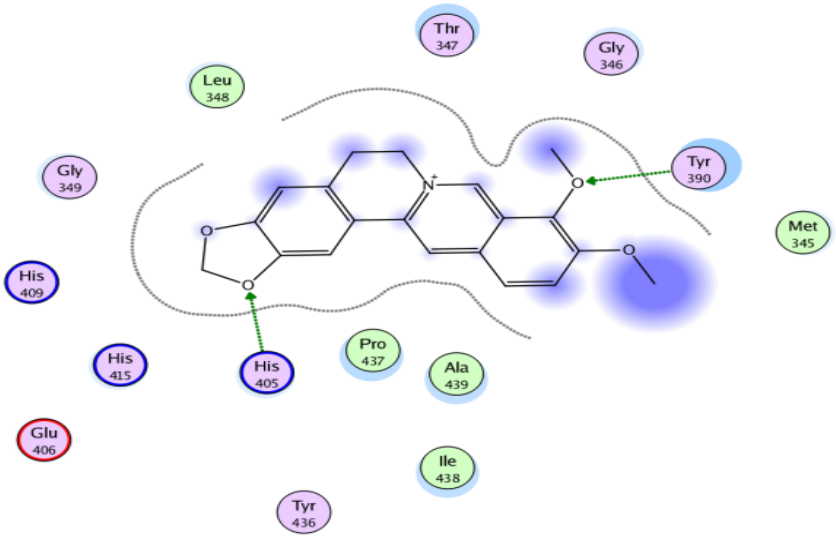




Molecular modeling analysis of berberine activity

Docking model for berberine (right image) and reference ligand (left one) 2D interactions to the binding pocket of Tumor Necrosis Factor-Alpha Converting Enzyme (TACE).





Animal model for brain damage related to liver disease and IR syndrome

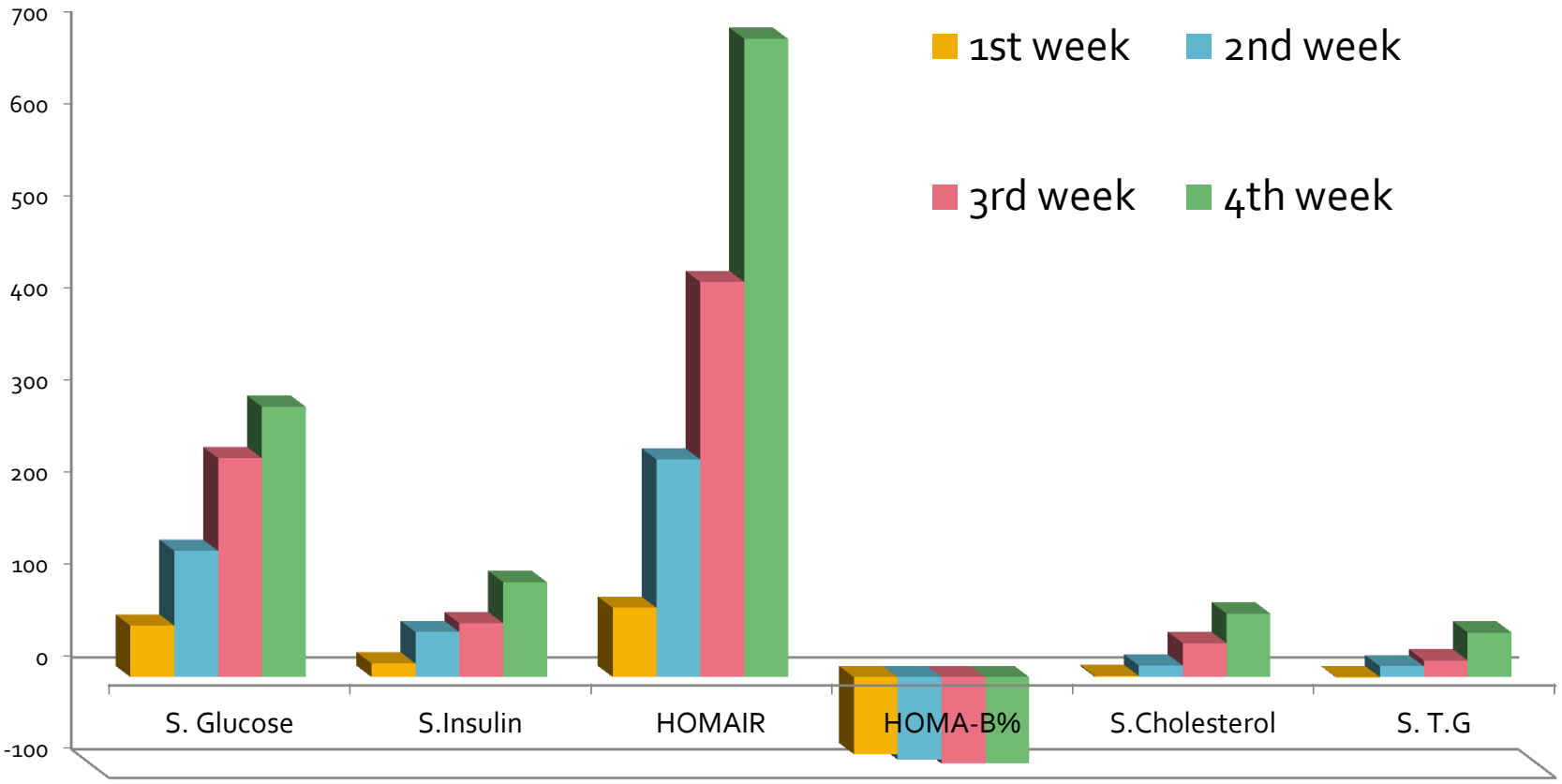


Figure: Blood Insulin resistance markers

Animal model for brain damage related to liver disease and IR syndrome

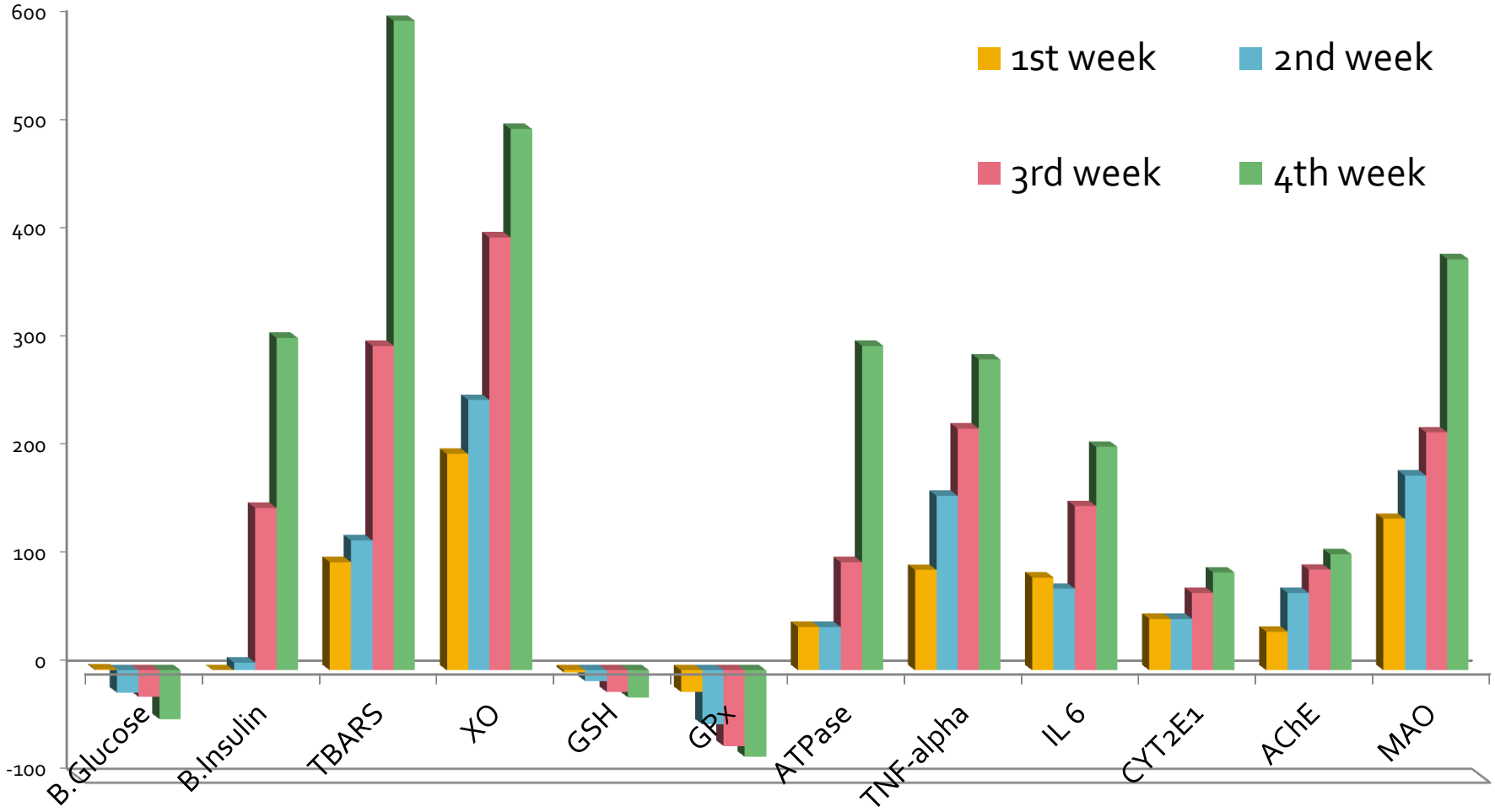


Figure: Brain damage markers

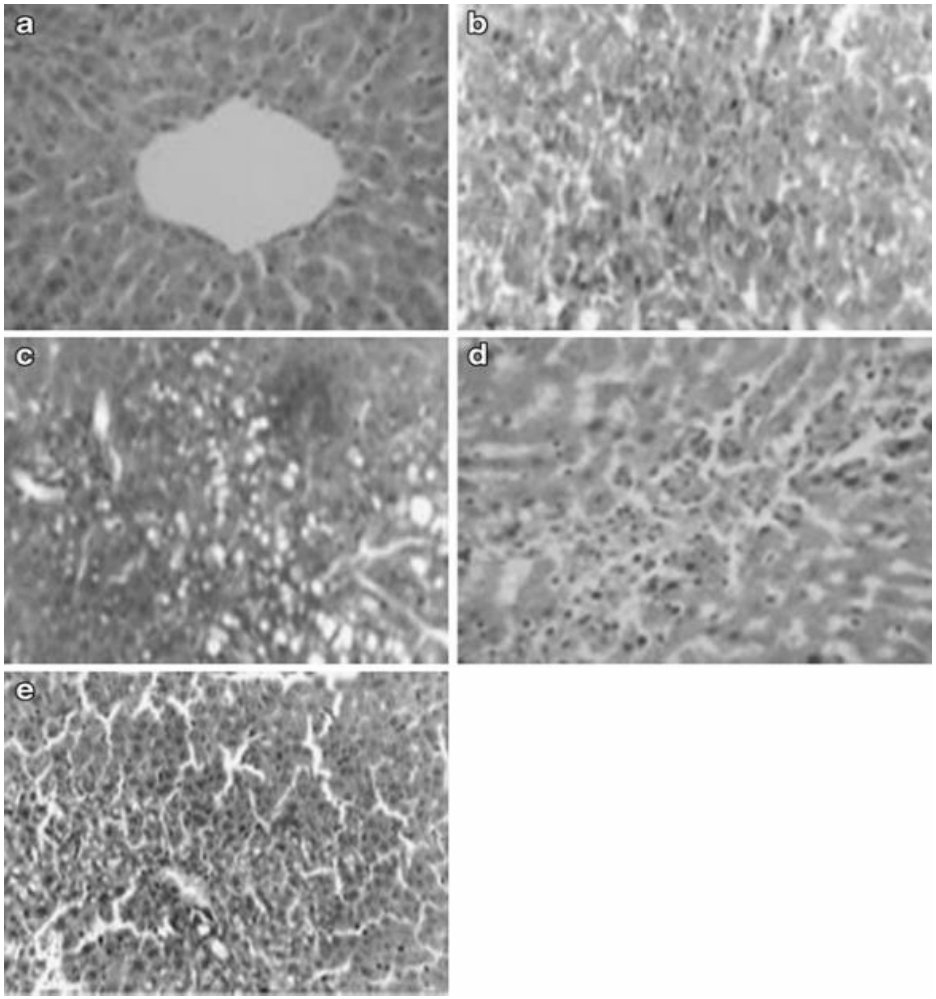


Fig. Effect of the NAFLD induction and progression on liver histology. Hematoxylineosin staining showed the cells in a longitudinal section at magnification 400× of light microscope: (a) Control (b) first week (c) second week (d) third week (e) Fourth week. Solid arrow shows steatosis, dashed arrow shows necrosis and dotted arrow shows inflammation

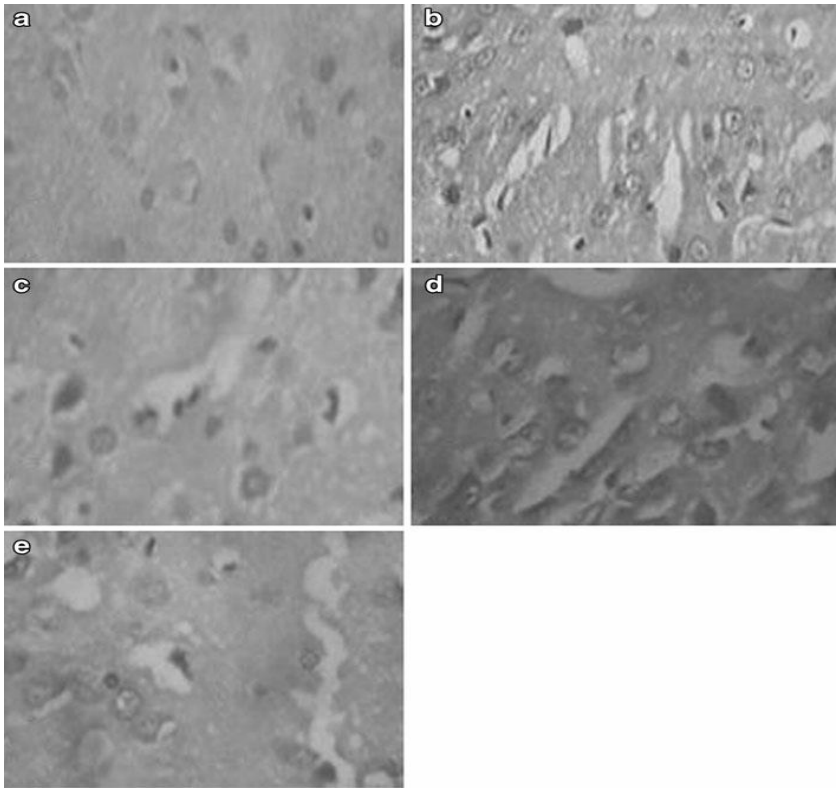
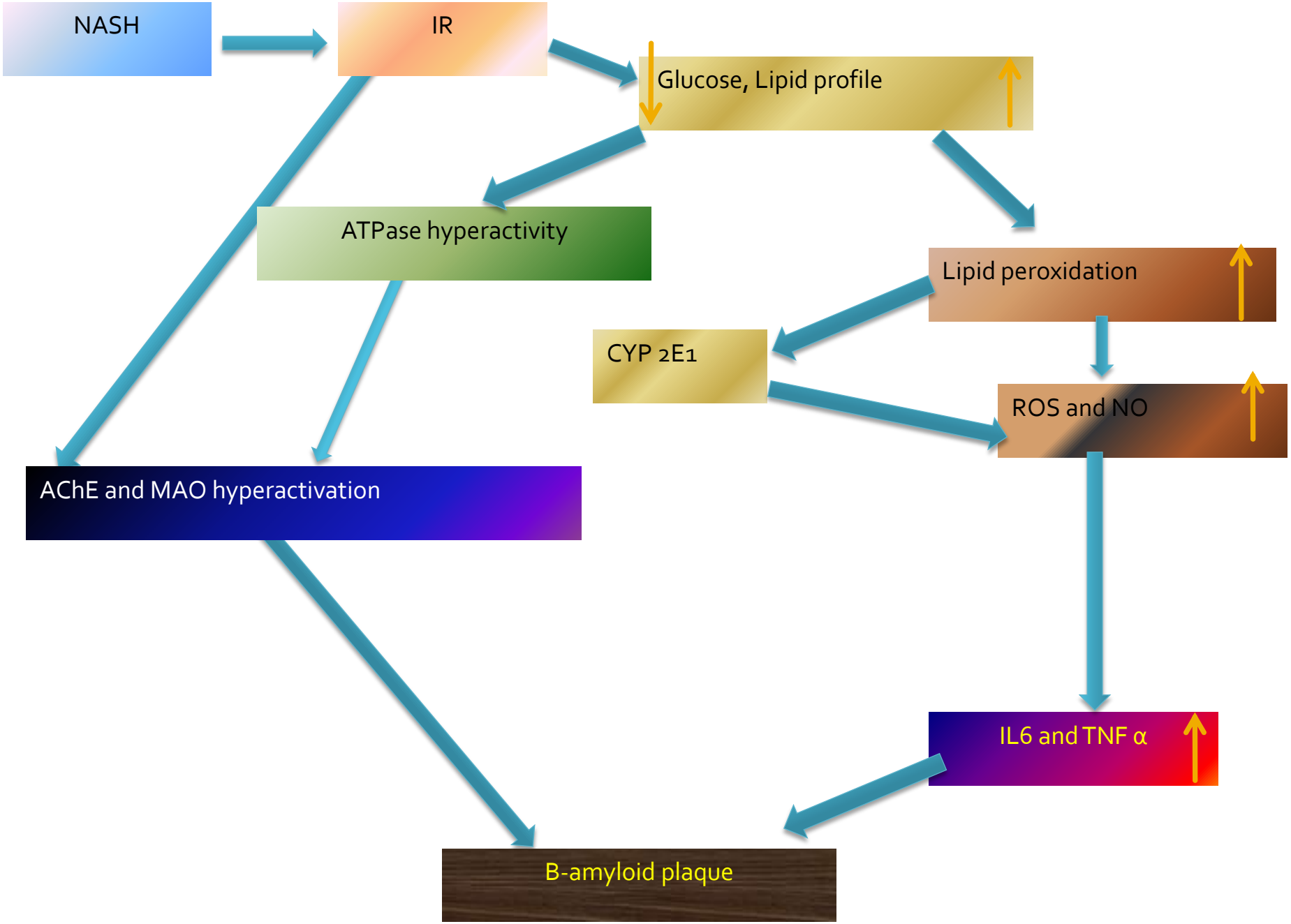
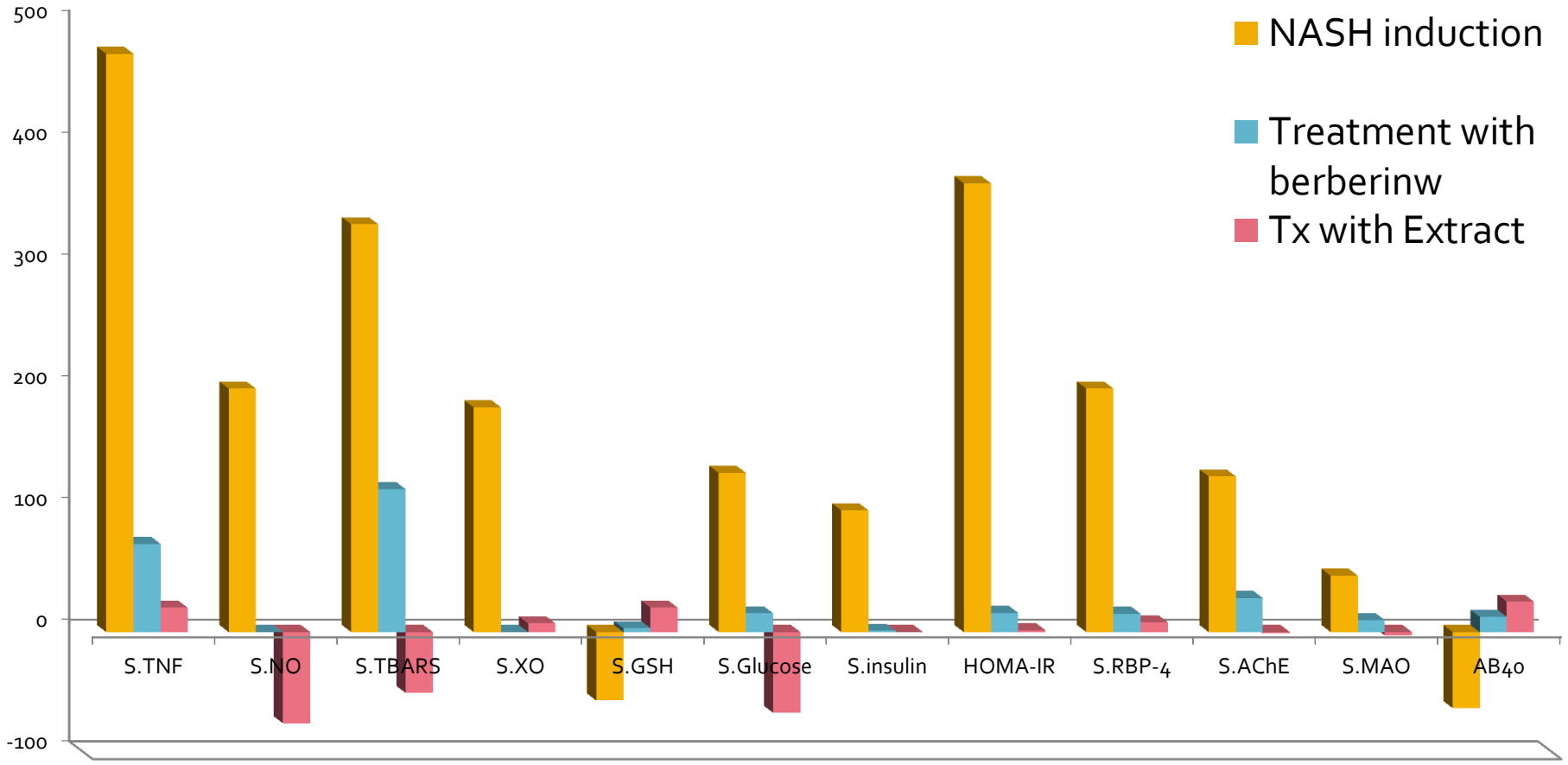


Fig. 4 showed that normal cellular architecture in the control group (Fig. 4a). During the first week of NAFLD induction, severe neurodegenerative changes with pyknosis and vacuolations was observed (Fig. 4b) that associated with cavitations in the second week of induction period (Fig. 4c). Furthermore, during the third week (NAFLD progression, neurodegeneration with eosinophilic cells, pyknosis and vacuolations were shown in Fig. 4d. Finally, severe neurodegeneration, pyknosis acuolations and
cavitations was observed during the fourth week (Fig. 4e).

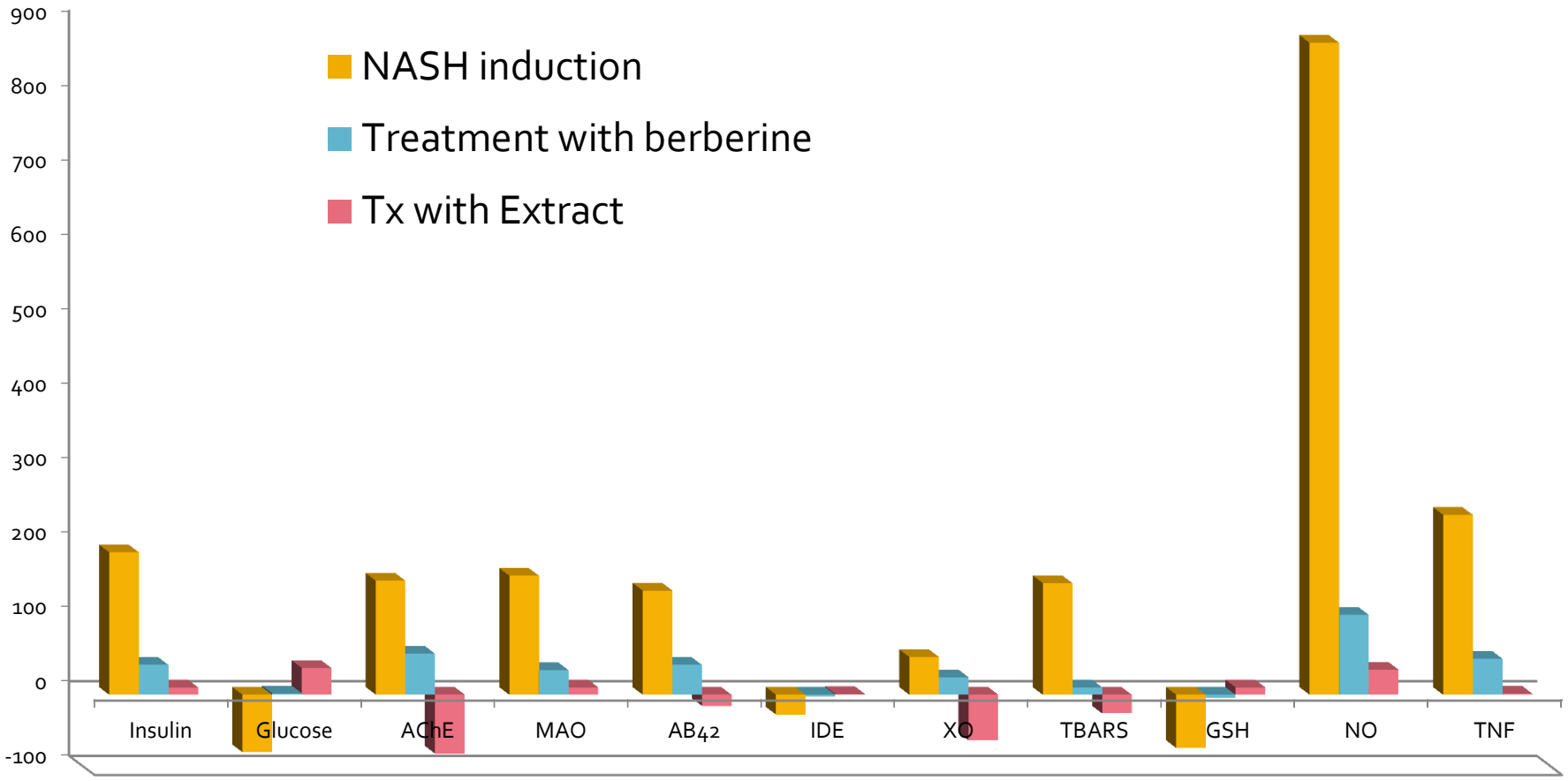

NASH
IR
Glucose, Lipid profile
ATPase hyperactivity
Lipid peroxidation
CYP 2E1
ROS and NO
AChE and MAO hyperactivation
IL6 and TNF α
B-amyloid plaque

Effect of Extract and Berberine on AD related to IR



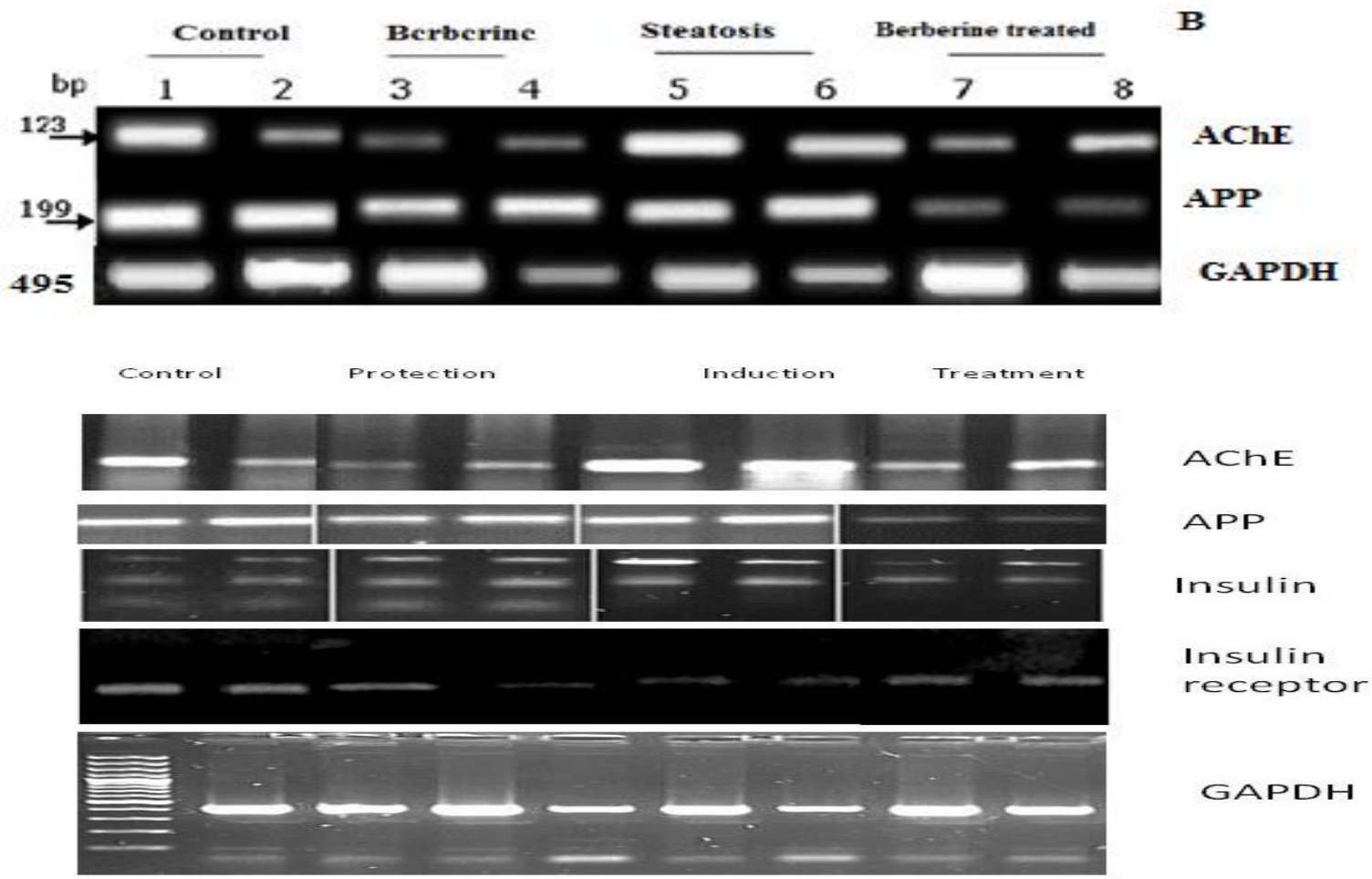
Effect of treatment on blood parameters

Effect of Extract and Berberine on AD related to IR

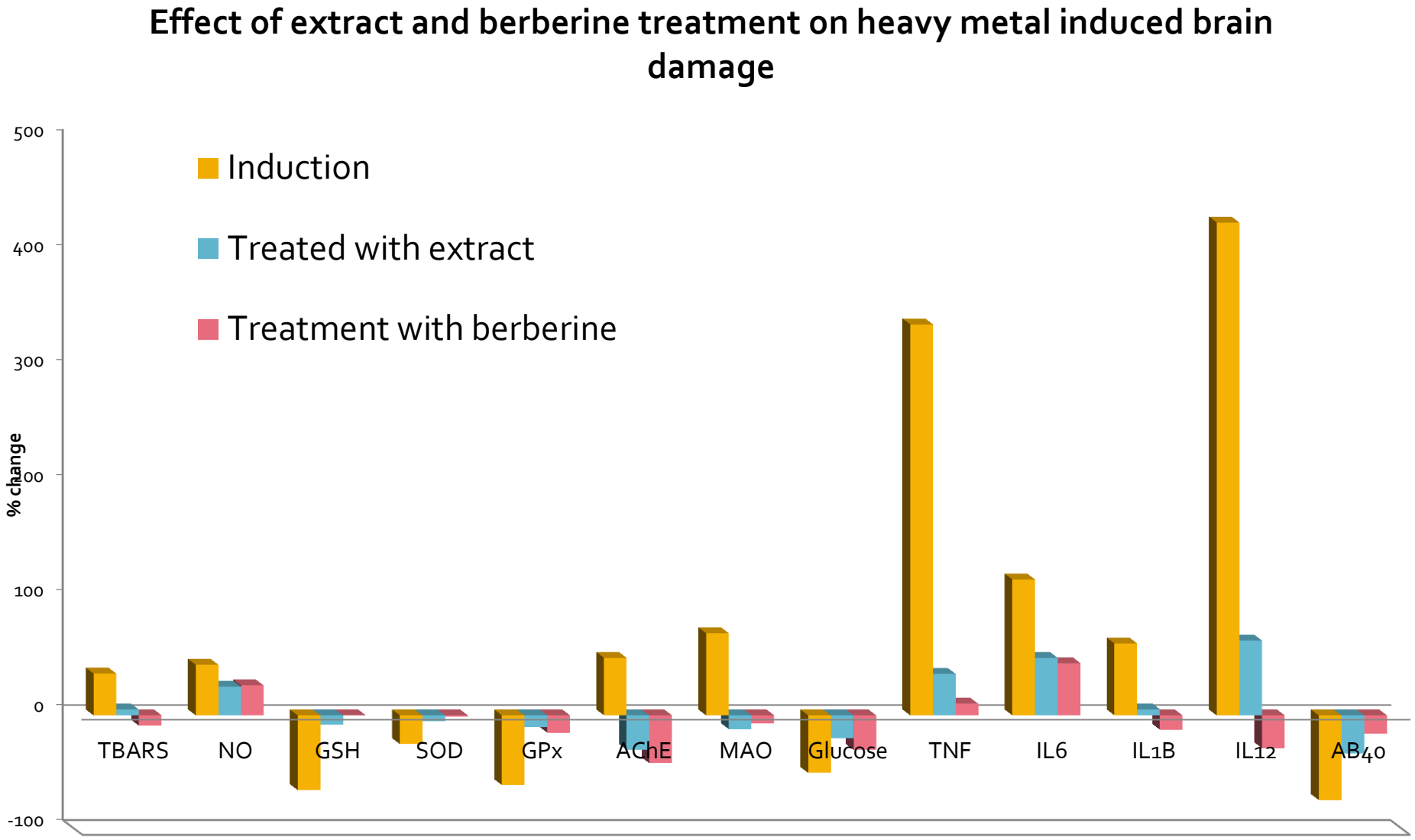


Effect of treatment on Brain parameters

Effect of Extract and Berberine on AD related to IR

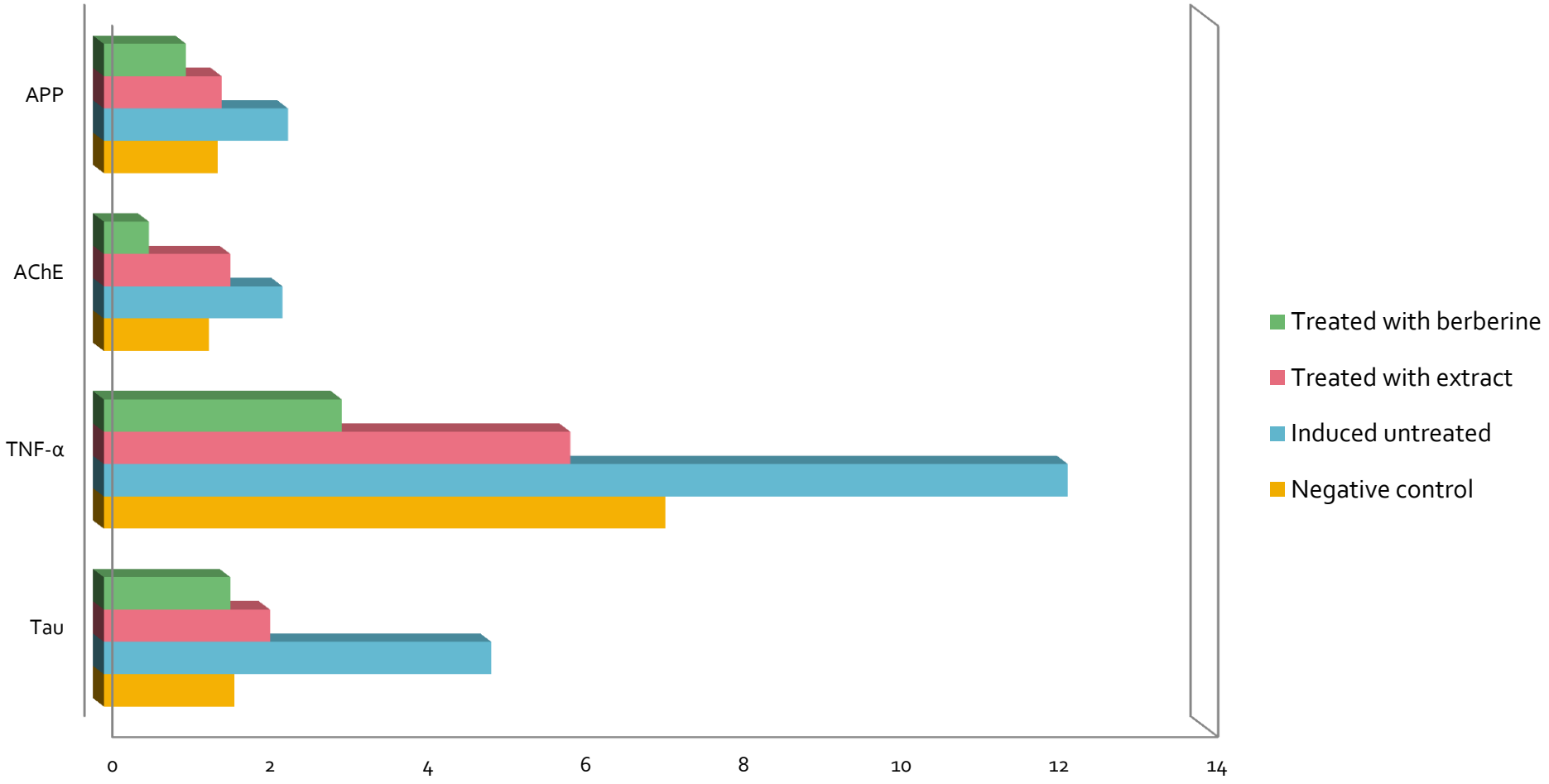


Effect of Berberine on AD related to Heavy metals intake

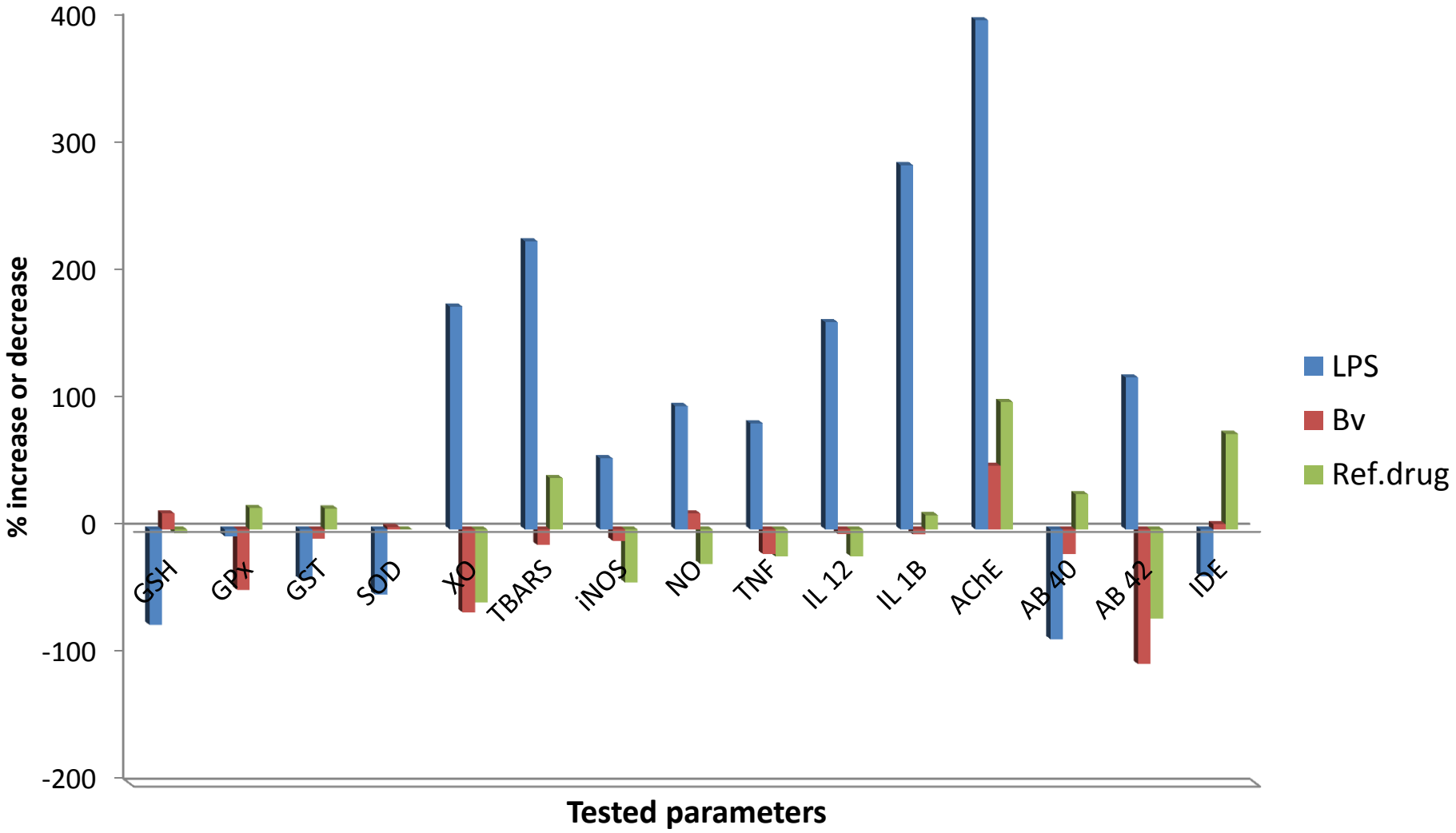


Effect of Berberine on AD related to Heavy metals intake

The effect of berberine treatment on brain gene expression of Tau, tumor necrosis factor (TNF-α), acetylcholinesterase (AChE), and amyloid precursor protein (APP) of rats administrated water contaminated with heavy metal mixture



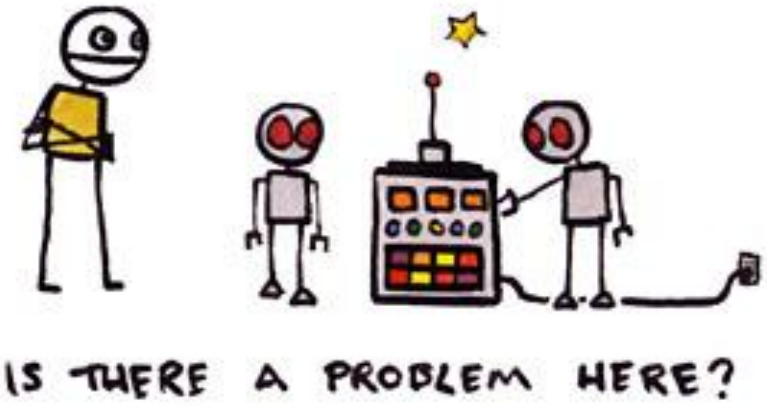
Effect of barberry extract on AD-like disease related to neuroinflammation




Focus

SO WHAT?

U want to say berberise is good candidate



The problem and solution

problem

Berberine has low bioavailability,

because the intestinal absorption of berberine is very low due to its solubility

solution

nanoparticles

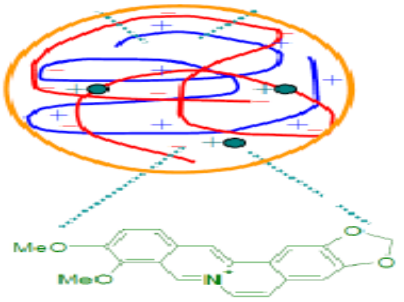
why?

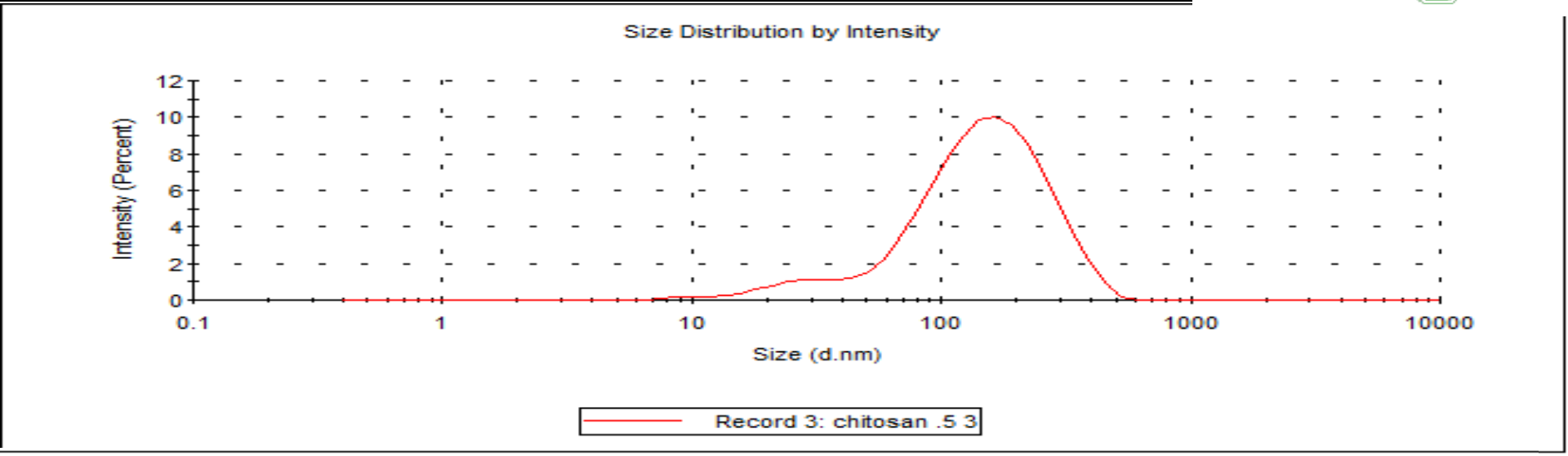
Administration by parental, oral, nasal and ocular routes.

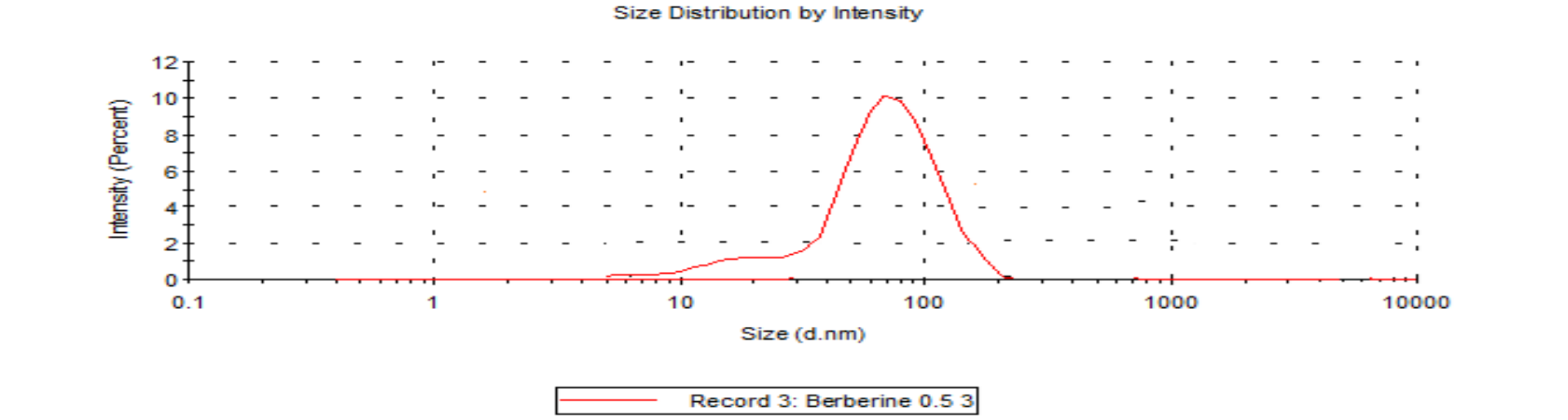
By attaching specific ligands on to their surfaces, nano particles can be used for directing the drugs to specific target cells.

Improve stability and therapeutics index and reduce toxic affect.

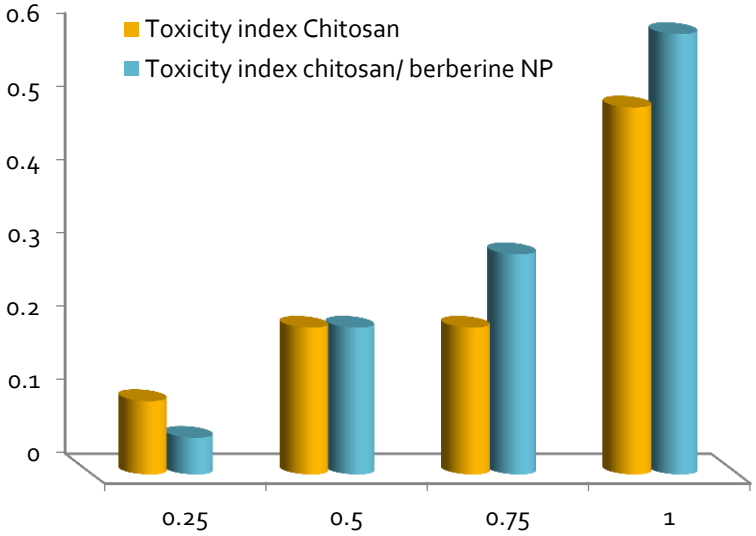
Chitosan/Ber NP

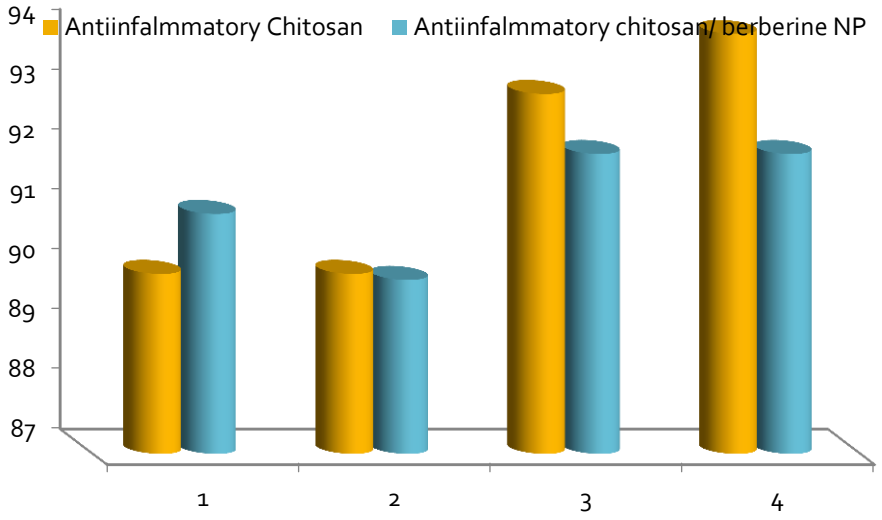


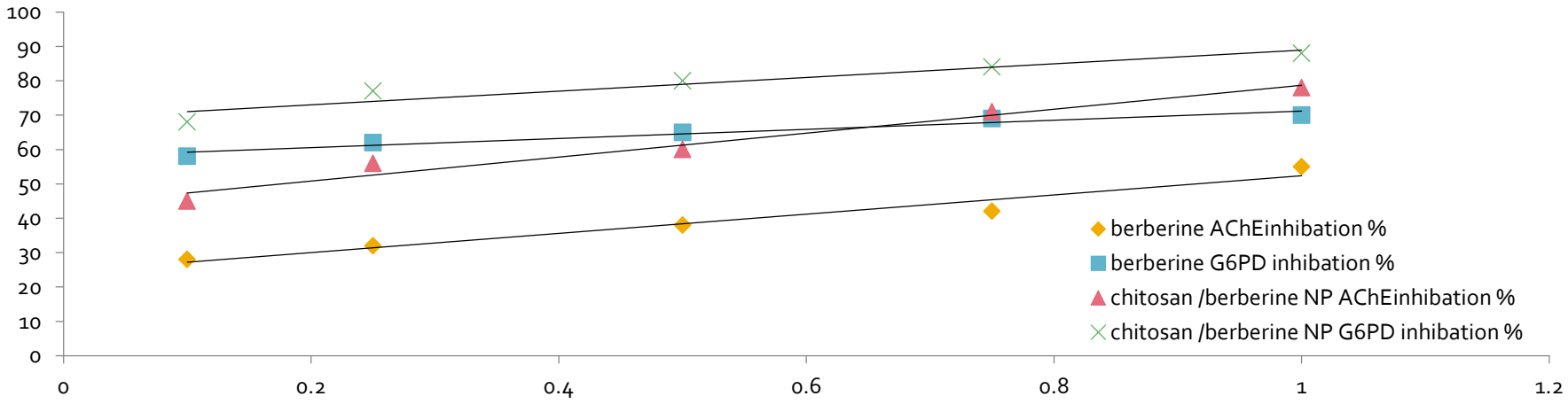




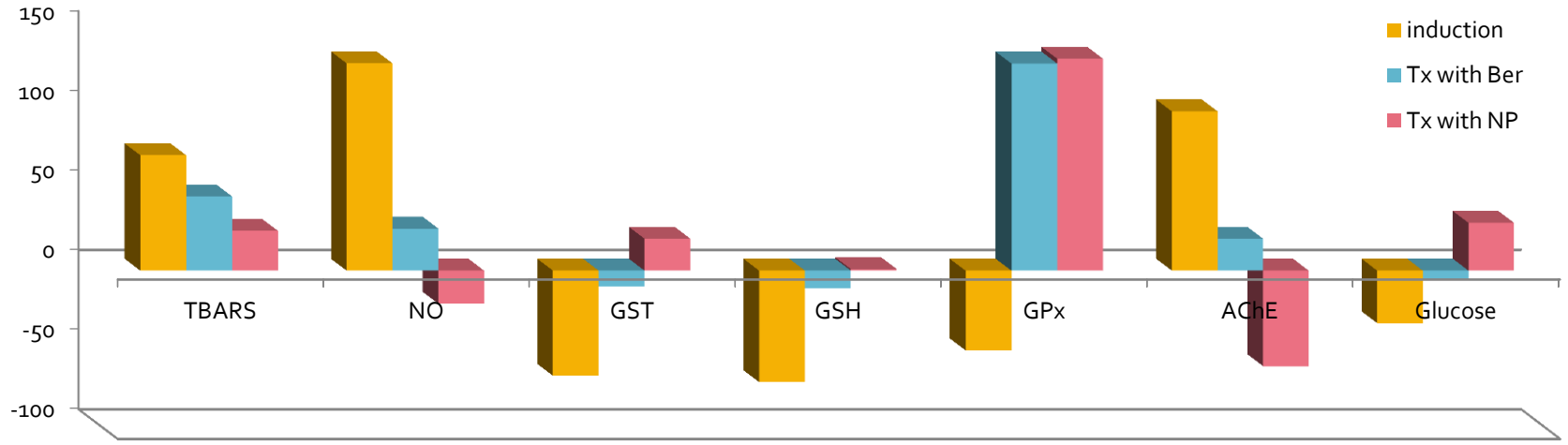
In vitro effect of Berberine nanoparticle



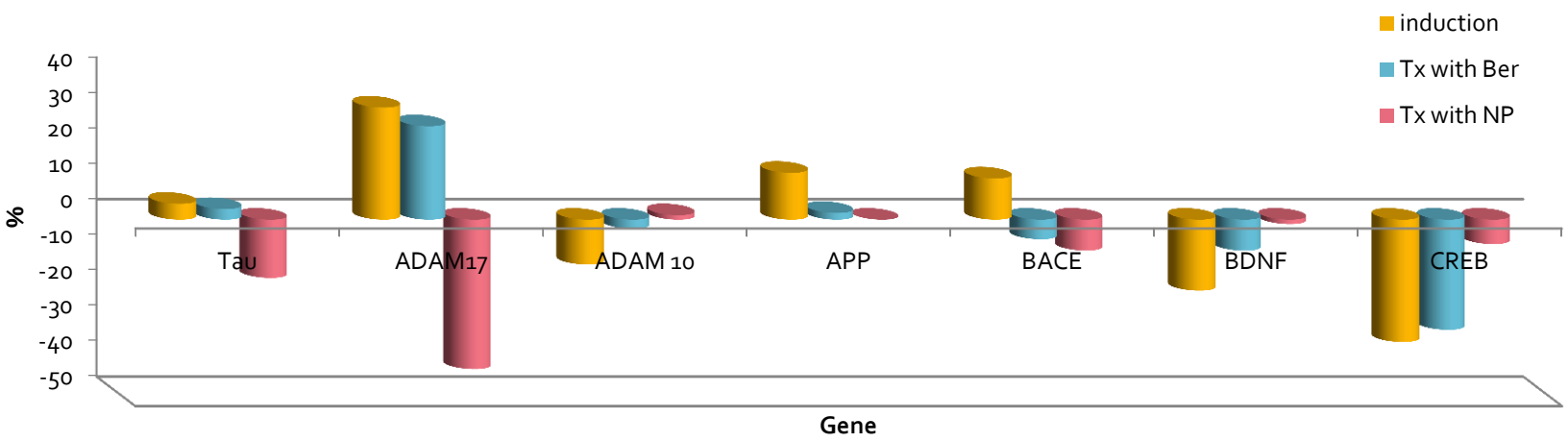




Effect of Berberine nanoparticles on AD treatment

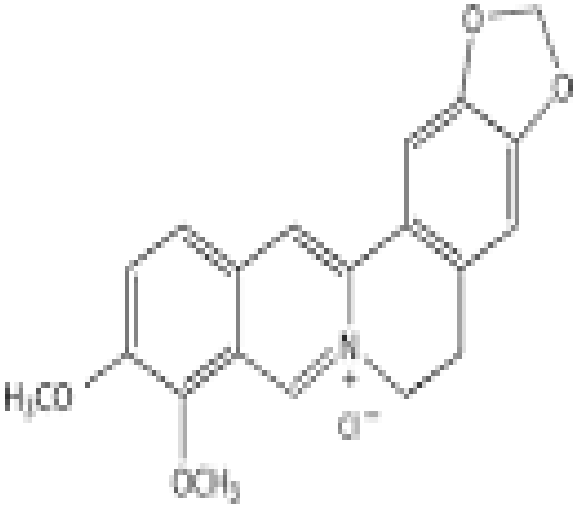


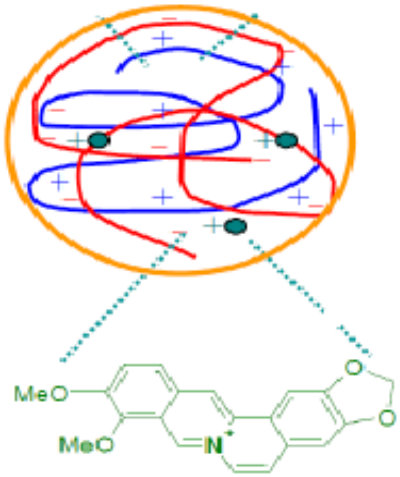
Effect of berberine or Ber-NP on relative gene expression in AD-like disease induced in animal

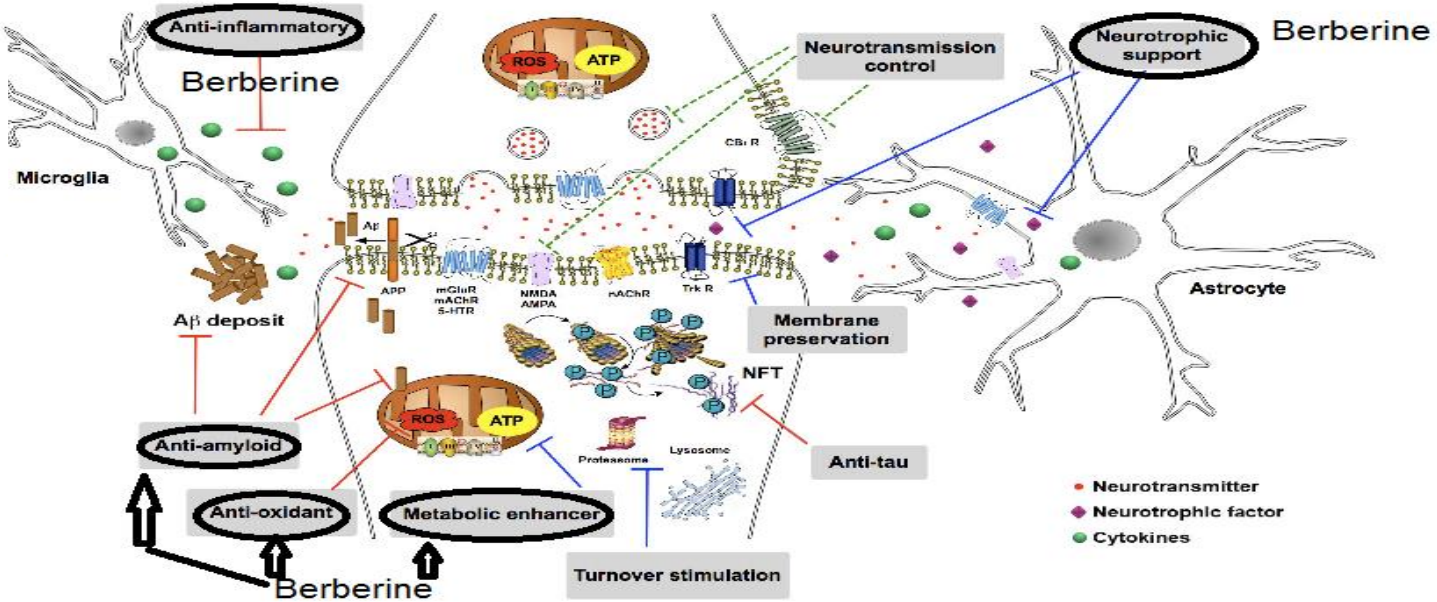


TARGET ACHIEVED

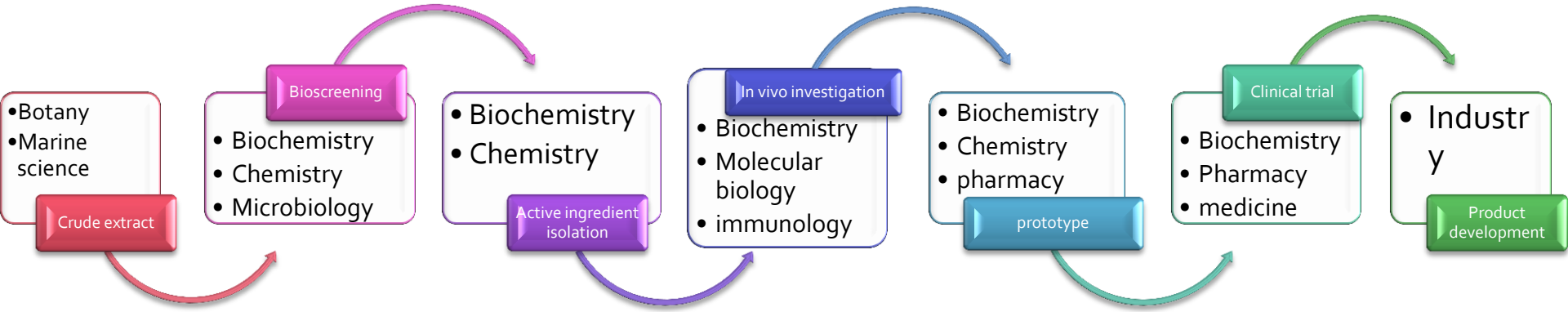
Neurotransmitter control	• Inhibits AChE
Neurotrophic factor	• Increases BDNF
Antioxidants	• Reduces ROS • Increases antioxidants
Anti-inflammatory	• Inhibits the production of TNF, ADAM, IL 1B, iNOS and COX
Metabolic enhancer	•Increases ATP, NADP
Neuron Plasticity	• increases CREB

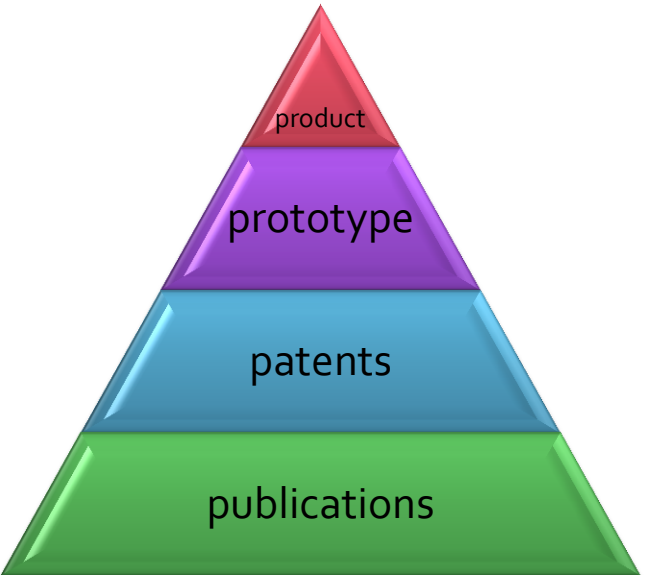






Interrelation between fields





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