V International Congress

of the Spanish Society
of Nutrition and
Orthomolecular Medicine

Madrid, 5-8th March 2020

Adaptogenic plants for stress and ageing related disorders

Alexander George Panossian, PhD, Dr.Sci.

PHYTOMED

PHYTOMED

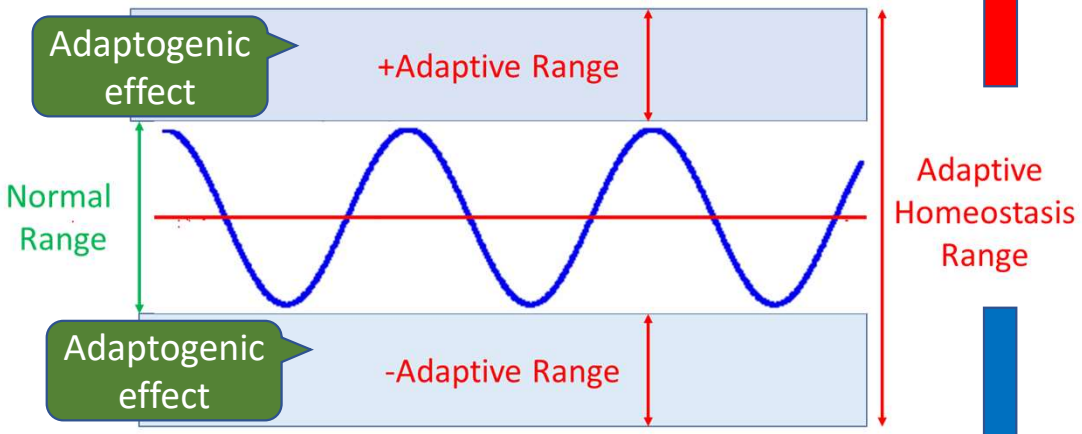
Adaptogens: definitions

- *Adaptogens* are natural stress-protective compounds or plant extracts that increase adaptability, resilience and survival of organisms.
- *Adaptability -* ability of an organism to alter itself or its responses to the changed circumstances or environment.
- *Resilience -* ability to recover readily from illness, depression, adversity or difficulties.
- Adaptogens - compounds which could increase "the state of non-specific resistance" of organisms.
- "Shanghuo" – as a state of increased susceptibility to stress and progression of diseases.

AP1

Adaptive homeostasis and homeostatic range

Any biological function, component, molecule, e.g. cortisol, CRH etc. oscillate around a mean or median, within a homeostatic range that is considered a 'normal'



Adaptive Homeostasis is the transient reversible adjustments of the homeostatic range in response to exposure to mild stressors (e.g. exercise or **adaptogens**).

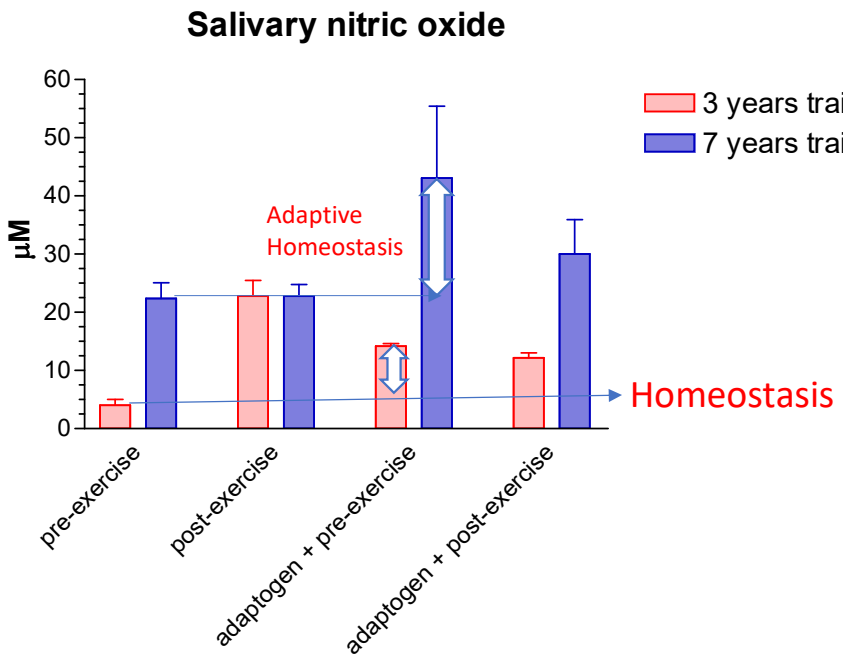
Chronically increased stress-responsive activity and increased CRH secretion is associated with:

- increased arousal or anxiety,
- increased blood pressure, tachycardia
- gastrointestinal dysfunction,
immune suppression,
melancholic depression,
suppression of feeding (anorexia),
loss of libido
chronic active alcoholism,
alcohol and narcotic withdrawal,
excessive exercising and malnutrition,

Chronically decreased stress-responsive activity and decreased CRH secretion is associated with:

- decreased arousal and performance of task,
- the chronic fatigue,
- fibromyalgia syndromes,
- increase in appetite and weight gain,
- somnolence, etc.

Adaptogens like physical exercise adjust the homeostatic range



Adaptogens are eustressors ("good stressors") - mild stressors, stress-mimetics, or challengers 'nonspecific stress- vaccines', inducing stimulating (stress-agonising) and stress-protective effect against subsequent stress.

The difference between stimulants and adaptogens

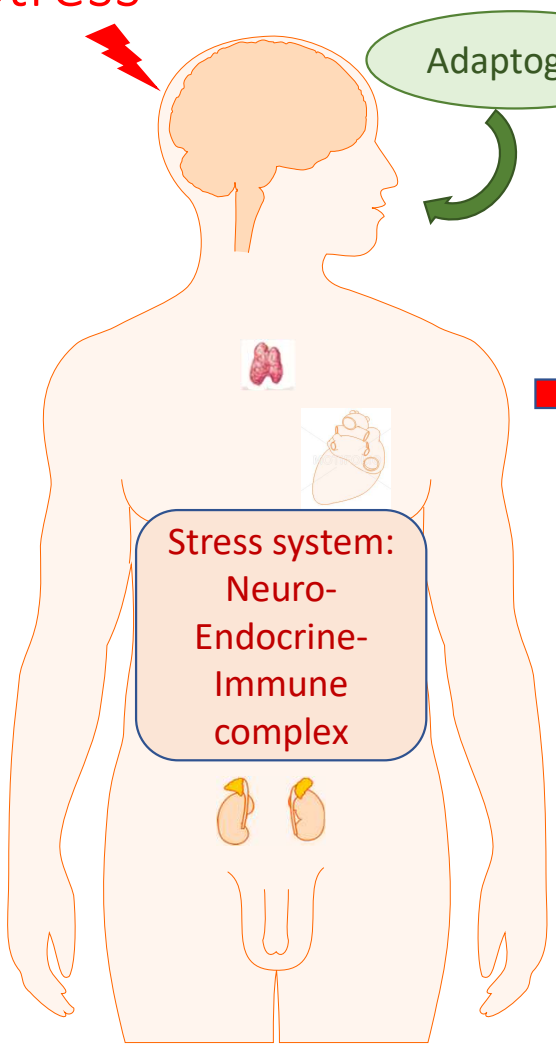
	Stimulants	Adaptogens
Stress protective (neuro-, hepato-, cardio-protective)	No	High
Recovery process after exhaustive physical load	Low	High
Energy depletion	Yes	No
Performance in stress	-	Increased
Survival in stress	-	Increased
Quality of arousal	Poor	Good
Addiction potential	Yes	No
Side effects	Yes	Rare
DNA/proteins synthesis	Decreased	Increased
NPY mediated activation of Hsp70	-	Increased

Adaptogens

- *Pharmacological activity:* adaptogenic
- *Health claims and indications for use:*
  - stress-induced fatigue,
  - stress-induced mental and behavioral disorders,
  - aging associated diseases.

Chronic stress induced symptoms

Stress



- Fatigue
- Exhaustion
- Lack of energy
- Difficulty to concentrate
- Headache
- Sleeplessness
- Irritability
- Anxiety
- Depression
- Behavioral disorders
- Eating disorders

- Muscular tension
- Backache

- High blood pressure

- Change of appetite
- Indigestion

- Sexual disfunction

Cognitive functions
Endurance

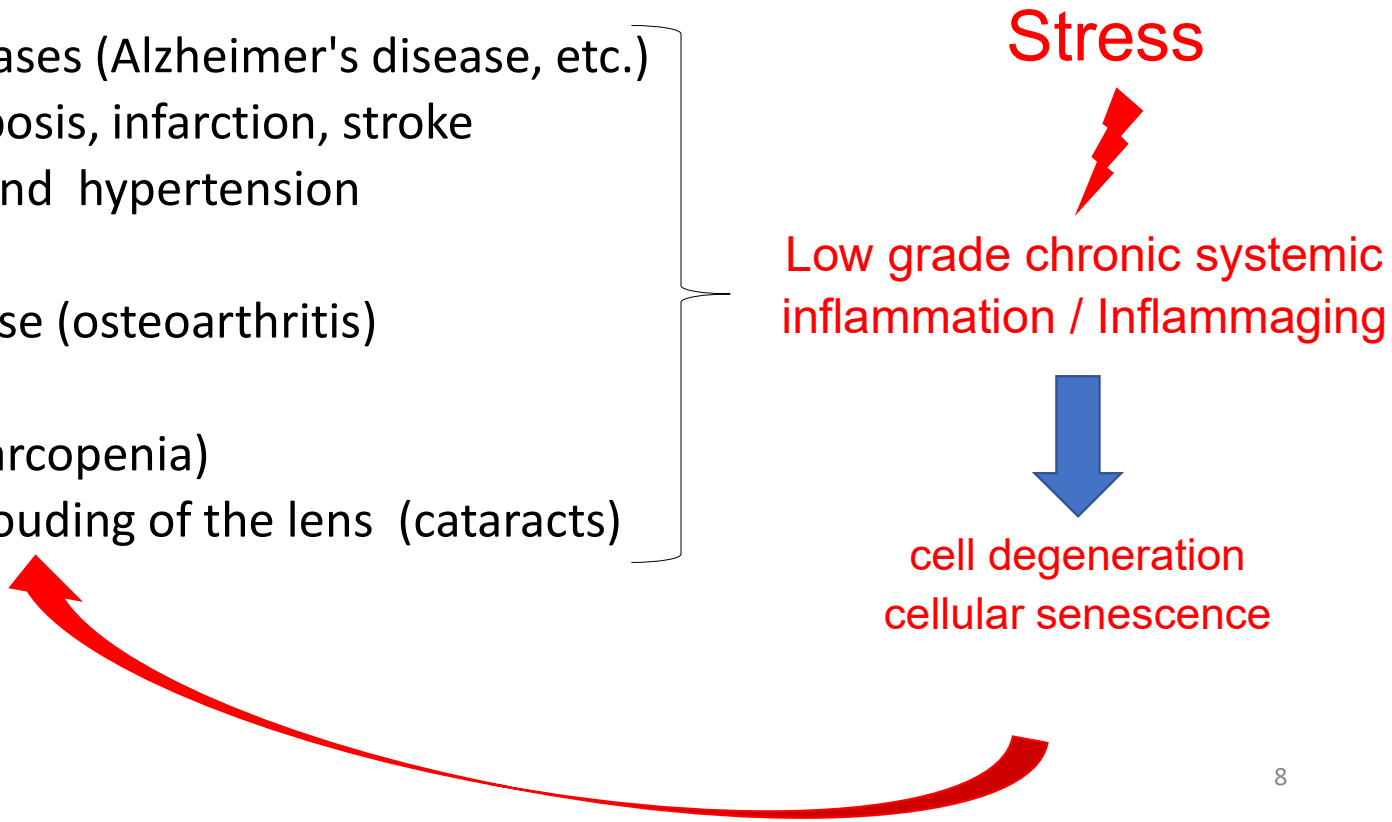
Mental performance:
- Attention
- Memory

Physical performance:
- Working capacity
- Precision
- Recovery

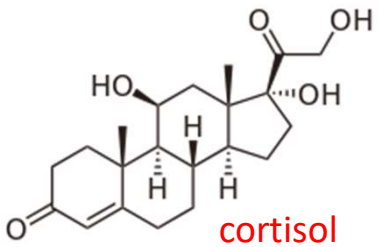
PHYTOMED

Age related diseases are health problems in senescence due to decreased adaptability to stress and an ability to maintain homeostasis

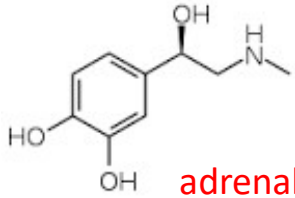
- neurodegenerative diseases (Alzheimer's disease, etc.)
- atherosclerosis - thrombosis, infarction, stroke
- cardiovascular disease and hypertension
- cancer
- degenerative joint disease (osteoarthritis)
- type 2 diabetes, obesity
- muscle degeneration (sarcopenia)
- visual loss because of clouding of the lens (cataracts)



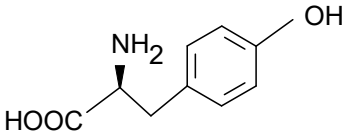
Chemistry of adaptogens



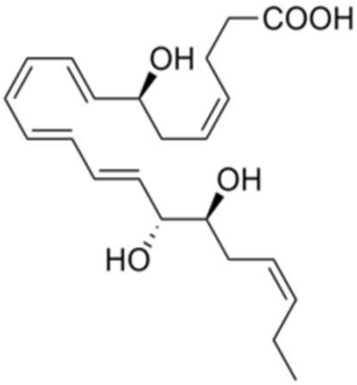
cortisol



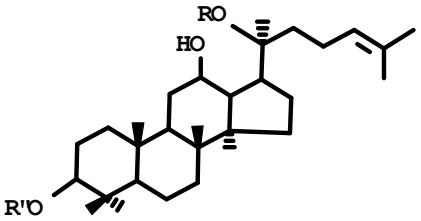
adrenalin



tyrosine

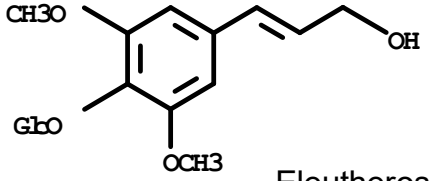


resolvine

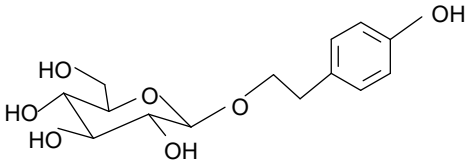


Ginsenosides Rb1, Rb2, Rc, Rd

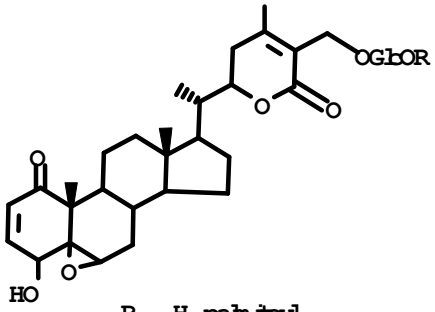
R- mono or disaccharide residue



Eleutheroside B

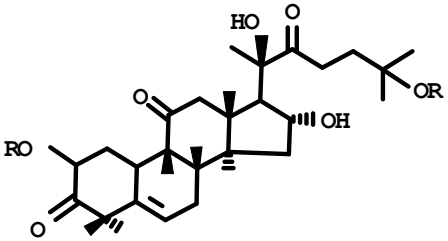


Salidroside



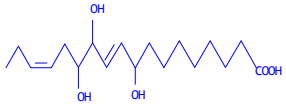
R – H, palmitoyl

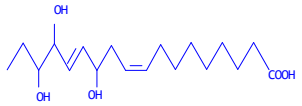
Sitondosides IX,X



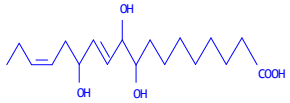
R – Glc

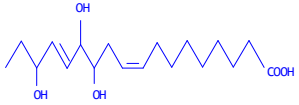
Cucurbitacin R diglugoside



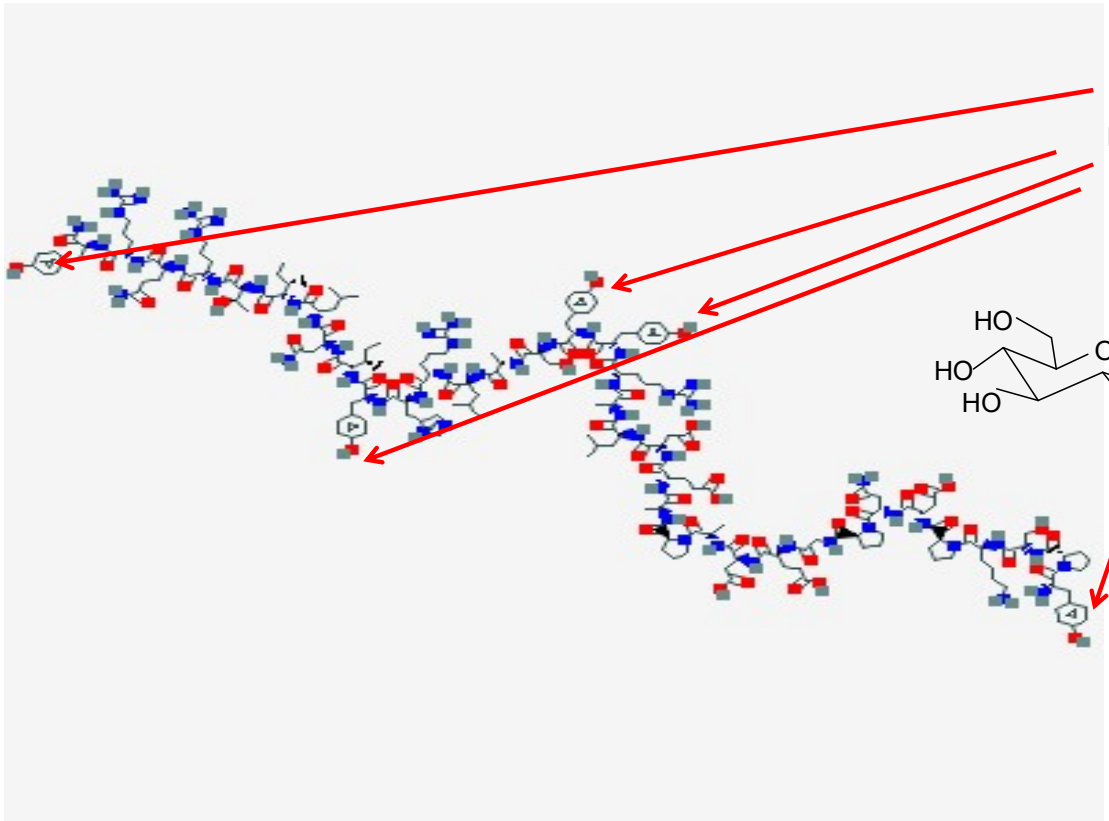


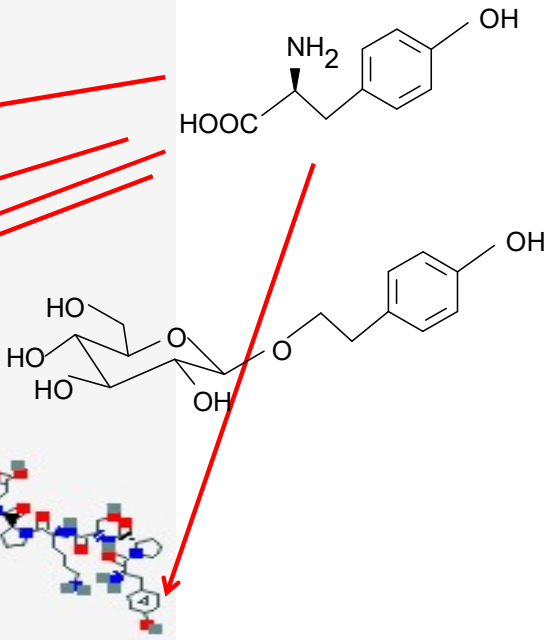
Oxylipins





Effect of salidroside on expression of NPY in neuroglia cells





Plants reported in literature as adaptogenic and antistressor

1968 - 12

Name of plant
Acanthopanax sessiliflorum Rupr.et Maxim.
Aralia manshurica Rupr.et Maxim
Aralia cordata Thunb
Aralia cordata var. sachalinensis (Regel) Nakai
Carlina biebersteinii Bernh
Echinopanax elatum Nakai
Eleutherococcus senticosis Maxim.,*
Kalopanax septemlobus (Thunb.) Koidz.
Panax ginseng C.A. Meyer
Rhaponticum carthamoides (Willd).Iljin,
Rhodiola rosea L.*,
Schizandra chinensis (Turcz.) Bail.*,

2003 - 34

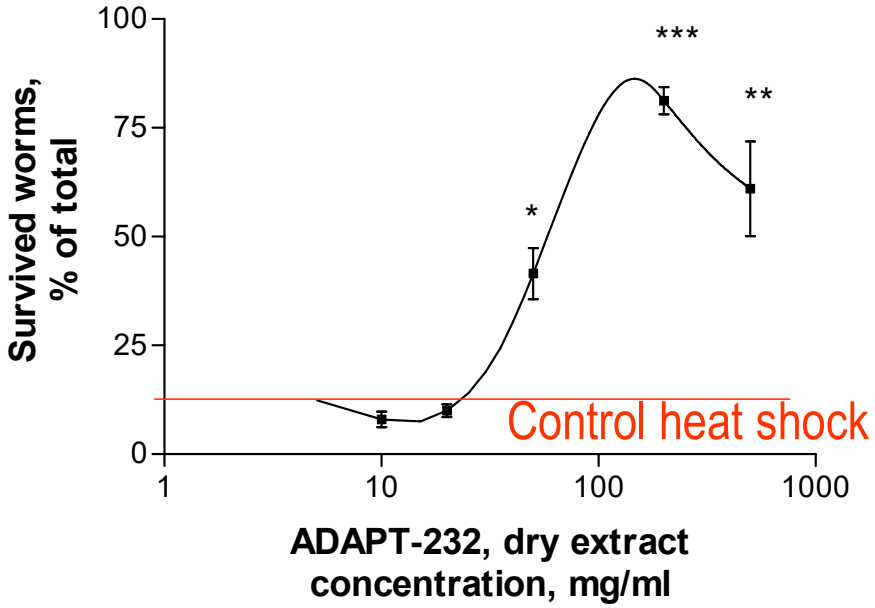
Name of plant	Family	Authors, year
Acanthopanax sessiliflorum Rupr.et Maxim.	Araliaceae	Brekhman and Dardimov, 1969
Albizzia julibrissin Durazz.	Fabaceae	Kinjo et al.,. 1991
Aralia elata (Miq) Seem.	Araliaceae	Hernandez et al., 1988
Aralia manshurica Rupr.et Maxim	Araliaceae	Baranov, 1982
Aralia schmidtii	Araliaceae	Baranov, 1982
Asparagus racemosus,	Liliaceae	Rege et al., 1999
Atragene sibirica L.	Ranunculaceae	Shilova et al., 2001
Azardirachta indica (Al, Neem),	Melaceae	Koner et al., 1997
Bergenia crassifolia (Fritsch),	Saxifragaceae	Suslov et al., 2002
Bryonia alba L.,*	Cucurbitaceae	Panossian et al., 1995
Cicer arietinum L.	Fabiaceae	Singh et al., 1983
Codonopsis pilosula (Franch.)Nannf.	Campanulaceae	Lin, 1991
Cordyceppt sinisis (Berk.)	Pyrenomycetales	
Echinopanax elatum Nakai	Araliaceae	Baranov, 1982
Eleutherococcus senticosis Maxim.,*	Araliaceae	Brekhman and Dardimov,
Emblica officinalis,(Phyllanthus emblica L)	Euphorbiaceae	Xia et al., 1997; Rege et al., 1999
Eucommia ulmoides Oliver	Eucommiaceae	Oshima et al., 1988
Hoppea dichoroma Wild.	Gentianaceae	Ghosal et al., 1985
Ocimum sanctum L.	Lamiaceae	Bhargava and Singh, 1981
Panax ginseng C.A. Meyer	Araliaceae	Brekhman and Dardimov,
Pfaffia paniculata(Marius)Kuntze	Amarantaceae	De Oliveira, 1986
Rhaponticum carthamoides (Willd).Iljin,	Asteraceae	Brekhman and Dardimov, 1969
Rhodiola crenulaya (Hook, f. et Thoms) H.Ohba	Crassulaceae	Wang and Wang, 1992
Rhodiola rosea L.*,	Crassulaceae	Saratikov et al., 1968
Scutellaria baicalensis (Georgi) .	Lamiaceae	Suslov et al., 2002
Schizandra chinensis (Turcz.) Bail.*,	Magnoliaceae	Brekhman, 1980
Sterculia plantanifolia L.	Streculiaceae	Brekhman, 1980
Terminalia chebula	Combretaceae	Rege et al., 1999
Tinospora cordiflora Miers	Menispermaceae	Parel et al., 1978; Rege et al., 1999
Trichopus zeylanicus Gaerten.	Trichopodaceae	Singh et al., 2001
Withania somnifera L.	Solanaceae	Singh et al., 1982

2019: 111 plants reported in literature as adaptogenic

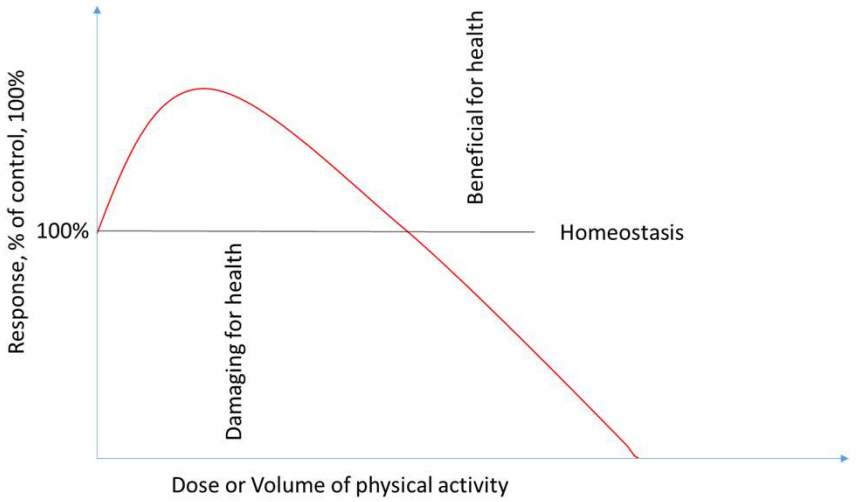
Acanthopanax sessiliflorum Rupr.et Maxim.	*Azardirachta indica (Al, Neem),*	Curcumin from Turmeric *(Curcuma longa)*	*Heteropterys aphrodisiaca Machado*	*Mussanenda frondosa*	*Ptychopetalum olacoides* Benth.	*Solanum torvum* SW.
Aegle marmelos	*Bacopa monnieri* (L.) Wettst	*Dioscorea deltoidea* Wall. ex Griseb.	*Hibiscus cannabinus*	*Nelumbo nucifera* Gaertn.	*Pueiaria tuberosa Roxb*	*Sterculia plantanifolia L.*
Ajuga turkestanica (Regel) Briq.	*Bergenia crassifolia* (L.) Fritsch	*Diospyros peregrina gurke*	*Hippophae rhamnoides L.*	*Nigella sativa*	*Rhaponticum carthamoides* (Willd.) Iljin	*Sutherlandia frutescens* (L.) R.Br.
Albizzia julibrissin Durazz.	*Boerhaavia diffusa*	*Drypetes roxburghii* (Wall.) Hurus.	*Holoptelea integrifolia* Planch	*Ocimum sanctum* L.	*Rhodiola crenulaya (Hook, f. et Thoms) H.Ohba*	*Terminalia chebula* Retz.
Alstonia scholaris (L.) R. Br.	*Bryonia alba* L.	*Echinopanax elatum Nakai*	*Hoppea dichotoma* Willd.	*Oplopanax elatus* (Nakai) Nakai	*Rhodiola heterodonta* (Hook. f. & Thomson) Boriss.	*Tinospora cordifolia* (Willd.) Miers
Allium sativum	*Butea monosperma*	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.	*Hypericum perforatum* L.	*Panax ginseng* C.A.Meyer.	*Rhodiola imbricata*	*Tinospora malabarica*
Anacyclus pyrethrum (L.) Lag.	*Caesalpinia bonduc* (L.) Roxb	*Eleutherococcus sessiliflorus (Rupr. & Maxim.) S.Y.Hu*	*Labisia pumila*	*Panax notoginseng* (Burk.) FH Chen	*Rhodiola rosea* L.	*Tribulus terrestris*
Andrographis paniculata (Burm.f.) Nees	*Carum carvi*	*Emblica officinalis* Gaetrn.	*Lagenaria siceraria*	*Panax pseudoginseng* Wall.	*Rostellularia diffusa* (Willd.) Nees .	*Trichilia catigua* A.Juss.
Annona muricata	*Centella asiatica* (L.) Urb.	*Eucommia ulmoides* Oliv.	*Lepidium peruvianum/ Lepidium meyenii* Walp.	*Pandanus odoratissimus* L.f.	*Rubia cordifolia*	*Trichopus zeylanicus* Gaertn.
Aralia elata (Miq) Seem.	*Chlorophytum borivilianum* Santapau & R.R.Fern.	*Eugenia caryaphullus*	*Ligusticum striatum DC.*	*Paullinia cupana* Kunth	*Salvia miltiorrhiza* Bunge	*Trigonella foenom graecum*
Aralia mandshurica Rupr. & Maxim	*Chrysactinia mexicana* A. Gray	*Evolvulus alsinoides* (L.) L.	*Melilotus officinalis (L.) Pall.*	*Pfaffia paniculata* (Mart.) Kuntze	*Schisandra chinensis* (Turcz.) Baill.	*Tylophora indica*
Aralia schmidtii	*Cicer arietinum* L.	*Fagopyrum esculentum*	*Mitragyna africanus*	*Piper longum* L.	*Scutellaria baicalensis* Georgi	*Turnera diffusa* Willd. ex Schult.
Argyreia nervosa (Burm. f.) Bojer	*Cnestis ferruginea(*	*Firmiana simplex* (L.) W.Wight	*Momordica charantia*	*Polyalthia cerasoids*	*Serratula inermis*	*Vitis vinifera* L.
Argyreia speciosa (L. f.) Sweet	*Codonopsis pilosula* (Franch.) Nannf.	*Gentiana pedicellata* (D.Don) Wall	*Morus alba* L.	*Potentilla alba* L.	*Sida cordifolia* L.	*Withania somnifera* (L.) Dunal
Asparagus racemosus Wild	*Convolvulus prostratus* Forssk.	*Ginkgo biloba*	*Mucuna pruriens* (L.) DC.	*Prunella vulgaris*	*Silene italica (L.) Pers.*	*Zingiber officinale*
Atragene sibirica L	*Curculigo orchioides* Gaertn.	*Glycyrrhiza glabra* L.	*Murraya koenigii(Rutaceae)*	*Psidium guajava*	*Sinomenium acutum (Thunb.) Rehder & E.H.Wilson*	

Stress-protective effect of ADAPT-232 in *C.elegans*

ADAPT-232 increases survival of *C. elegance* treated with heat shock at the seventh day of their life span in a dose dependent manner



Adaptive (hormetic) stress response



This phenomenon has been commonly observed in biology and medicine, and has been described as adaptive stress response, preconditioning, 'hormesis' or adaptive homeostasis

Key points in understanding adaptogenic activity

- Evolutionary, adaptogens together with other plant secondary metabolites play a role in defense and adaptive response against various environmental stressors including physical (e.g., intense sunlight, UV, darkness, heat, cold), chemical, and biological (e.g., microorganisms, insects and other pests) .
- At the relatively small doses these natural compounds are not toxic in humans, but still induce mild cellular stress responses.
- One basic mechanism of action of adaptogens that is that they activate adaptive stress response in humans .
- Adaptogens trigger adaptive stress response by stimulating cellular and organismal defense systems, activating intracellular and extracellular adaptive signaling pathways, expression of stress-activated proteins, resulting in transient change in protection or repair capacity and increased of non-specific resistance and adaptation to stress.

Mediators and effectors of adaptive stress response signaling system regulated by adaptogens

ADAPTIVE STRESS RESPONSE FACTORS

- exercise
- dietary energy restriction
- **nutrition and medications, adaptogens**
- cognitive stimulation / emotions
- toxins
- radiation
- temperature

MEDIATORS OF CELL ADAPTIVE STRESS RESPONSE SIGNALING SYSTEM

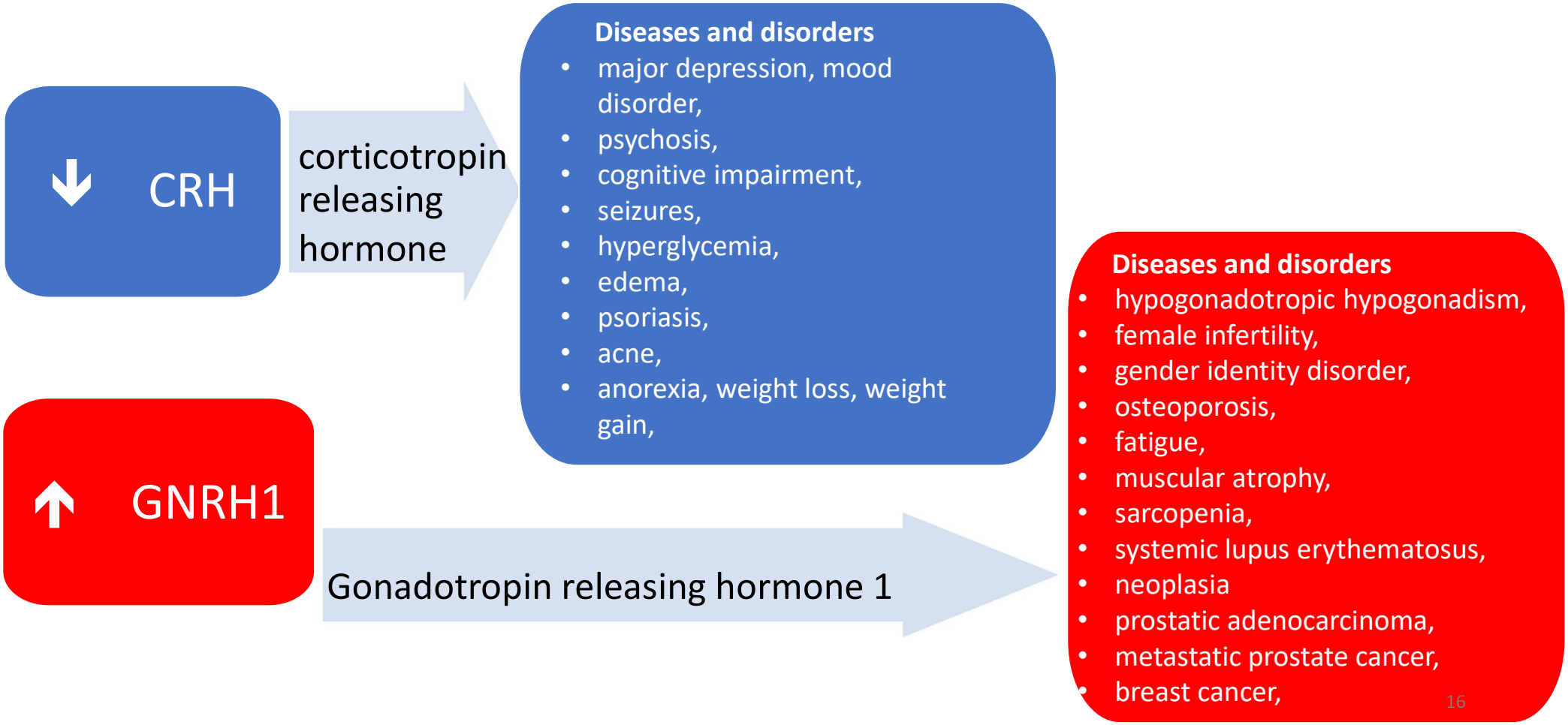
- Hormones: CRH, UCN, GNRH1
- Receptors: GPCR (CHRM4, VIPR2), TLR9, PRLR , CHNRE, RORA
- Ion channels: Ca+2 and K+ voltage-gated channels proteins, etc.
- Enzymes (PLC, AC,GC) and second messengers (IP3, DAG, cAMP)
- Kinases: PKC, PI3K, MAPK10, MAPK13, PRKCH
- Phosphatases: PTPRD, PTPRR
- Transcription and nuclear factors: STAT5A , FOS, **FOX0**, SCX, **Nrf-2,** CREB, NF-kB, Zinc finger proteins

ADAPTIVE STRESS RESPONSE EFFECTORS

Antioxidant enzymatic system: superoxide dismutase, catalase. glutathione peroxidase

Protein chaperones, growth factors and defense response proteins: HSP-70, HSPA6, STIP1, PDE9A, PDE3B, GUCY1A2, LDHD, CEL, AOC3, LIPE, etc.

Effect of adaptogens on HPA axis hormones encoding genes expression



Transmembrane receptors

TLR9 ↑ — Toll-like receptor

Biological processes

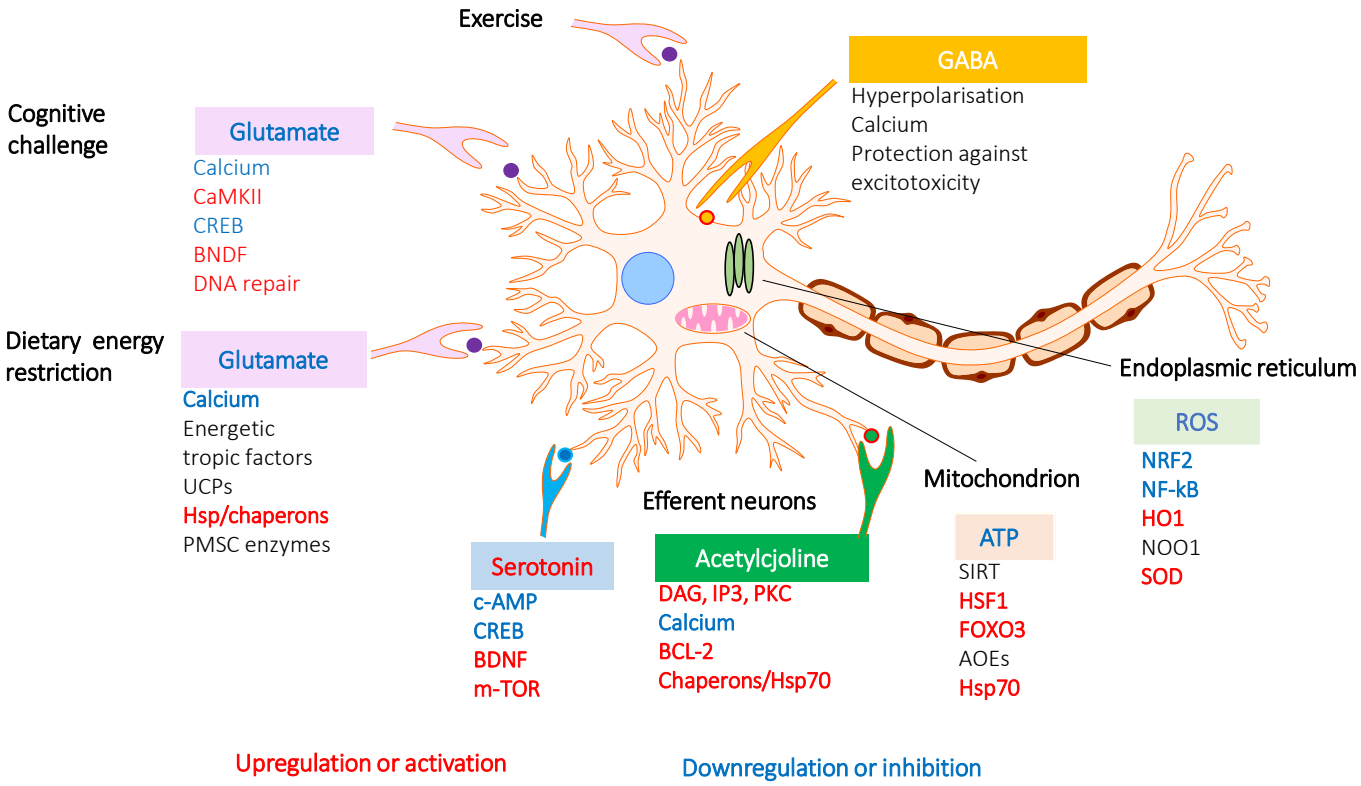
- pathogen recognition
- activation of innate immunity
- defense response to bacteria and viruses;
- inflammatory response;
- maintenance of gastrointestinal epithelium;
- male gonad development;
- microglial cell activation and axonogenesis;

Diseases and disorders

- hyperprolactinemia,
- cancer,
- ulceration,
- insulin resistance,
- impaired glucose tolerance,
- hyperleptinemia,
- hyperglycemia,
- hypoglycemia,
- hypocalcemia,
- hypoinsulinemia,
- obesity.

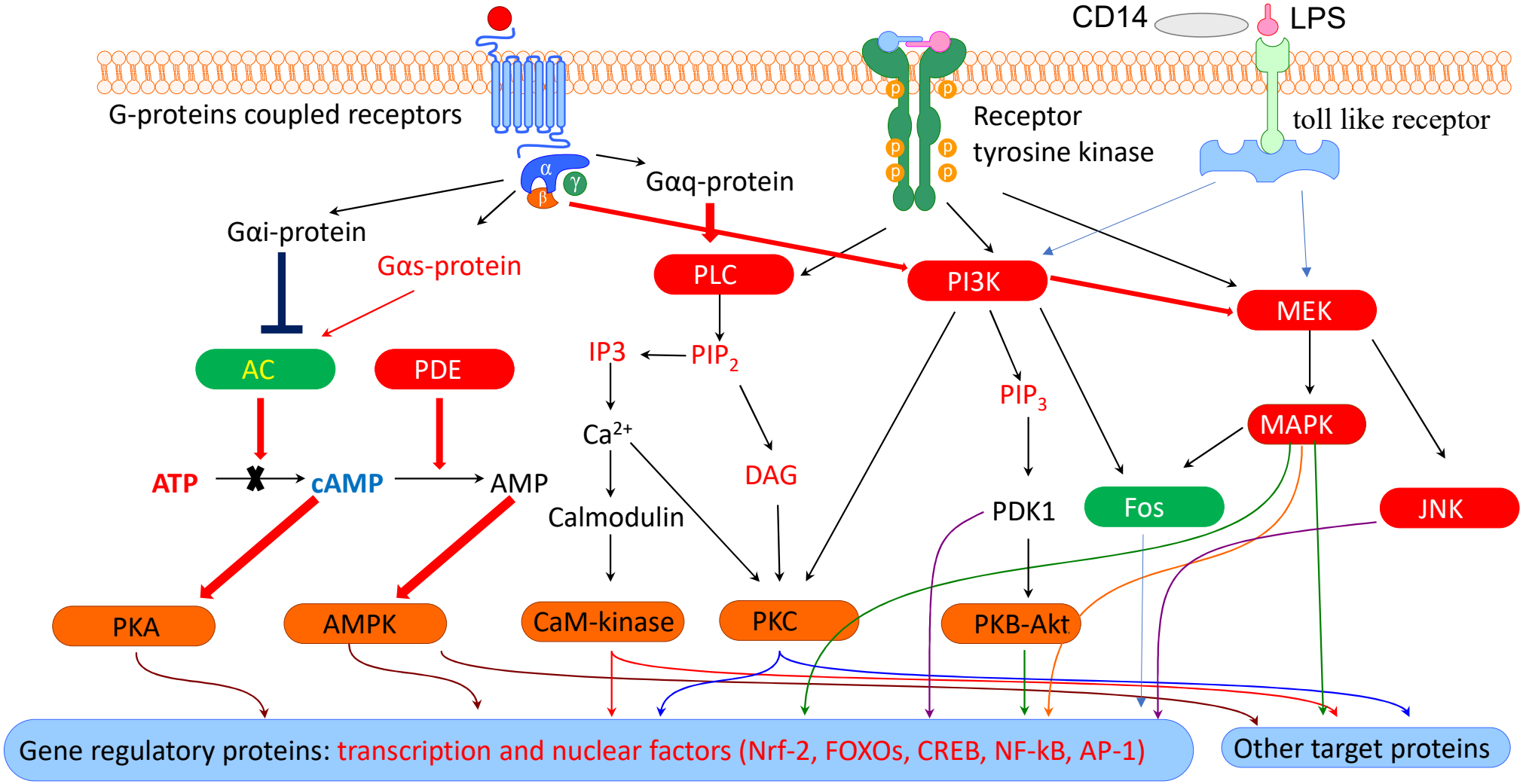
PRLR ↓ — prolactin receptor

Effects of adaptogens on adaptive stress response signaling pathways that protect neurons against degeneration and promote synaptic plasticity.

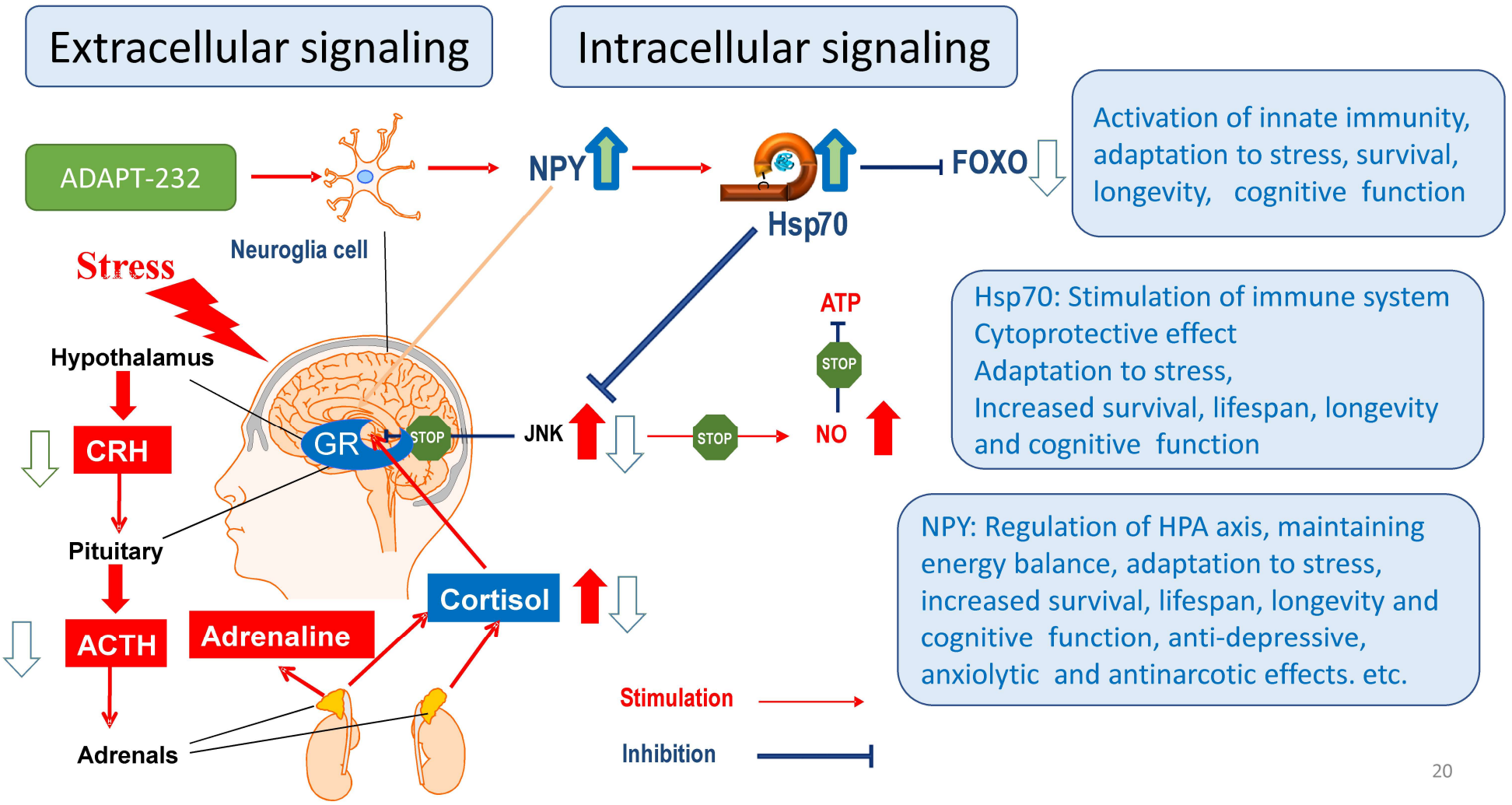


Stranahan, A.M. &M.P.Mattson. 2012. Recruiting adaptive cellular stress responses for successful brain ageing. *Nat. Rev. Neurosci.* **13:** 209–216.
Panossian A.G. 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N.Y. Acad. Sci. 1401(1):49-64.

The effect of adaptogens on adaptive stress response signaling pathways



Effects of adaptogens on adaptive stress response in HPA axis

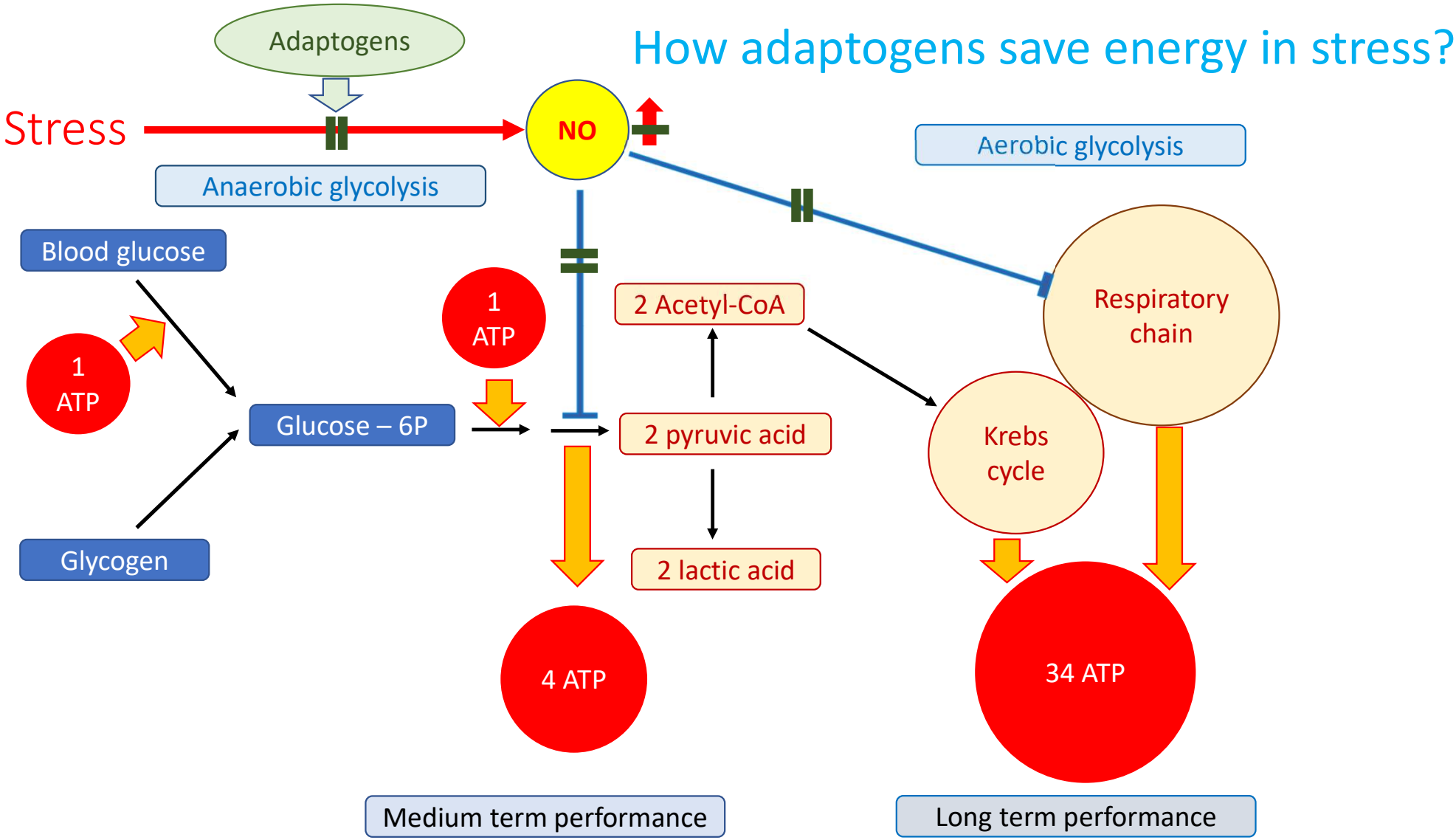


Definition based on the mechanisms of action

Criterias of adaptogenic activity

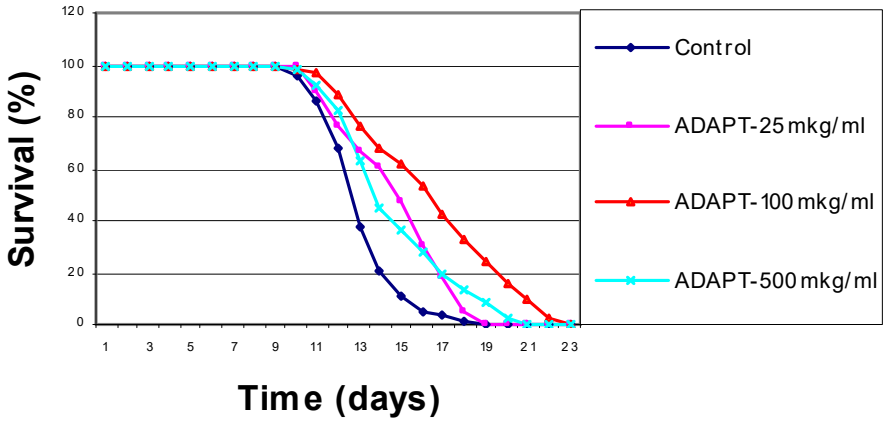
- *Mechanism of action.* Multitarget effect on neuroendocrine-immune system including:
  - triggering of intracellular and extracellular adaptive signaling pathways that promote cell survival and organismal resilience in stress
  - regulation of metabolism and homeostasis via effects on expression of stress hormones (corticotropin and gonadotropin releasing hormones, urocortin, cortisol, neuropeptide Y, heat shock proteins Hsp70) and their receptors.

Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. Phytomedicine, 50 (2018) 257-284. https://doi.org/10.1016/j.phymed.2018.09.204
https://www.sciencedirect.com/science/article/pii/S0944711318304835?via%3Dihub

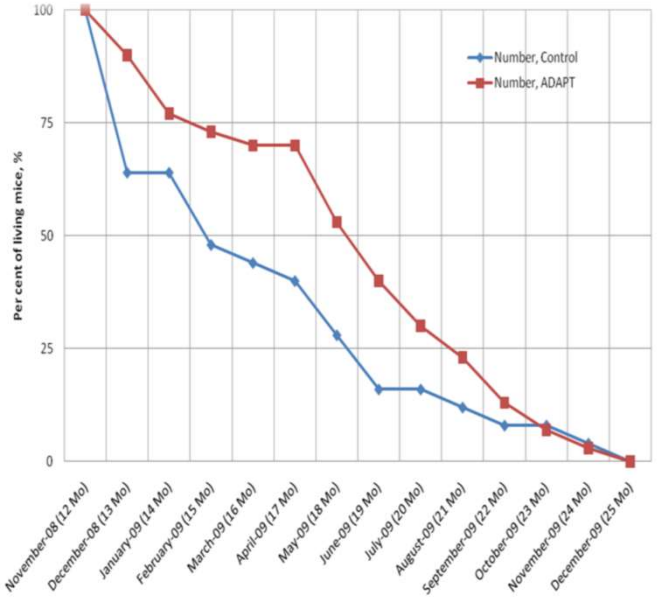

How adaptogens save energy in stress?
Adaptogens
Stress
NO
Anaerobic glycolysis
Aerobic glycolysis
Blood glucose
1 ATP
Glucose – 6P
Glycogen
1 ATP
2 Acetyl-CoA
2 pyruvic acid
2 lactic acid
Respiratory chain
Krebs cycle
4 ATP
34 ATP
Medium term performance
Long term performance

Why adaptogens are useful in ageing?

Effect of ADAPT-232 on the lifespan of *C.elegans*



Effect of ADAPT on the lifespan of mice in stressful environment

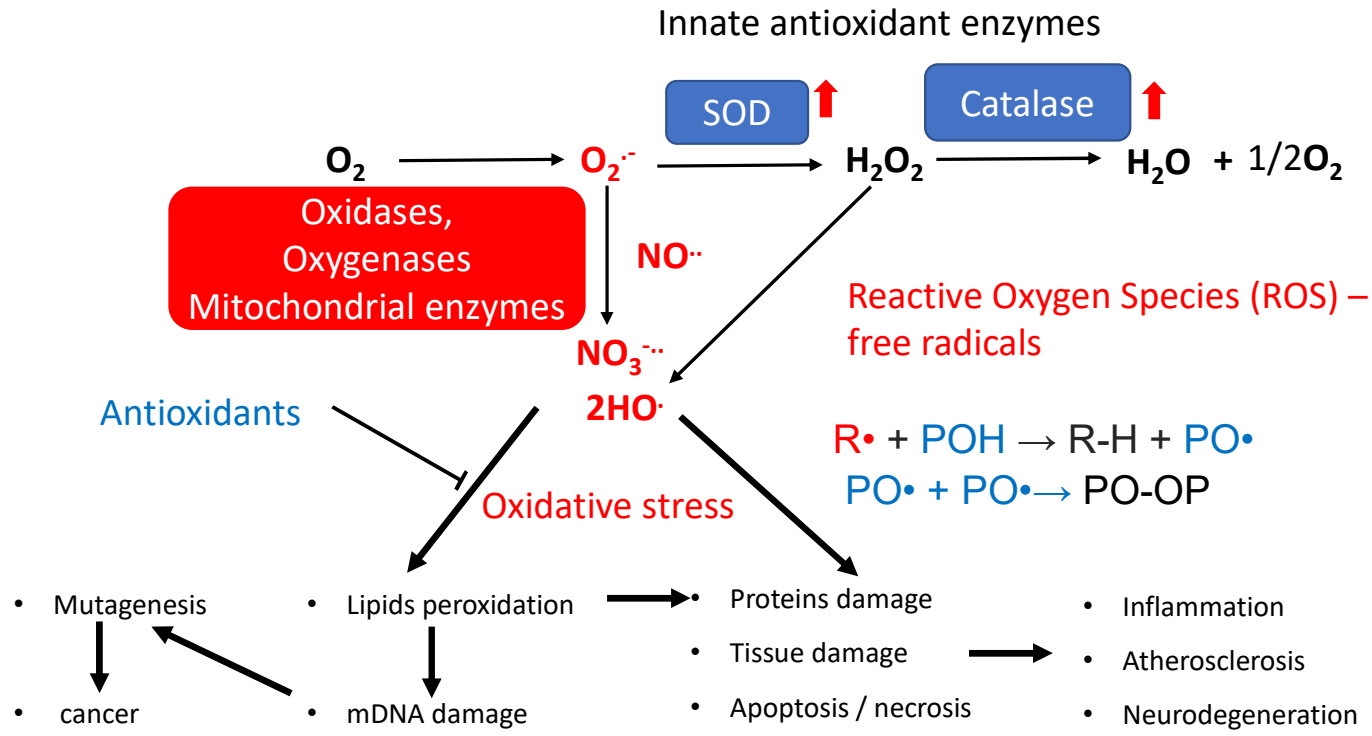


Effect of ADAPT on ageing related disorders in two years old rats

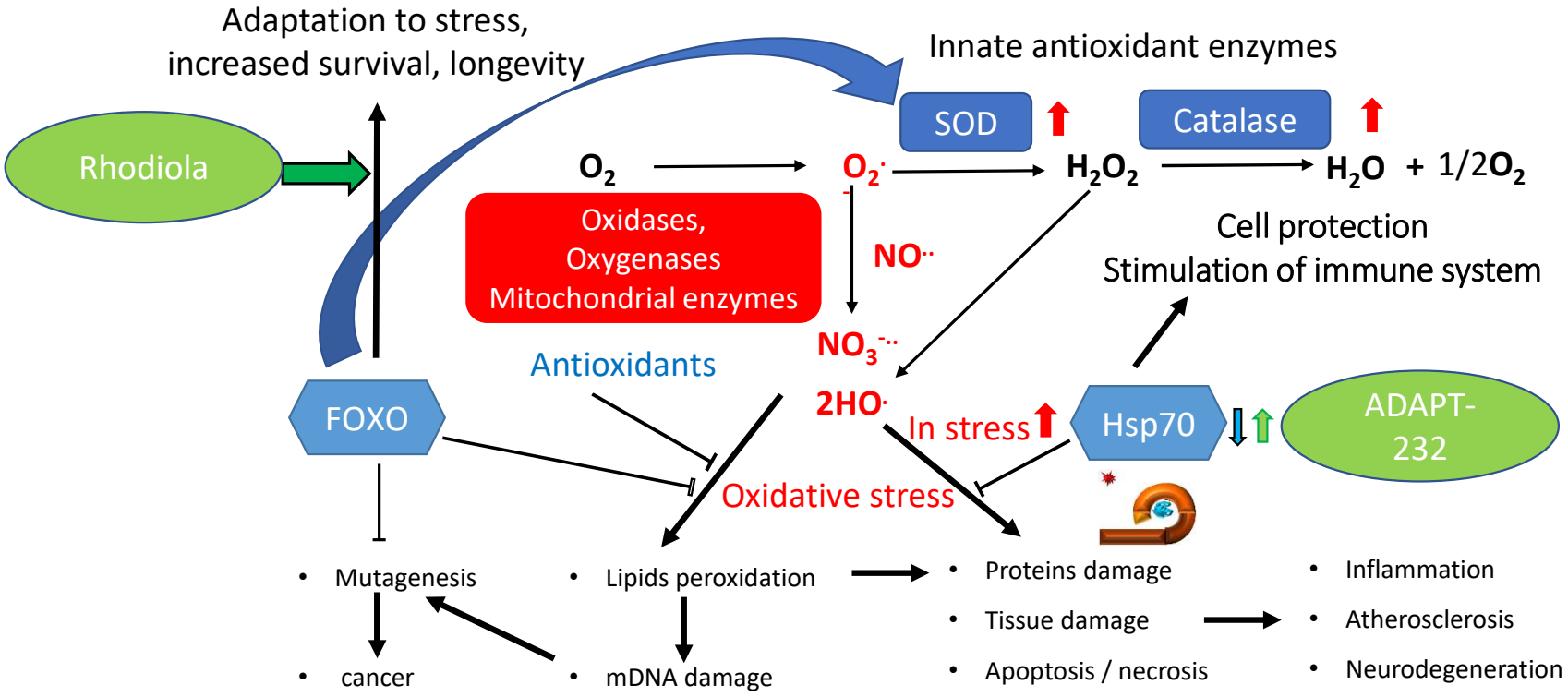
A 4 months treatment of 2 years old rats showed that in comparison with the control group the ADAPT-232 group showed:

- no development and progression of cardiac insufficiency and hypercholesterolemia ,
- better CNS functioning (prevention of losses of memory and learning ability),
- normal protein synthesis and activity of hormonal system,
- less stress sensitivity (hypodynamia induced damages in stomach and adrenals),
- better endurance at physical load,
- better liver detoxifying function,
- no impaired apoptosis,
- no spontaneous tumorigenesis.

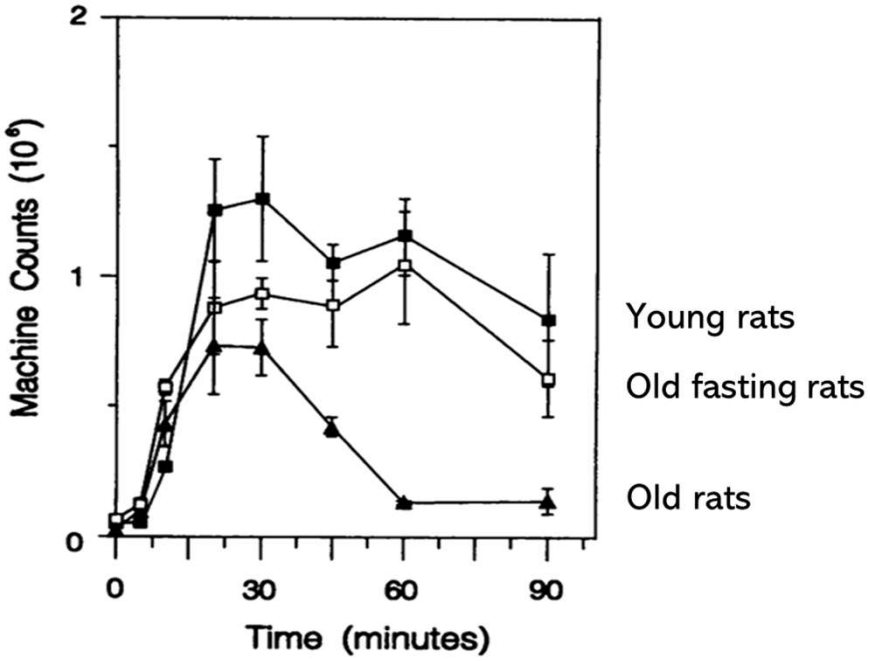
Current theory of ageing



The role of Hsp70 and FOXO in current theory of ageing



Panossian A.G. 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N.Y. Acad. Sci. 1401(1):49-64.



Hsp70. Heydari, et al., 1998;

- Characteristic feature of aging cell is a significantly reduced expression of Hsp70
- Dramatic reduction of expression of inducible Hsp70 correlates with a decrease in the ability of cells to cope with stress.
- Malfunction in expression of hsp70 in response to stress is a common phenomenon underlying the senescence and aging progression
- Hsp70 and FOXO are considered as pharmacological targets for antiaging therapies

- Cytoprotective and effect of Hsp70 is not the only beneficial effect of this molecular chaperone in aging and longevity.
- Hsp70 plays an important role in regulation of apoptosis and longevity by inhibition of stress activated JNK-mediated apoptosis signaling pathway.

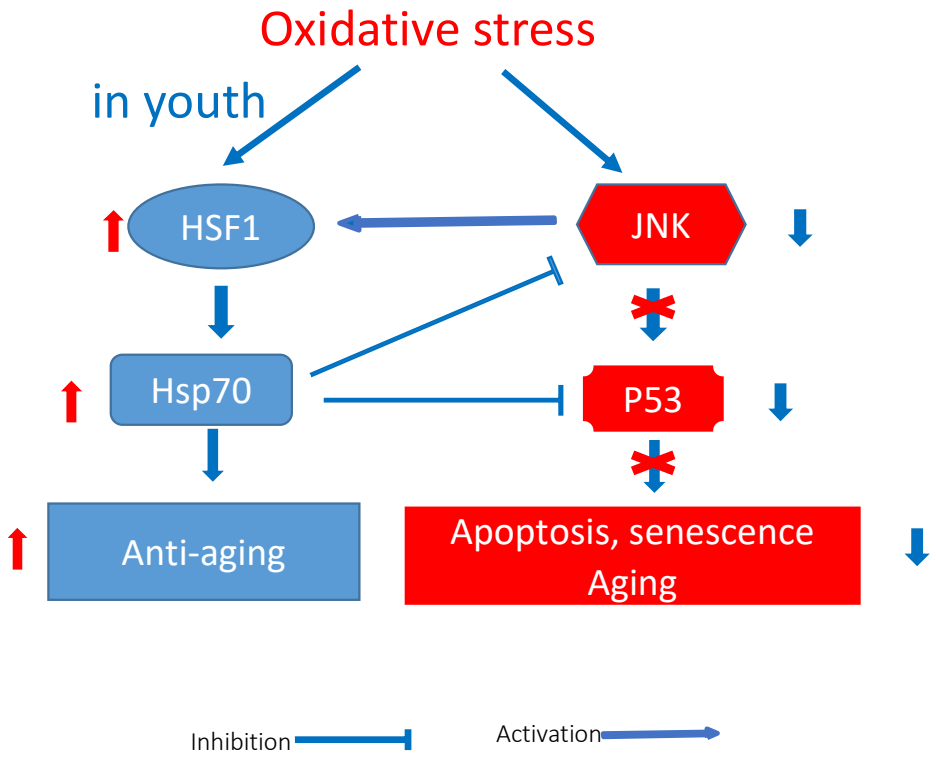
Ageing and antiaging programs

When cells are exposed to protein damage, HSF1 initiates the production of Hsp70, which repairs proteins, increases adaptability and lifespan.

Oxidative stress can trigger two signaling pathways through the activation of JNK kinase:

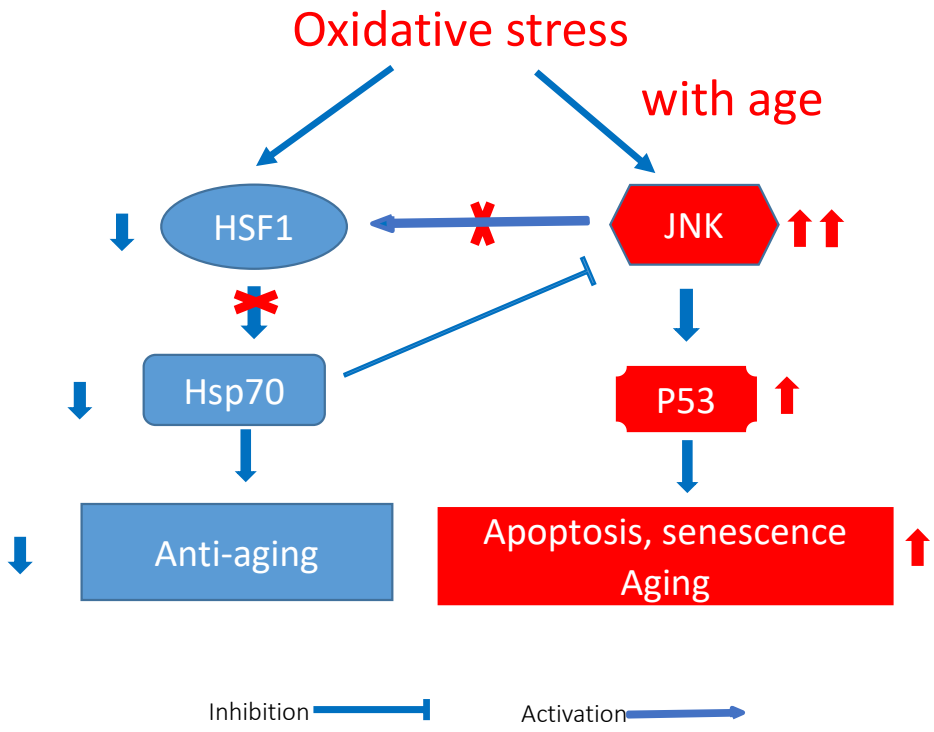
- the aging program by up-regulation of p-53 transcription factor and
- the anti-aging program, which is Hsp70-dependent.

At young ages, activation of HSF1-Hsp70 inhibits JNK-mediated aging, senescence, and apoptosis pathway



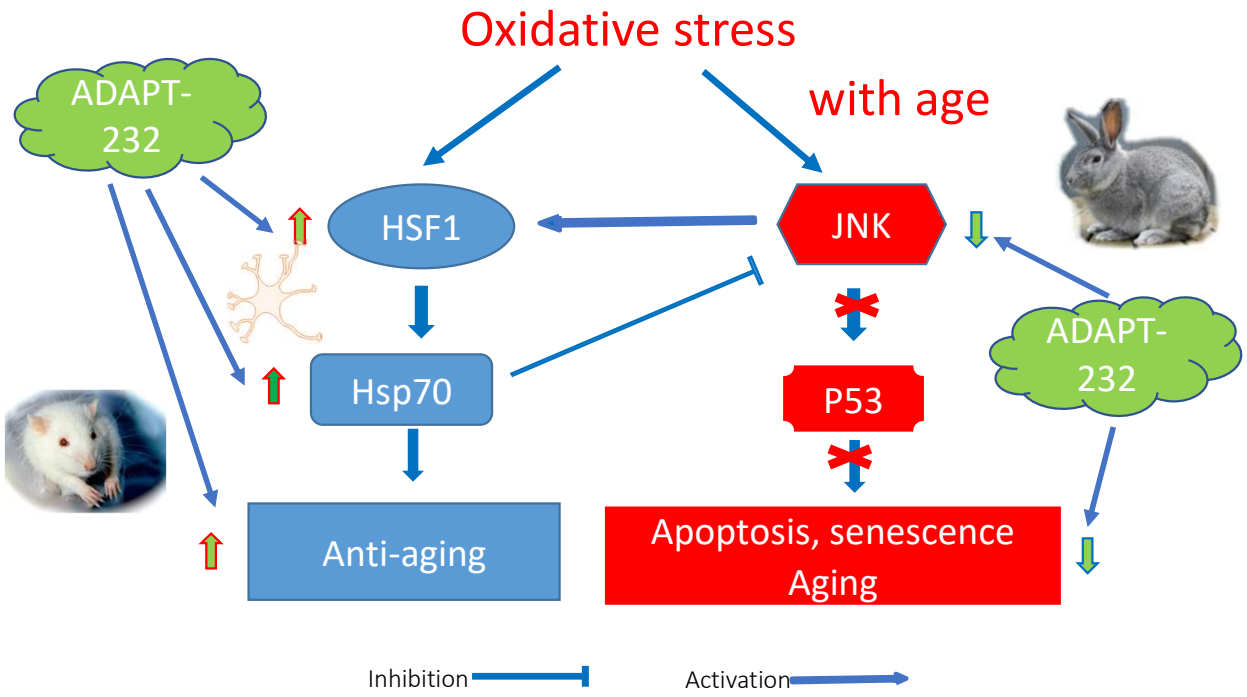
Ageing and antiaging programs

- With aging, induction of Hsp70 is depressed, and the balance shifts in favor of the aging and apoptosis programs. Consequently, even weak oxidative stress can induce the degeneration of neuronal cells and the progression of aging-related diseases
- In aging cells, significantly reduced expression of heat shock protein Hsp70 and its precursor, heat shock transcription factor HSF1, correlates with a decreased ability to cope with stress.
- In most humans, decline in induction of Hsp70 by stress is associated with aging and age-related disease .
- Hsp70 does not decrease with age in some individuals who live more than 100 years.
- In brain cells, the inhibition of HSF1 and Hsp70 expression occurs in Alzheimer's disease.
- Age-related decline of hepatic Hsp70 expression contributes to reduced liver detoxification.
- Attenuation of Hsp70 is associated with up-regulation of stress-activated protein kinase (JNK) dependent apoptosis and progression of cancer.



Effects of ADAPT on key regulators of aging

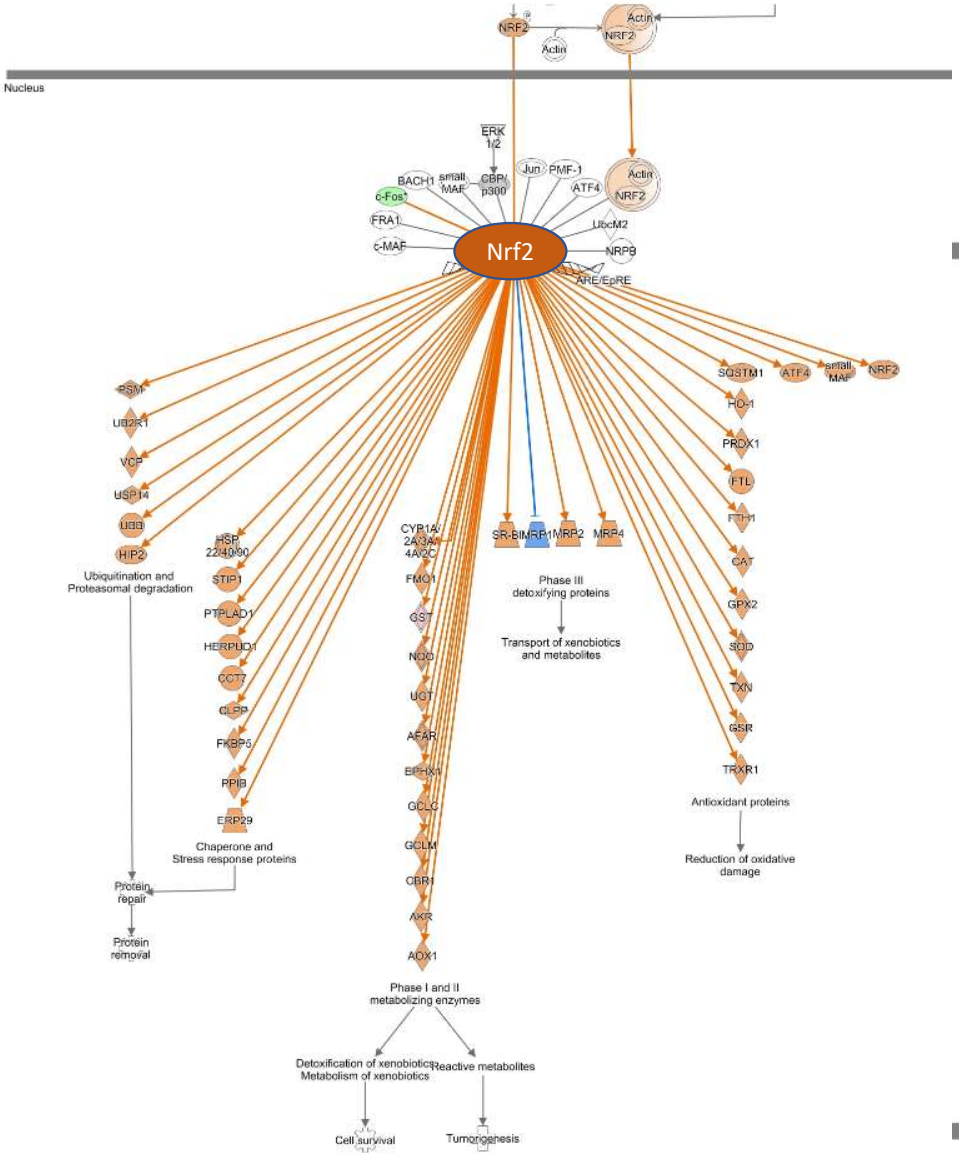
- ADAPT-232 upregulates HSF1-Hsp70 in vitro and Hsp70 in vivo;
- ADAPT-232 down-regulates JNK in vivo;
- ADAPT-232 inhibits aging, senescence, and apoptosis in vivo.
- Exercise can also up-regulate Hsp70 contributing to maintenance of muscle fiber integrity, regeneration and recovery.
- Conversely, Hsp70 expression is reduced during muscle inactivity and aging.
- Malfunction of HSP70 generation may drive muscle atrophy, contractile dysfunction, and reduced regeneration.



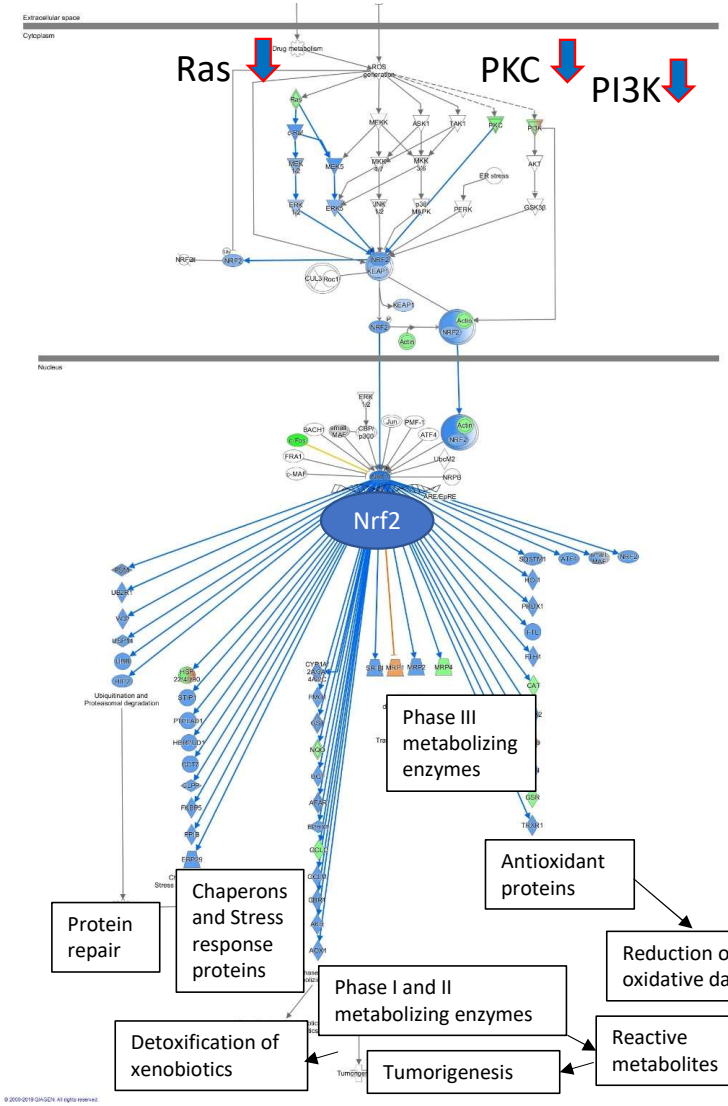
Panossian A, Gerbarg P. 2016. "Potential Use of Plant Adaptogens in Age-related Disorders". Complementary, Alternative, and Integrative Interventions in Mental Health and Aging. H. Lavretsky, M. Sajatovic & C.F. Reynolds III, Eds.: 197-211. New York: Oxford University Press.

Effect of adaptogens on NRF2-mediated Oxidative Stress Response Signaling Pathw

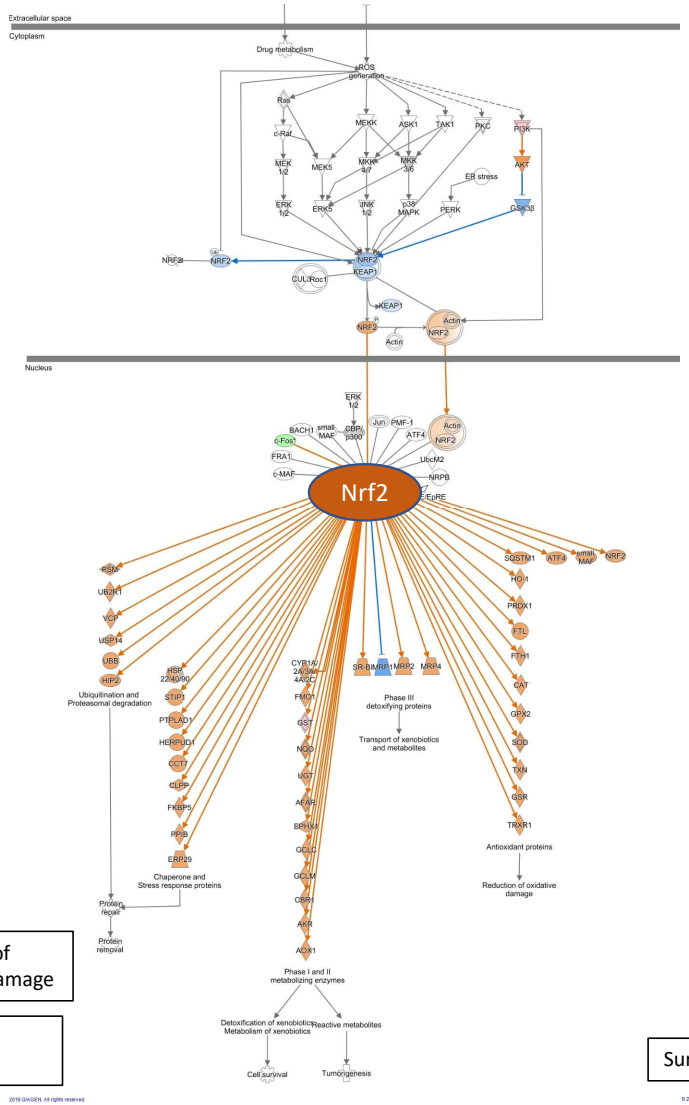
- Oxidative stress is increasing in Alzheimer disease and aging related diseases and disorders.
- The feedback cellular response is associated with activation of defense mechanisms including induction of antioxidant and detoxifying enzymes and molecular chaperons.
- Nuclear factor erythroid 2-related factor 2 (Nrf2) is a principal regulator of the redox homeostasis normally retained in the cytoplasm, where it is associated Keap1 protein.
- Upon exposure of cells to oxidative stress, Nrf2-Keap complex dissociates and Nrf2 translocate to the nucleus where it triggers expression of antioxidant and detoxifying genes including, superoxide dismutase (SOD), glutathione S-transferase (GST), NAD(P)H quinone oxidoreductase 1 (NQO1) and heme oxygenase 1 (HO1).
- Thus, activation of Nrf2 translocation or upregulation of genes expression resulting in activation of Nrf2 signaling pathway is the key mechanism of cellular defense associated with antioxidant effects of medicinal plants and particularly of adaptogenic plants, which are useful in stress and aging related diseases.



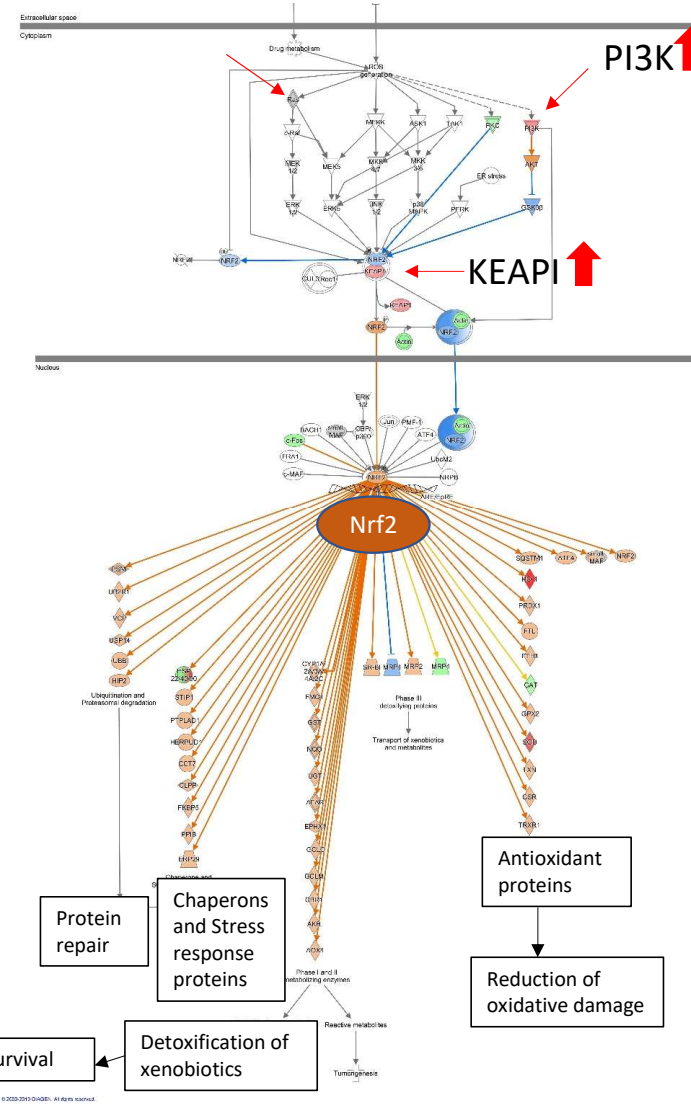
5-fluorouracil + epirubicin + cyclophosphamide=FEC



FEC+ES

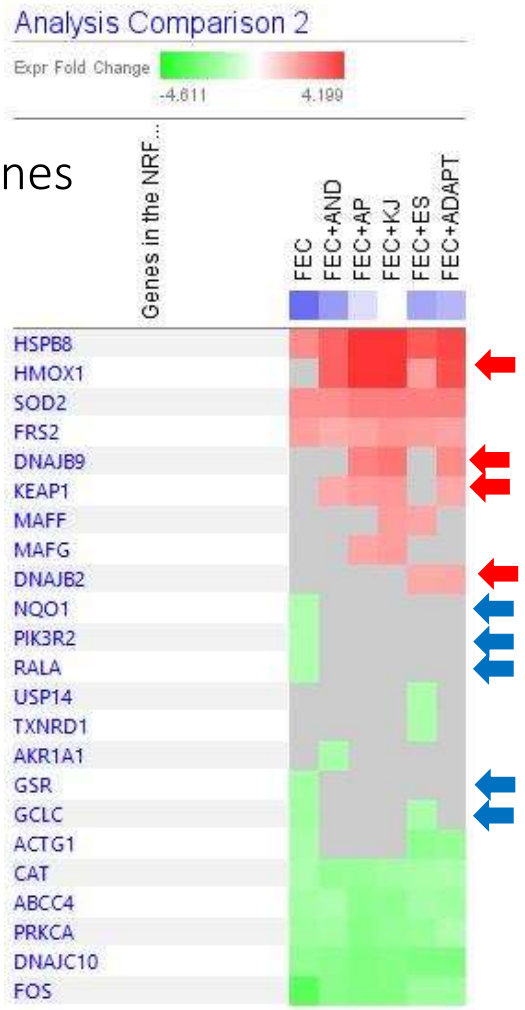


FEC+ADAPT



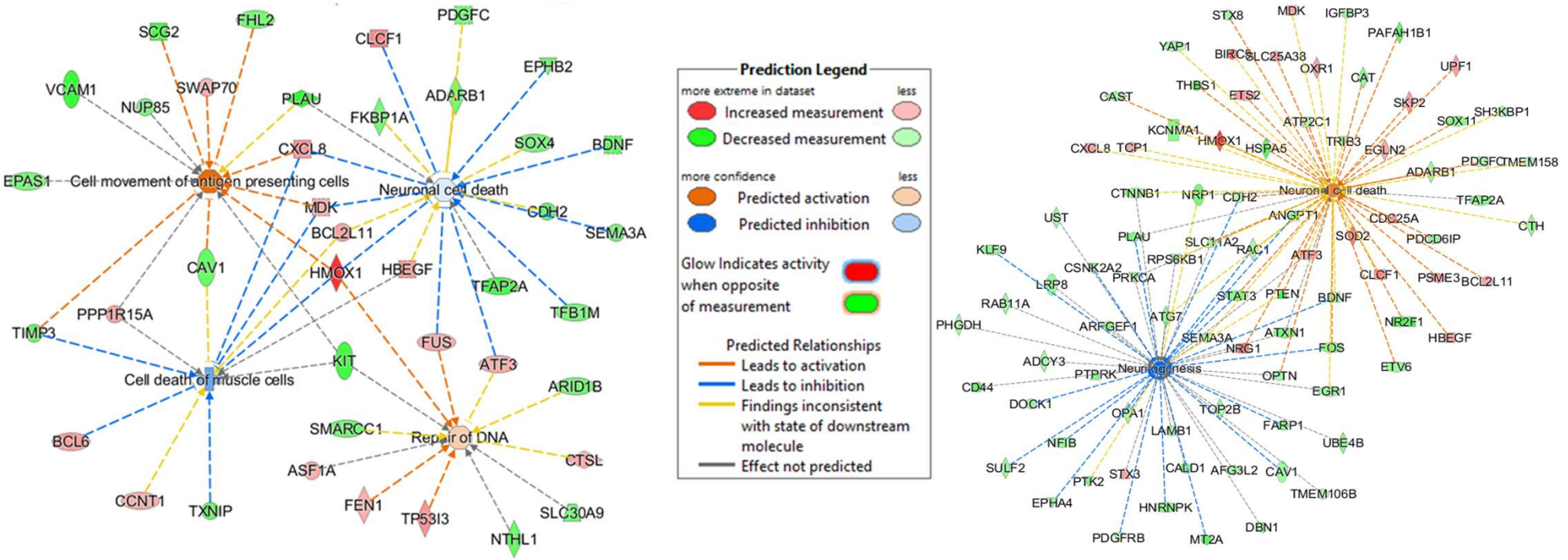
Adaptogens **prevent** chemotherapeutics-induced downregulation of genes activating production of antioxidant and detoxifying proteins and upregulate genes Involved in reduction of oxidation damage

Symbol	Entrez Gene Name	FEC	FEC+AND	FEC+AP	FEC+KJ	FEC+EI	FEC+ADAPT
GSR	**glutathione-disulfide reductase**	**-1.85**					
GCLC	**glutamate-cysteine ligase catalytic subunit**	**-1.93**				-1.77	
NQO1	**NAD(P)H quinone dehydrogenase 1**	**-1.63**					
PIK3R2	**phosphoinositide-3-kinase regulatory subunit 2**	**-1.66**					
RALA	**Ras-related protein Ral-A**	**-1.67**					
ACTG1	actin gamma 1	**-1.75**				-2.22	-2.11
HMOX1	**heme oxygenase 1**		3.23	4.76	5.70	2.01	3.62
KEAP1	**kelch like ECH associated protein 1**		**1.72**	**2.04**	**2.11**		**1.75**
MAFF	MAF bZIP transcription factor F				1.98	1.84	
MAFG	MAF bZIP transcription factor G			1.82	1.98		
DNAJB2	DnaJ heat shock protein family (Hsp40) member B2					1.74	1.78
DNAJB9	DnaJ heat shock protein family (Hsp40) member B9			2.54	2.81		2.39



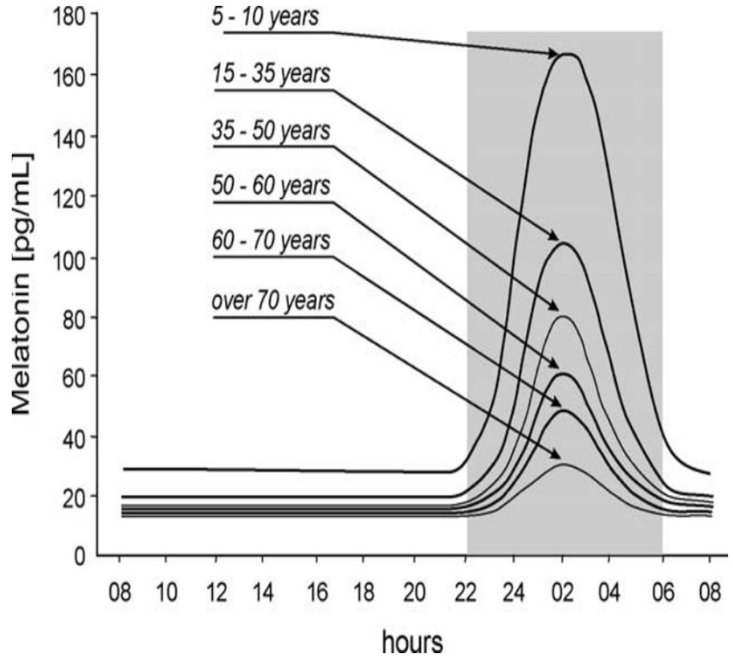
Co-incubation of AP with FEC activates genes involved in DNA repair, movement of antigen presenting cells, and inhibition of neuronal cells death in human T98G neuroglia cell culture.

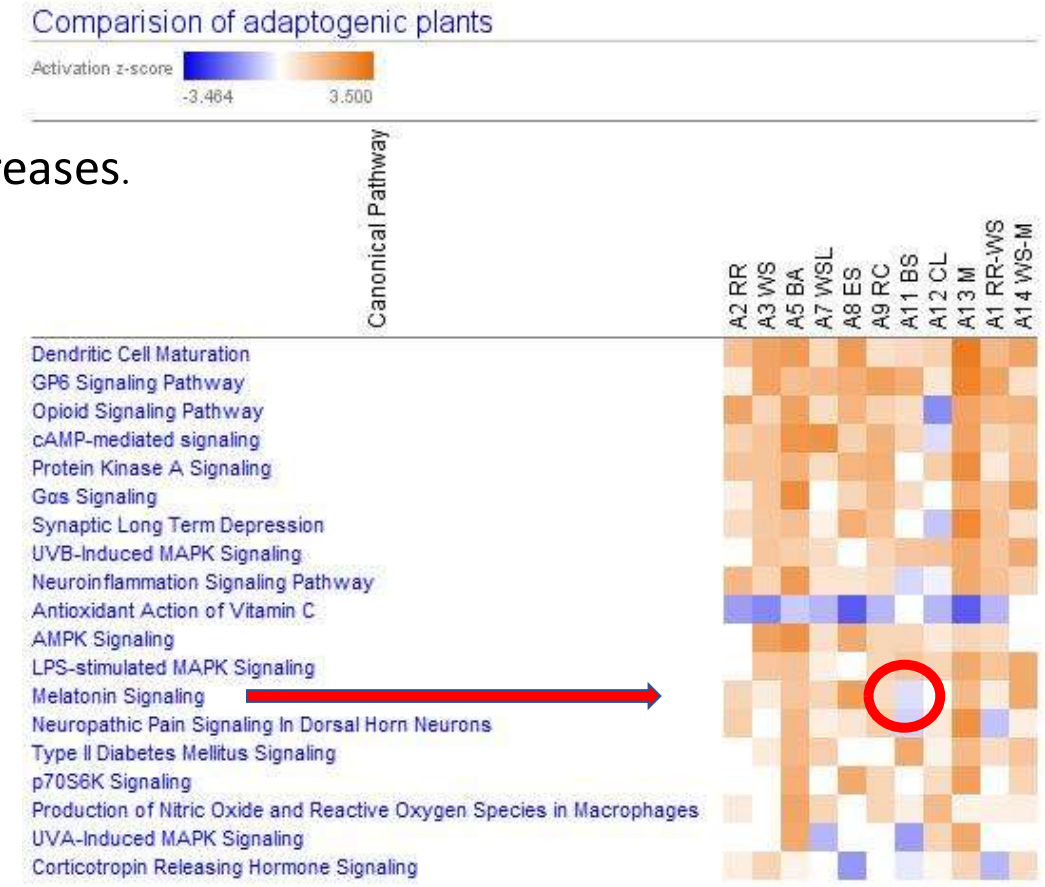
Co-incubation of T98G neuroglial cells with AP suppresses FEC-induced deregulation of large number of genes involved in predicted activating neuronal death and inhibiting neurogenesis



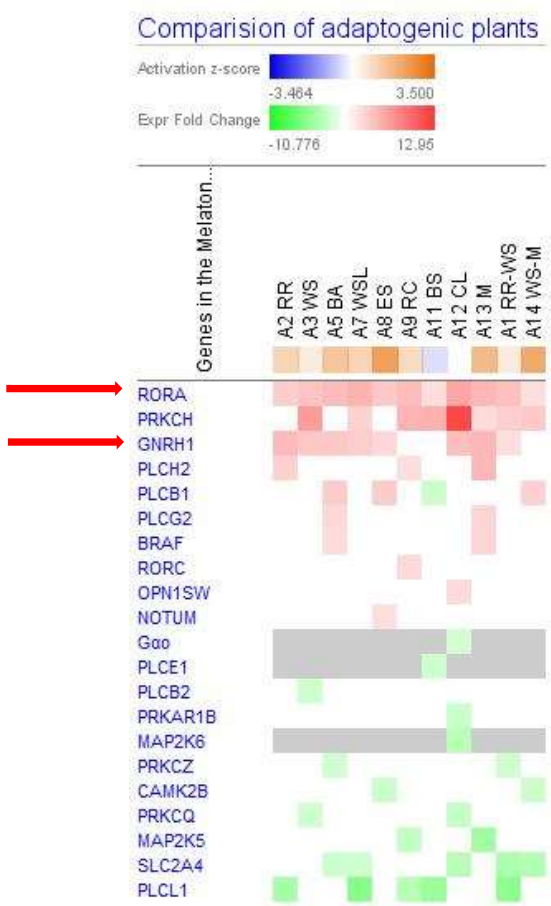
Adaptogens activate melatonin signaling pathway, therefore should be beneficial in sleep disorders and mild cognitive impairment in ageing

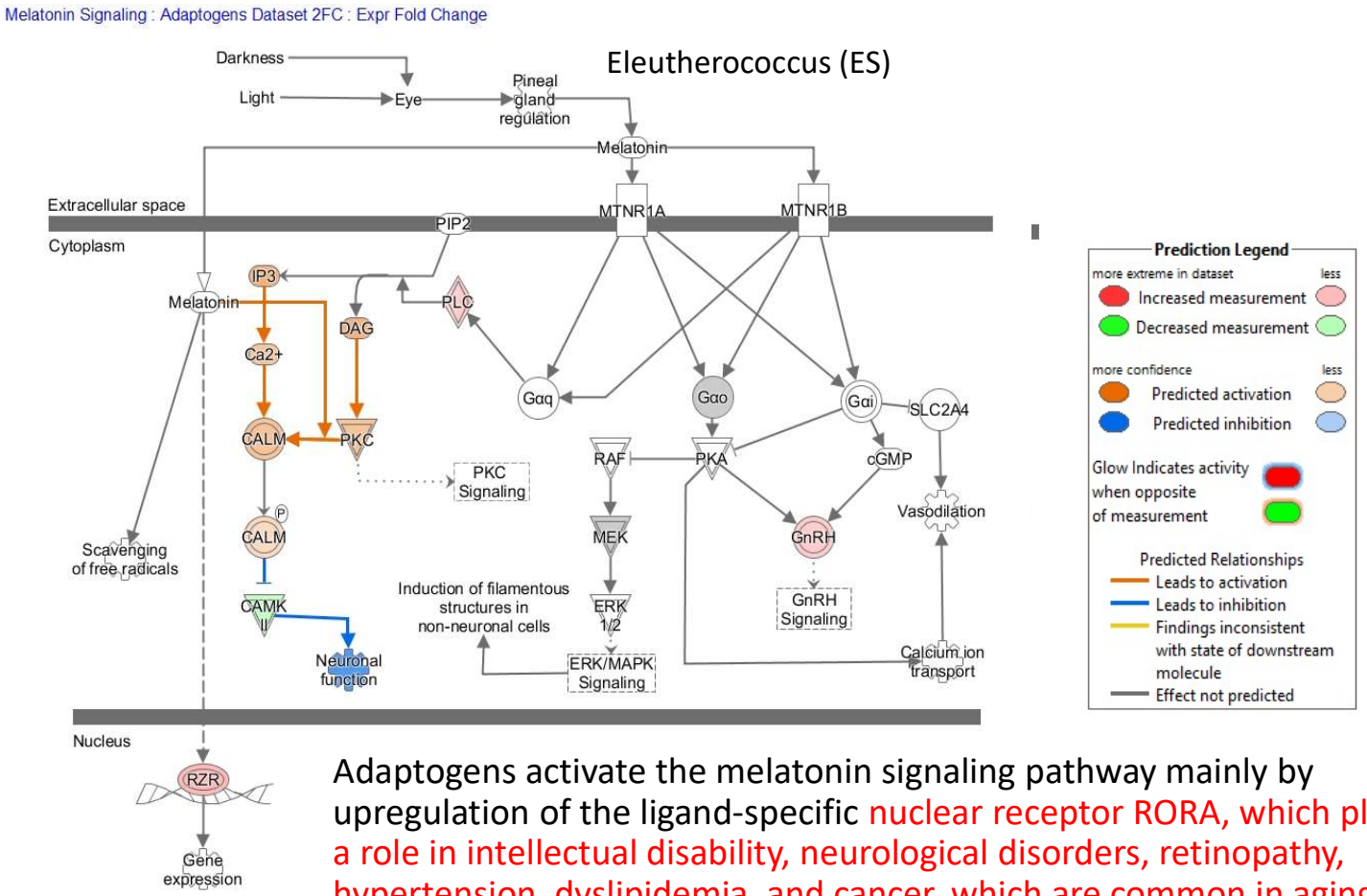
With age, the level of night melatonin decreases.





Gene maps of melatonin signaling pathway





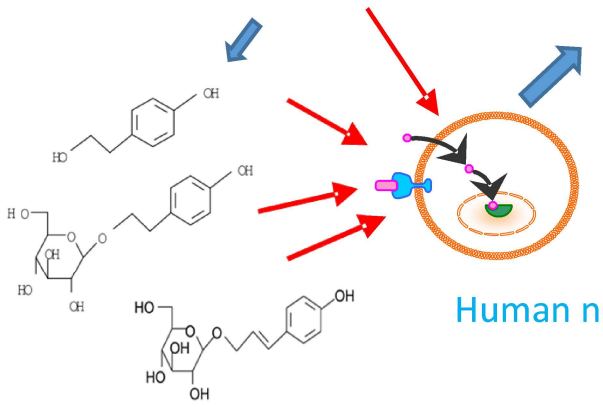
Eleutherococcus (ES)

Adaptogens activate the melatonin signaling pathway mainly by upregulation of the ligand-specific nuclear receptor RORA, which plays a role in intellectual disability, neurological disorders, retinopathy, hypertension, dyslipidemia, and cancer, which are common in aging.

Assessment of adaptogens using systems pharmacology approach, molecular biology technologies and in silico models

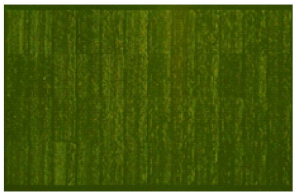
Radix Rhodiola

SHR-5 extract



Human neuroglia cells

RNA hybridization-based Microarray or
RNA-Seq next-generation sequencing

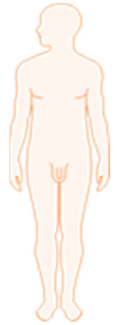


Gene Expression profiling

Data Analysis using Ingenuity Pathway Analysis (IPA)
Interactive pathways downstream effect analysis

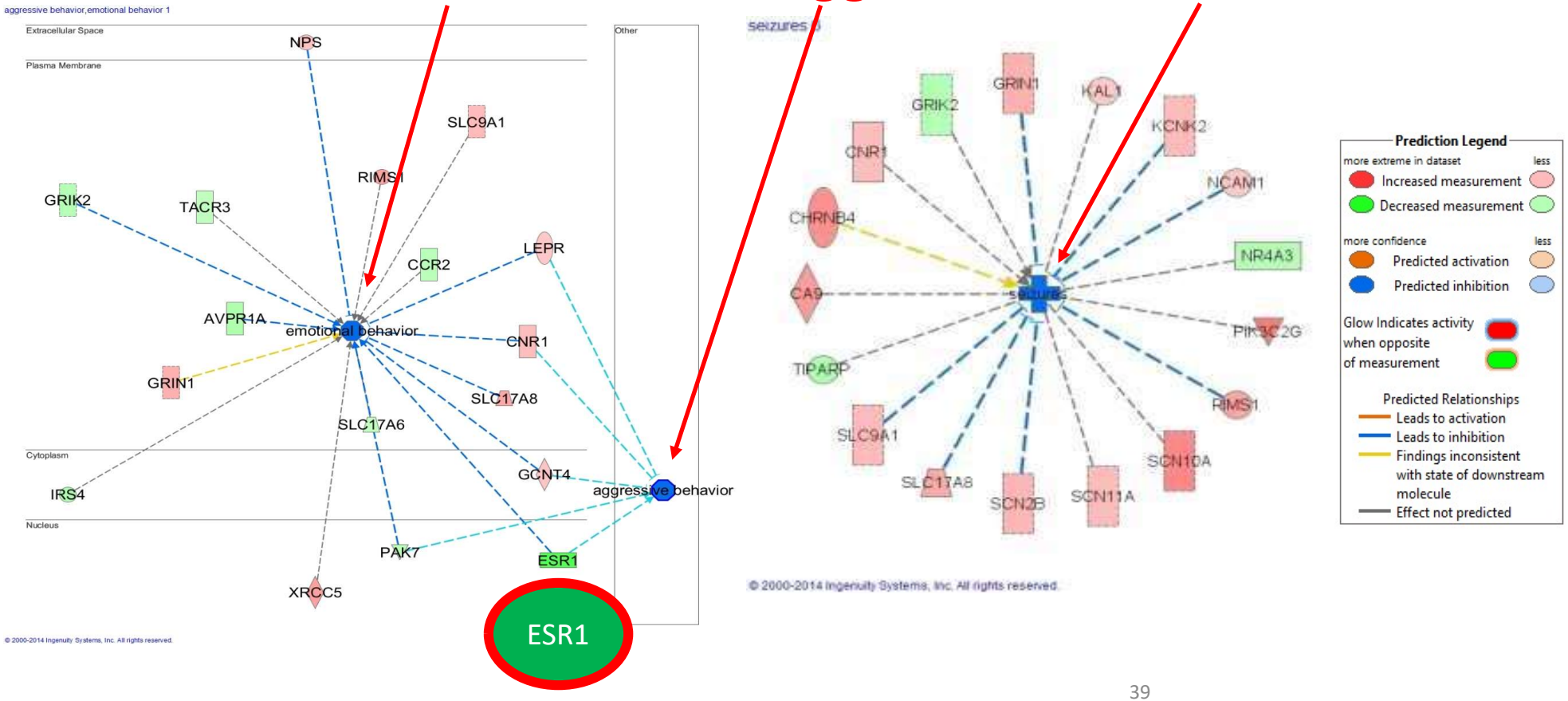
Rhodiola modulates expression of genes deregulated in:

- cardiovascular diseases (72 deregulated genes),
- metabolic diseases (63 genes),
- gastrointestinal diseases (163 genes),
- neurological diseases (95 genes),
- endocrine disorders (60 genes),
- behavioral disorders (50 genes),
- psychological disorders (62 genes).

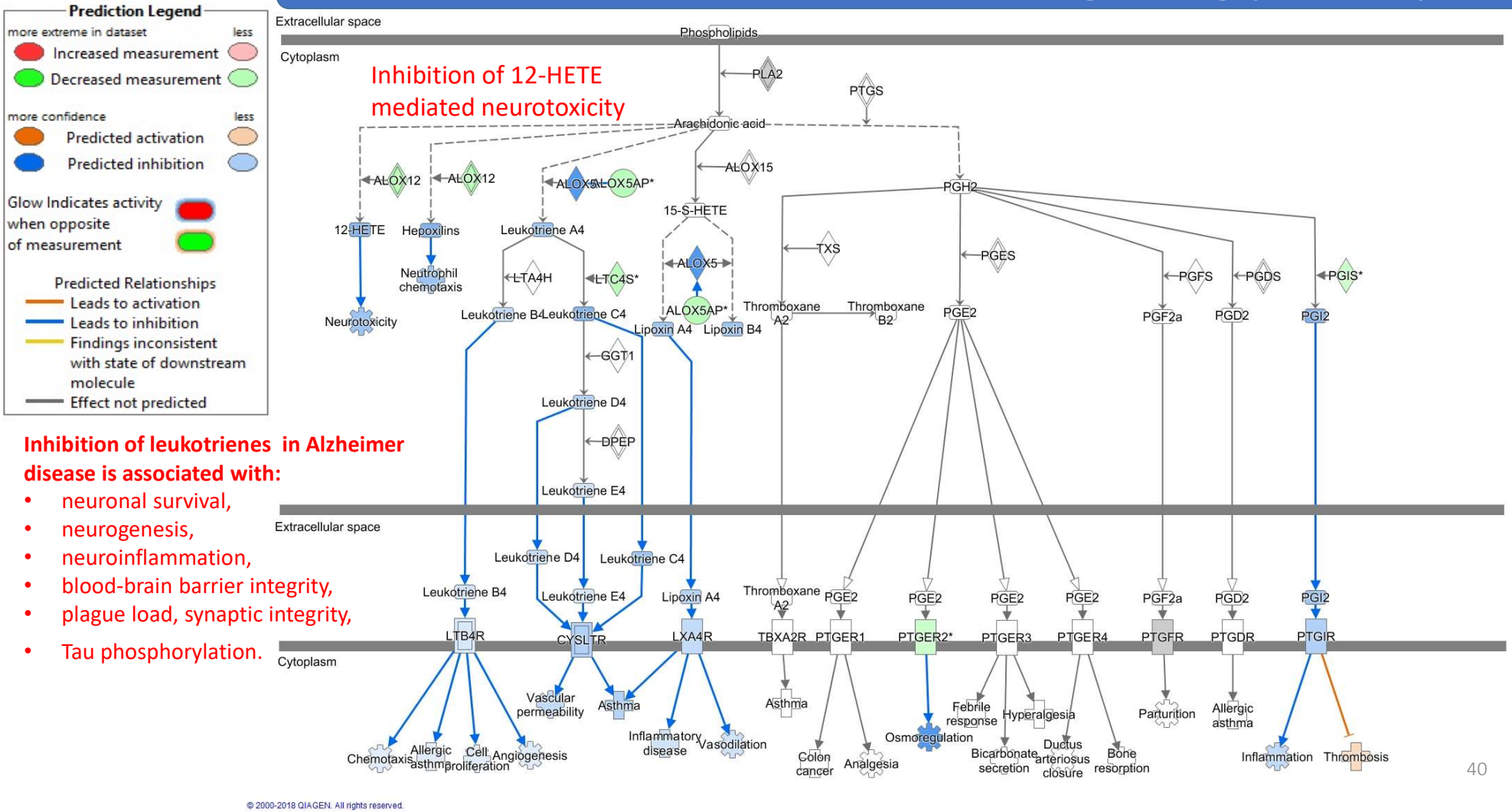


IPA software (QIAGEN Bioinformatics), performs different calculations on transcriptomic datasets based on the Ingenuity Knowledge Base, containing approximately 5 Mio findings manually curated from the biomedical literature or integrated from third-party databases.

The effects of Rhodiola on molecular network associated with emotional behavior, aggression and seizures



Effect of Rhodiola on eicosanoids signaling pathways



Inhibition of 12-HETE mediated neurotoxicity

Inhibition of leukotrienes in Alzheimer disease is associated with:

- neuronal survival,
- neurogenesis,
- neuroinflammation,
- blood-brain barrier integrity,
- plague load, synaptic integrity,
- Tau phosphorylation.

Main biochemical processes most influenced (in terms of altered gene activity) by Rhodiola, Eleutherococcus, and Schisandra.

	Genes
➢ catabolism of cyclic AMP and metabolism of cyclic GMP ➢ conversion of leukotriene A4 and lipoxin A4 ➢ oxygenation of docosahexaenoic acid ➢ synthesis of synthesis of steroid and bile acid ➢ translocation, exchange and redistribution of cholesterol ester and triacylglycerol ➢ transmission of triacylglycerol and phosphatidylcholine ➢ inactivation of glucocorticoid ➢ efficacy of beta-estradiol ➢ decarboxylation of beta-alanine and L-aspartic acid ➢ deamination of cytidine ➢ removal of hypoxanthine	**AICDA, AIPL1, AKR1D1, ALOX12, APOBEC2, CETP, ESR1, GADL1, NR4A3, PDE11A, PDE3A, PDE4D, PFKFB1, SERPINA1, SLC27A2**

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

Main cellular functions most influenced (in terms of altered gene activity) by Rhodiola, Eleutherococcus, and Schisandra.

Cellular function	Genes
Cellular Compromise: – oxidative stress response of blood cells – degranulation of beta islet cells – damage of mitochondria – degeneration of hepatocytes – cytotoxicity of cytotoxic T cells – fragmentation of photoreceptor outer segments – degeneration of retinal cone cells	AIPL1, ALOX12, CDHR1, NGB3, GNLY, HLA-B, NCAM1, SERPINA1, ULBP3,XRCC5,
Cell Signalling	PDE3A, MUC20, PDE4D, PDE11A, ESR1, CCKBR
DNA Replication, Recombination, and Repair	PARPBP, PDE3A, APLF, PDE4D ,PDE11A, XRCC5, AICDA
Nucleic Acid Metabolism	PFKFB1,MTNR1A,PDE3A,APOBEC2,TAAR1,PDE4D,PDE11A,AIPL1,ESR1,AICDA
Lipid Metabolism	NR4A3,RGS3,SLC27A2,AKR1D1,TNXB,SERPINA1,ALOX12,ESR1,CCKBR,CETP,NCAM1

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

The most significantly affected canonical pathways and gene targets that are responsive (in-vitro) to adaptogen therapy .

Canonical Pathways	Genes
tRNA Splicing	PDE3A,PDE4D,PDE11A
Protein Kinase A Signaling	PDE3A,HIST1H1T,CNGB3,PDE4D,PDE11A,PLCD4,DUSP21,TCF7L2
G-Protein Coupled Receptor Signaling	PDE3A,TAAR1,PIK3C2G,PDE4D,PDE11A,AVPR1A
Leptin Signaling in Obesity	PDE3A,PIK3C2G,PLCD4
Cardiac β-adrenergic Signaling	PPP1R1A,PDE3A,PDE4D,PDE11A
Relaxin Signaling	PDE3A,PIK3C2G,PDE4D,PDE11A
cAMP-mediated signaling	PDE3A,TAAR1,CNGB3,PDE4D,PDE11A
Salvage Pathways of Pyrimidine Nucleotides	APOBEC2,AK9,AICDA
Colorectal Cancer Metastasis Signaling	MMP8,TLR8,PIK3C2G,WNT16,TCF7L2
Inositol Pyrophosphates Biosynthesis	PPIP5K1
Airway Pathology in Chronic Obstructive Pulmonary Disease	MMP8
Axonal Guidance Signaling	NTNG1,EPHB1,RGS3,MMP8,PIK3C2G,WNT16,PLCD4
Superpathway of Inositol Phosphate Compounds	PPP1R1A,PIK3C2G,PPIP5K1,PLCD4
Sperm Motility	CNGB3,PDE4D,PLCD4
Telomere Extension by Telomerase	XRCC5
Melatonin Signalling and degradation	MTNR1A,PLCD4, UGT2A3,CYP4X1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	MMP8,PIK3C2G,WNT16,TCF7L2
eNOS Signalling	PIK3C2G,CNGB3,ESR1

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

Age associated disease, and the genes involved in their pathogenesis and progression, that are significantly deregulated by adaptogens

Category	Diseases	Genes affected by adaptogens
Organismal Injury and Abnormalities	physical disability	PDE11A,PDE3A,PDE4D - all upregulated
	degeneration of retinal cone cells - inhibition	AIPL1- down regulated,CNGB3 upregulated
	atrophy of gastric mucosa	CCKBR- down regulated
	hypoestrogenism	ESR1- down regulated
	postmenopausal vulvar atrophy	ESR1ϭ MTNR1A - down regulated,
	nociception	KCNK10, PDE11A,PDE3A,PDE4D,SCN2B - all upregulated
	cone dystrophy	CDHR1- down regulated,CNGB3 - upregulated
	pelvic organ prolapse	ESR1 - down regulated, SERPINA1 - - upregulated
Inflammatory and Pulmonary Disease	pulmonary emphysema- inhibition	PDE11A,PDE3A,PDE4D,SERPINA1- all upregulated
	bronchiectasis	PDE11A,PDE3A,PDE4D - all upregulated
	chronic bronchitis	MMP8,MTNR1A – both down regulated
	chronic obstructive pulmonary disease-inhibition	PDE11A,PDE3A,PDE4D,SERPINA1- all upregulated
Neurological and psychological Disease	non 24 hour sleep-wake disorder	MTNR1A - down regulated
	sleep-wake schedule disorder	PDE3A- upregulated
Cardiovascular Disease	ischemic cardiomyopathy	PDE11A,PDE3A,PDE4D,PPP1R1A - all upregulated
	cholesteryl ester transfer protein deficiency	CETP - down regulated
	angina pectoris	PDE11A,PDE3A,PDE4D – all upregulated
	cerebral small vessel disease	PDE3A - unregulated
Skeletal and Connective Tissue	osteochondrodysplasia	COL9A1 - down regulated, PDE4D -up regulated
Metabolic Disease	estrogen resistance	ESR1 – down regulated

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

The effects of Rhodiola on genes involved in regulating age-associated disorders

Inflammation – atherosclerosis –

- Down regulation of CETP,
- Deregulation of GPCR,

Neurodegeneration – impaired cognitive functions (learning, memory, abstract thinking, planning)

- Down regulation of cAMP
- Down regulation of ESR1
- Upregulation of serpine
- Deregulation of GPCR,

Impaired apoptosis – Cancer –

- Down regulation of ESR1, OLFM
- Up regulation of IP3, PLC, DAG, PI3K, NFkB
- Deregulation of GPCR

Metabolic disorders and energy metabolism

- Down regulation of cAMP
- Inhibition of ATP metabolism

Conclusions

- Stress response and adaptation to environmental challenge are multistep processes that involve intracellular and extracellular signaling pathways at all levels of stress regulation.
- Adaptogens are stress-response modifiers and have many molecular targets.
- Adaptogens exert a polyvalent biological activity and provoke multiple effects at all levels of regulation of cellular metabolism and homeostasis.
- Therefore, adaptogens have pharmacologically pleiotropic effects, which explain their traditional use for a wide range of conditions.