Adaptogens

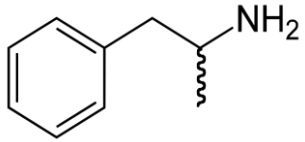
historical overview and evolution of adaptogenic concept from 1958 to 2019

Alexander Panossian , PhD

Phytomed AB , Sweden

PHYTOMED

The origin of adaptogenic concept: Historical background



Adapted from “Turbocharging the Brain”; October 2009; Scientific American Magazine; by Gary Stix

The resolution No 4654-p

of the People’s Commissars Council of the USSR

“… to study Limonnik (*Schisandra chinensis*) with the purpose of finding of **tonic** substances…”

4th March 1943, Moscow

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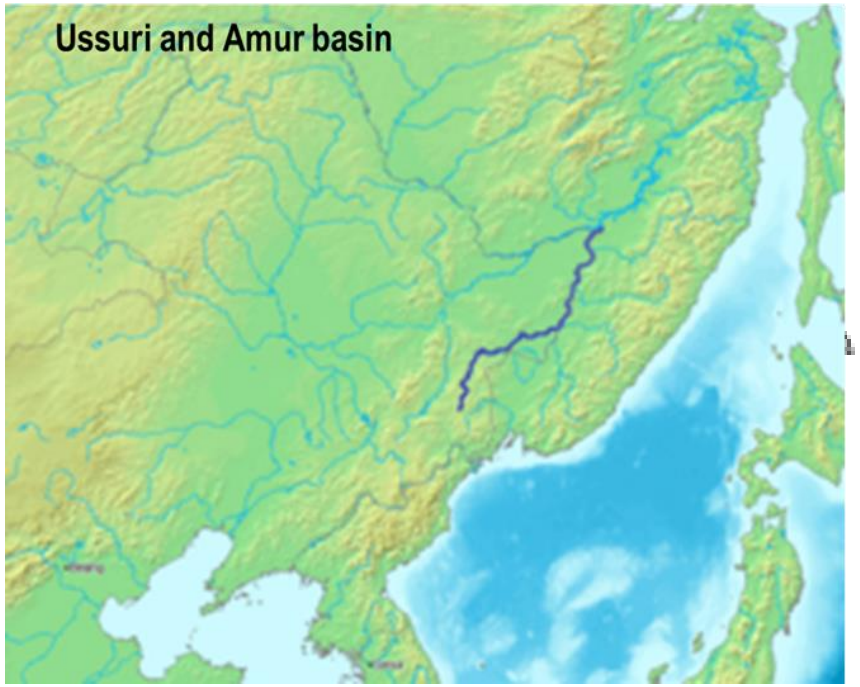
Traditional use of Schisandra in Far East of Russia

Nanai and Goldi hunters used Schisandra berry to improve night vision and as a tonic and to reduce hunger, thirst and exhaustion.

"… it gives forces to follow a sable all the day without food…" V. Arsenyev, 1906



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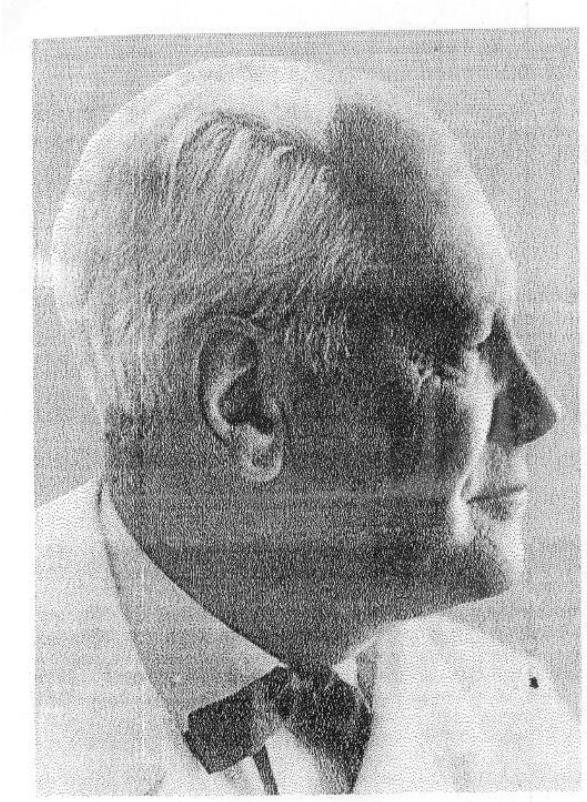
Expedition of 1906-1907: Vladimir Arsenyev and Dersu Uzala



Николай Васильевич Лазарев
(1895—1974)

Lazarev

First definition of adaptogens

"Adaptogens" - compounds which could increase "the state of non-specific resistance" in stress

Lazarev NV. 1958. General and specific in action of pharmacological agents. Farmacol.Toxicol, 21(3): 81-86.
Lazarev NV. Ljublina EI, Rozin MA. 1959. State of nonspecific resistance. Patol.Fiziol.Experim.Terapia, 3(4): 16-21.

Lazarev

Н. В. ЛАЗАРЕВ

МЕСТО ЖЕНЬ-ШЕНЯ И ЭЛЕУТЕРОКОККА СРЕДИ ДРУГИХ ЛЕКАРСТВЕННЫХ СРЕДСТВ

Институт онкологии АМН СССР

Иначе обстоит дело на данной конференции. Представленными докладами четко показано значительное сходство (не доходящее впрочем до тождества) фармакологических свойств жень-шеня и элеутерококка: наличие у обоих средств свойства быть стимуляторами, т. е. повышать после однократного приема работоспособность человека, оказывать на организм тонизирующее действие (мы считаем надежным критерием наличия у препарата «тонизирующих» свойств повышение при длительном его приеме регистрируемой объективными методами работоспособности), стимулировать внутреннюю секрецию гонад и снижать повышенный уровень сахара в крови. К этому можно было бы добавить, что и жень-шень, и элеутерококк повышают сопротивляемость организма к различным неблагоприятным воздействиям (хотя эта сторона действия данных средств еще нуждается в более обстоятельном изучении), т. е. делают более успешной, более выраженной адаптацию организма к неблагоприятным условиям внешней среды (для веществ с таким действием, примером которых может быть дибазол, мы предложили применять термин «адаптогены»).

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avi

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Homeostasis

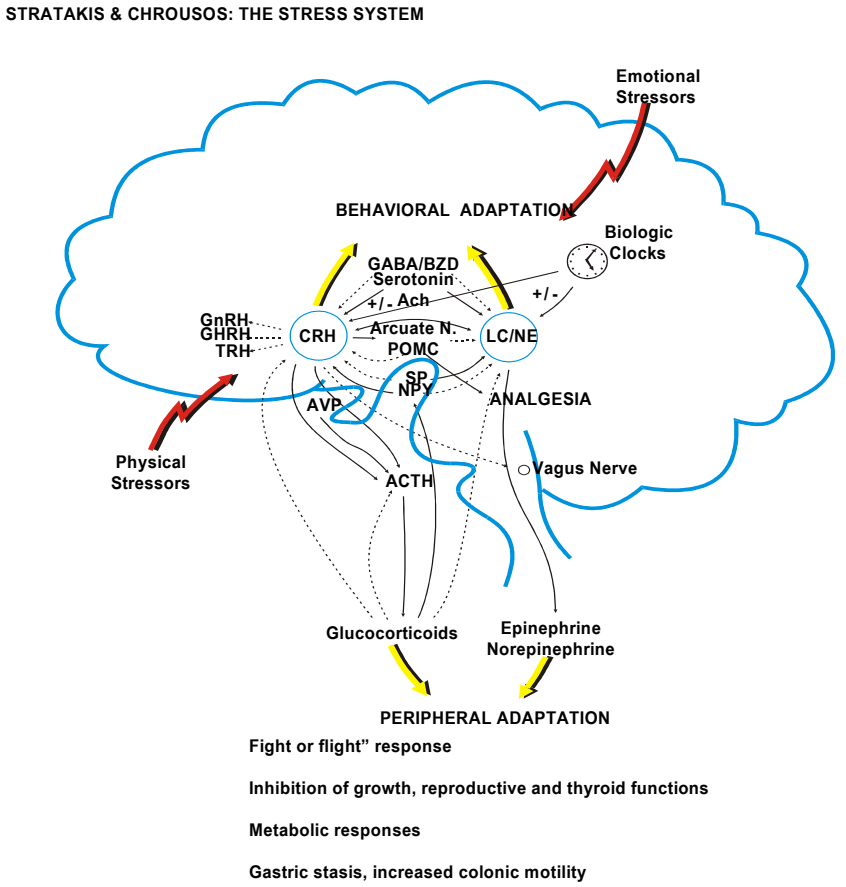
Walter Bradford Cannon (1871–1945).
The Harvard Physiologist who coined the term Homeostasis to describe and extend Bernard's milieu interieur concept .

Homeostasis is a complex dynamic equilibrium / steady state, maintained by coordinated physiological processes in the organism. Cannon, 1926.

Stress is a state of threatened homeostasis. Cannon,1935

The Stress system

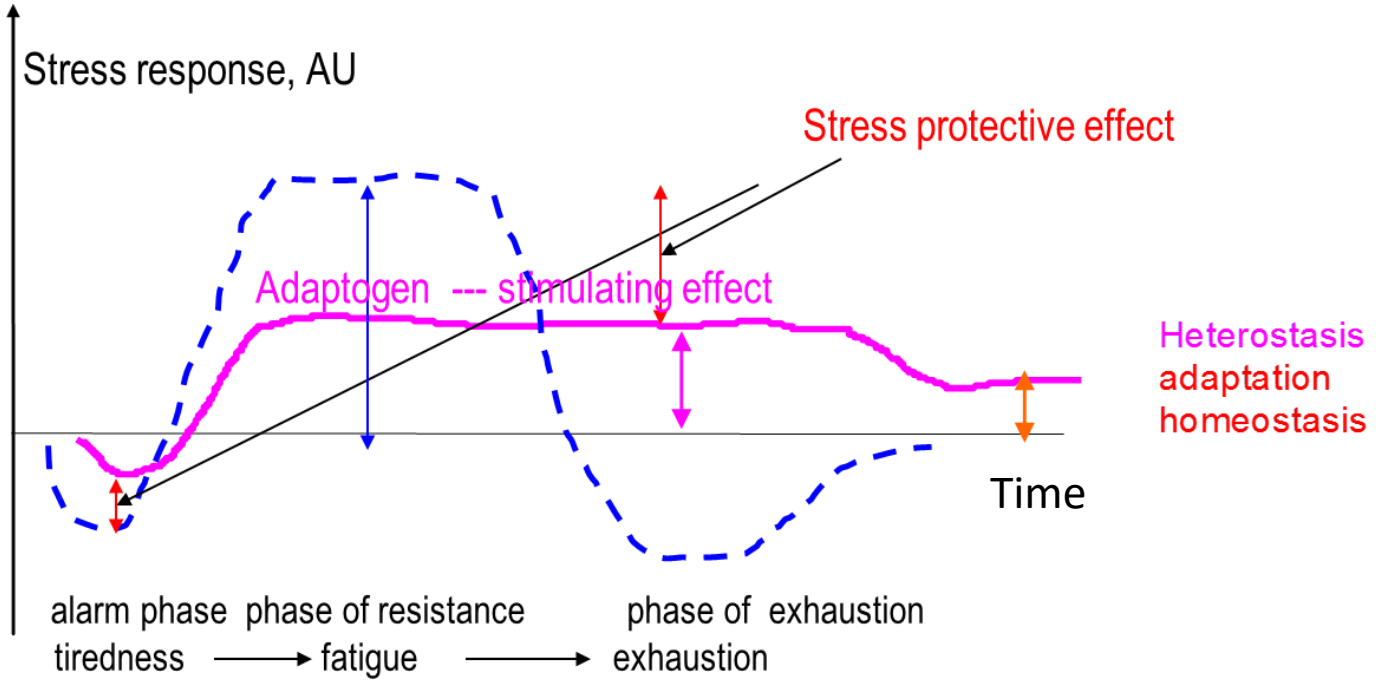
Neuroendocrine – immune complex



General adaptation syndrome

Selye, 1950

Effect of adaptogens – stress response modifiers increasing the resistance to stress



- Sense of fatigue is a bio-alarm defense response of psycho neuroendocrine-immune system to stress, like pain or fever.

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Evolution of definition

Israel Brekhman, 1968.

Postulated characteristics of adaptogens

Adaptogens are innocuous *agents*,
nonspecifically increasing resistance against physically, chemically, biologically and psychologically noxious factors (‘‘stressors’’), normalizing effect independent of the nature of pathologic state

Brekhman II, Dardymov IV. 1968. New substances of plant origin which increase non-specific resistance. Ann Rev Pharmacol, 8:419-30.

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Experience of Traditional Chinese Medicine, Kampo and Ayurveda

Herbalists refer adaptogens to rejuvenating herbs, qi tonics, rasayanas, or restoratives.

- ***China***: *Panax ginseng* activates Qi - the state of health and lifespan. Tonic - nourishing effect in fatigue
- ***India:*** *Withania somnifera* activates Prana - the life vital energy, activating body and mind.
- ***Japan:*** fixed combinations of herbal extracts containing adaptogenic plants - "support medicine" for mitigating of the symptoms of degenerative diseases and the restoration of weakened physical performance

- Astragali Radix
- Ginseng Radix
- Atractylodis macrocephalae Rhizoma
- Bupleuri Radix
- Jujubae Fructus
- Citri reticulatae Pericarpium
- Angelicae sinensis Radix
- Cimicifugae Rhizoma
- Glycyrrhizae Radix
- Zingiberis Rhizoma

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Use of adaptogens in official medicine in USSR

Psychotropic drugs: CNS stimulants

- Various CNS busting preparations

Russia - 2019: Active substances – 36; Products – 1417.

- *Indications:*
  - As a stimulant or tonic (single or repeated doses) in over-exhausted healthy persons in fatigue after/in somatic or infectious diseases
    - to speed up recovery after surgeries, poisoning, heart attacks and in ischemia
    - to reduce adverse reactions in chemotherapy and psychiatric disorders
  - Sports medicines: to promote quicker recovery after hard exercise and to reduce damages etc. from overstraining
  - Occupational medicine: protection against negative environmental factors.

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Applications of adaptogens in USSR

- Exciting Space programs associated with various stressful conditions,
- Developed Nuclear weapon industry with very high risk of radiation induced injury,
- Powerful Military Air Forces, Navy where chronic hypoxia, burnout syndrome and other stresses are very common,
- Great athletes and chess players experienced physical and mental overload
- Numerous Arctic and Antarctic expeditions where people are in permanent exposure to cold stress
- And a huge staff of elderly members of politburo , a governing body of USSR which need to use magic kremlin pills and an elixir of youth, energy and stamina

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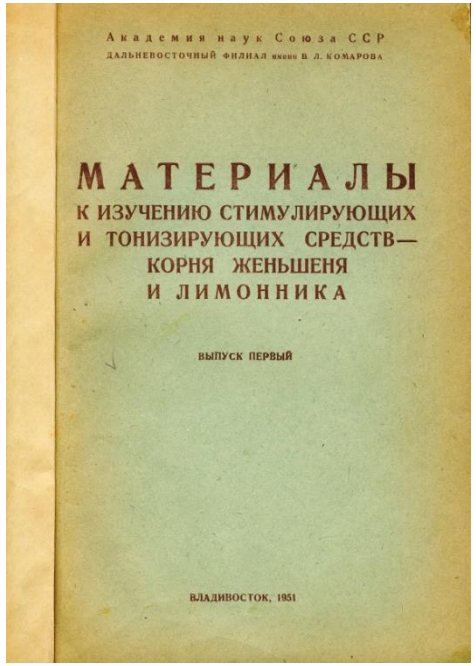
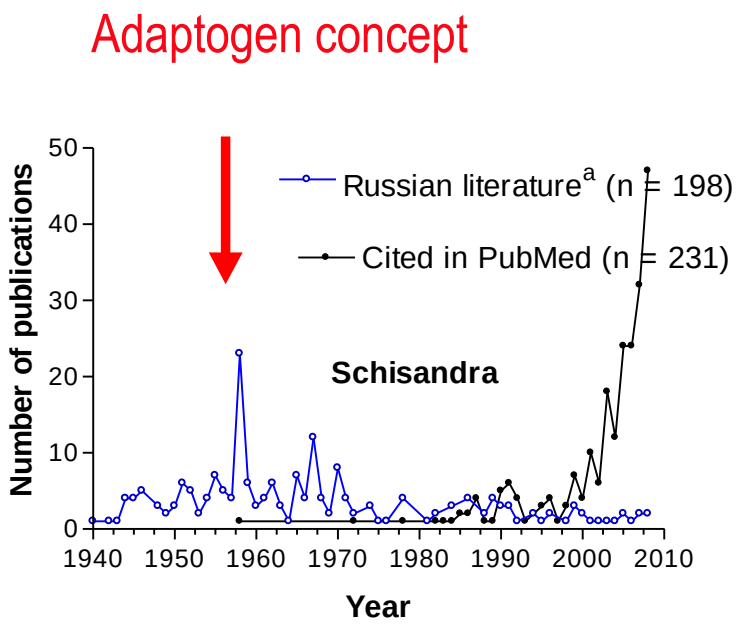
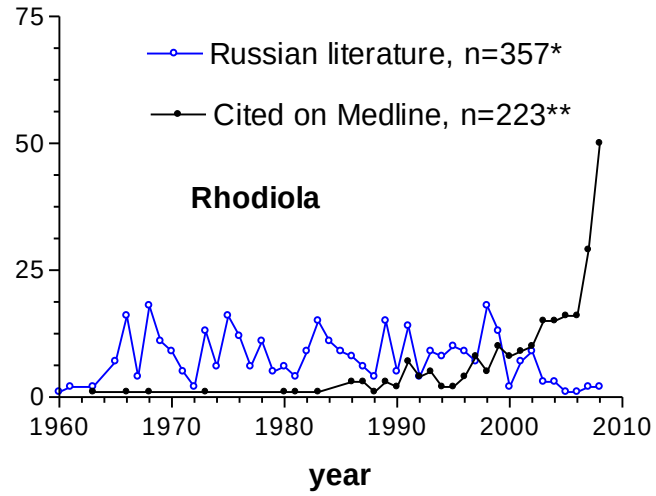
Number of publications on *Schisandra chinensis* and Rhodiola rosea published in Russian and cited in PubMed between 1940 and October 2007.







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Plants described in the literature as adaptogenic

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
Acanthopanax sessiliflorum Rupr.et Maxim.
Albizzia julibrissin Durazz.
Aralia elata (Miq) Seem.
Aralia manshurica Rupr.et Maxim
Aralia schmidtii
Asparagus racemosus,
Atragene sibirica L.
Azardirachta indica (Al, Neem),
Bergenia crassifolia (Fritsch),
Bryonia alba L.,*
Cicer arietinum L.
Codonopsis pilosula (Franch.)Nannf.
Cordyceppt sinisis (Berk.)
Echinopanax elatum Nakai
Eleutherococcus senticosis Maxim.,*
Emblica officinalis,(Phyllanthus emblica L)
Eucommia ulmoides Oliver
Hoppea dichoroma Wild.
Ocimum sanctum L.
Panax ginseng C.A. Meyer
Pfaffia paniculata(Marius)Kuntze
Rhaponticum carthamoides (Willd).Iljin,
Rhodiola crenulaya (Hook, f. et Thoms) H.Ohba
Rhodiola rosea L.*,
Scutellaria baicalensis (Georgi) .
Schizandra chinensis (Turcz.) Bail.*,
Sterculia plantanifolia L.
Terminalia chebula
Tinospora cordiflora Miers
Trichopus zeylanicus Gaerten.
Withania somnifera L.

2017 - 74

Ajuga turkestanica (Regel) Briq.	*Emblica officinalis* Gaetrn.	*Piper longum* L.
Alstonia scholaris (L.) R. Br.	*Eucommia ulmoides* Oliv.	*Potentilla alba* L.
Anacyclus pyrethrum (L.) Lag.	*Evolvulus alsinoides* (L.) L.	*Ptychopetalum olacoides* Benth.
Andrographis paniculata (Burm.f.) Nees[98]	*Firmiana simplex* (L.) W.Wight	*Rhaponticum carthamoides* (Willd.) Iljin
Aralia mandshurica Rupr. & Maxim	*Gentiana pedicellata* (D.Don) Wall	*Rhodiola heterodonta* (Hook. f. & Thomson) Boriss.
Argyreia nervosa (Burm. f.) Bojer	*Glycyrrhiza glabra* L.	*Rhodiola rosea* L.
Argyreia speciosa (L. f.) Sweet	*Heteropterys aphrodisiaca* Machado	*Rostellularia diffusa* (Willd.) Nees.
Asparagus racemosus Wild	*Hippophae rhamnoides* L.	*Salvia miltiorrhiza* Bunge
Bacopa monnieri (L.) Wettst	*Holoptelea integrifolia* Planch	*Schisandra chinensis* (Turcz.) Baill.
Bergenia crassifolia (L.) Fritsch	*Hoppea dichotoma* Willd.	*Scutellaria baicalensis* Georgi
Bryonia alba L.	*Hypericum perforatum* L.	*Serratula inermis* Poir
Caesalpinia bonduc (L.) Roxb	*Lepidium peruvianum/Lepidium meyenii* Walp.	*Sida cordifolia* L.
Centella asiatica (L.) Urb.	*Ligusticum striatum* DC.	*Silene italica* (L.) Pers.
Chlorophytum borivilianum Santapau & R.R.Fern.	*Melilotus officinalis* (L.) Pall.	*Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson
Chrysactinia mexicana A. Gray	*Morus alba* L.	*Solanum torvum* SW.
Cicer arietinum L.	*Mucuna pruriens* (L.) DC.	*Sutherlandia frutescens* (L.) R.Br.
Codonopsis pilosula (Franch.) Nannf.	*Nelumbo nucifera* Gaertn.	*Terminalia chebula* Retz.
Convolvulus prostratus Forssk.	*Ocimum sanctum* L.	*Tinospora cordifolia* (Willd.) Miers
Curculigo orchioides Gaertn.	*Oplopanax elatus* (Nakai) Nakai	*Trichilia catigua* A.Juss.
Curcuma longa L. Curcumin[97]	*Panax ginseng* C.A.Mey.	*Trichopus zeylanicus* Gaertn.
Dioscorea deltoidea Wall. ex Griseb.	*Panax pseudoginseng* Wall.	*Turnera diffusa* Willd. ex Schult.
Drypetes roxburghii (Wall.) Hurus.	*Pandanus odoratissimus* L.f.	*Vitis vinifera* L.
Echinopanax elatus Nakai	*Paullinia cupana* Kunth	*Withania somnifera* (L.) Dunal
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.	*Pfaffia paniculata* (Mart.) Kuntze	

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Evolution of definition

European Medicines Agency
Evaluation of Medicines for Human Use

- Adaptogenic *substances* have the capacity to normalize body functions and strengthen systems compromised by stress.
- They have a protective effect on health against a wide variety of environmental assaults and emotional conditions.

EMEA/HMPC/102655/2007

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Evolution of definition

- *Botanical* adaptogens are *plant extracts*, or specific constituents of plant extracts, which function to increase survival in animals and humans by stimulating their adaptability to stress by inducing adaptive responses (Panossian and Amsterdam, 2017).
- Adaptogens are stress-response modifiers that increase an organism's nonspecific resistance to stress by increasing its ability to adapt and survive. (Panossian, 2017).
- Botanical adaptogens are metabolic regulators that increase survival by increasing adaptability in stress. (Panossian, 2017).
- Adaptogens *are natural compounds or plant extracts* that increase adaptability and survival of living organisms to stress.
- Like vitamins and antioxidants, adaptogens constitute *a category of nutritional and herbal medicinal products*.

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Adaptability

- Ability of an organism to alter itself or its responses to the changed circumstances or environment.
- Adaptability shows the ability to learn from experience, and improves the fitness of the learner as a competitor.

Health is the ability to adapt to one's environment

George Canguilhem
1943

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Adaptogens - stimulants

- A characteristic feature of adaptogens is that they act as eustressors or challengers. Thus, a **single** administration of an adaptogen mainly produces a challenging (stimulating or stress-agonising) effect, a fact that is used in sports medicine where a single dose of adaptogen can increase the performance of athletes by making them more alert.

Adaptogens –stress protectors

- Stress-protective effect achieved by multiple administration of adaptogens is **not** the result of inhibition of the stress response of an organism, but actually of **adaptive changes** in the organism as a response to the repeated stress-agonistic effect of the drug. In other words, using pharmacological terminology, adaptogens are mild stress-agonists and not stress-antagonists

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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

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Summary: definitions update for adaptogens

- *Definition*: adaptogens are natural compounds or plant extracts that increase adaptability and survival of living organisms to stress.
- *Chemical class:* various, predominantly tetracyclic triterpene, phenethyl-and phehylpropanoids glycosides, lignans, etc.
- *Pharmacological activity*: adaptogenic, stress-protective, stimulating
- *Mechanism of action:* multitarget effects on neuroendocrine-immune system; adaptogens are stress response modifiers of cellular and organismal defense systems, activating intracellular and extracellular adaptive signaling pathways, that promote cell survival; adaptogens trigger generation of hormones (cortisol, corticotropin and gonadotropin releasing hormones, urocortin, neuropeptide Y), playing key role in metabolic regulation and homeostasis.
- *Indications/health claims:* stress-induced fatigue, mental and behavioral disorders, aging associated diseases.
- *Conclusive note*: adaptogens, like vitamins and antioxidants constitute a separate category of nutritional and herbal medicinal products.

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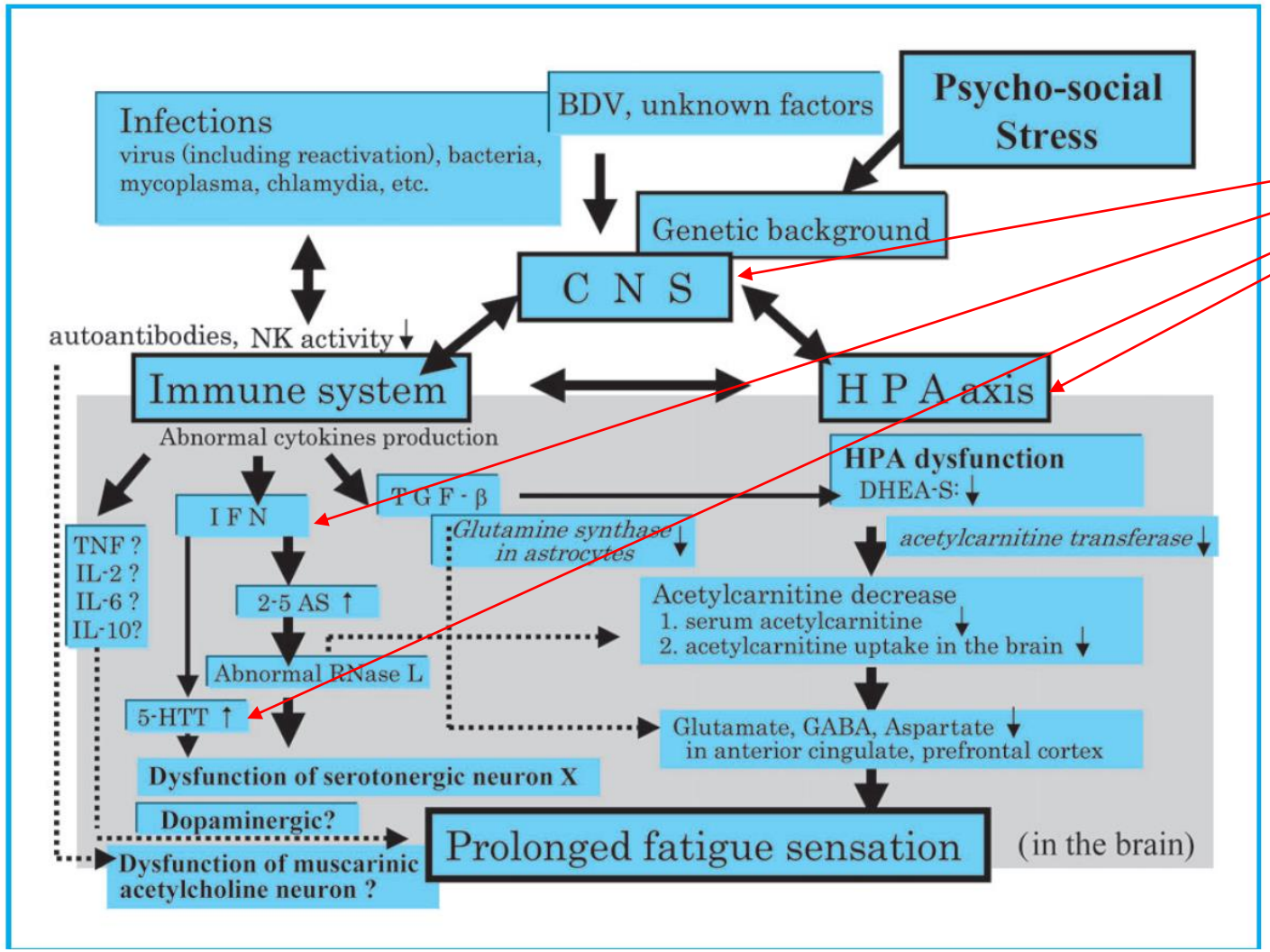
Sense of fatigue is a bio-alarm defense response of psycho neuroendocrine-immune system to stress, like pain or fever.



Adaptogens

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Watanabe and Kuratsune, 2006, Brain science on chronic fatigue. JMAJ 49 (1), 19-26.

When to use adaptogens ?

When we need to:

- adapt organism to stress
- increase resistance to stress
- increase recovery of stress induced damages
- provide energy in tiredness, fatigue and exhaustion
- activate innate defense system
- reduce aging associated decline of functioning of neuro-endocrine immune system

What are basic mechanisms of action of adaptogens?
What is common and what is specific for various adaptogens?
What new health benefits and indications for use which we can predict based on human genomic studies?

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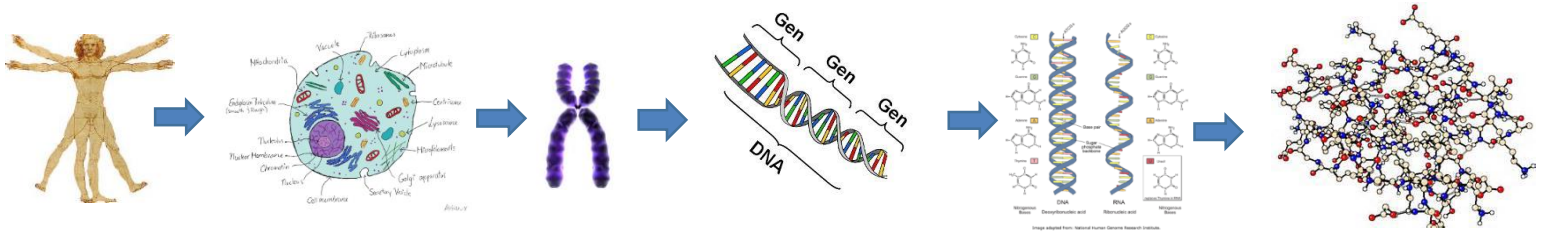
The reductionist concept in drug discovery and development

The reductionist methods of dissecting biological systems into their constituent parts



Bioassay guided fractionation of herbal extracts with the purpose to isolate an active principle dominates on the West for almost last 20 centuries and was fundamental principle in drug developing strategy in pharmaceutical science and industry.

It is based on assumption that a herbal preparation contains one or two active principles, while other constituents are just an inactive ballast.

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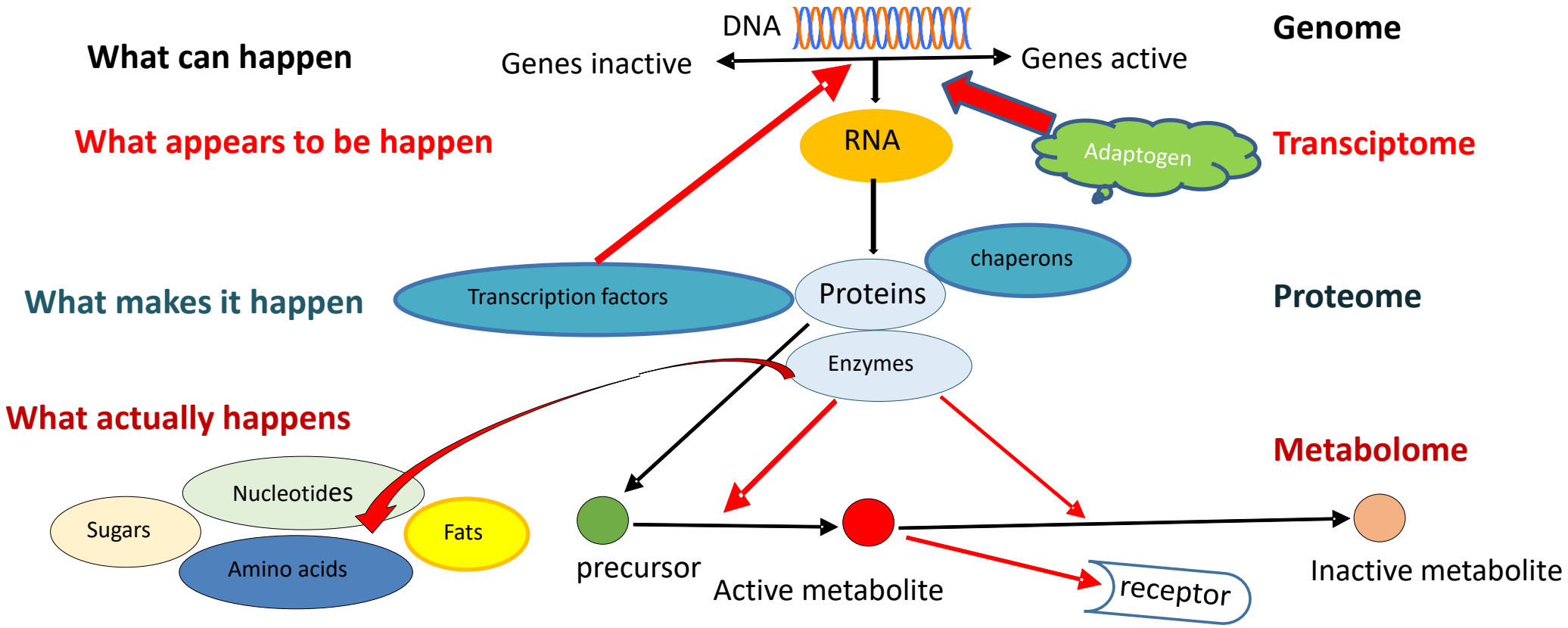
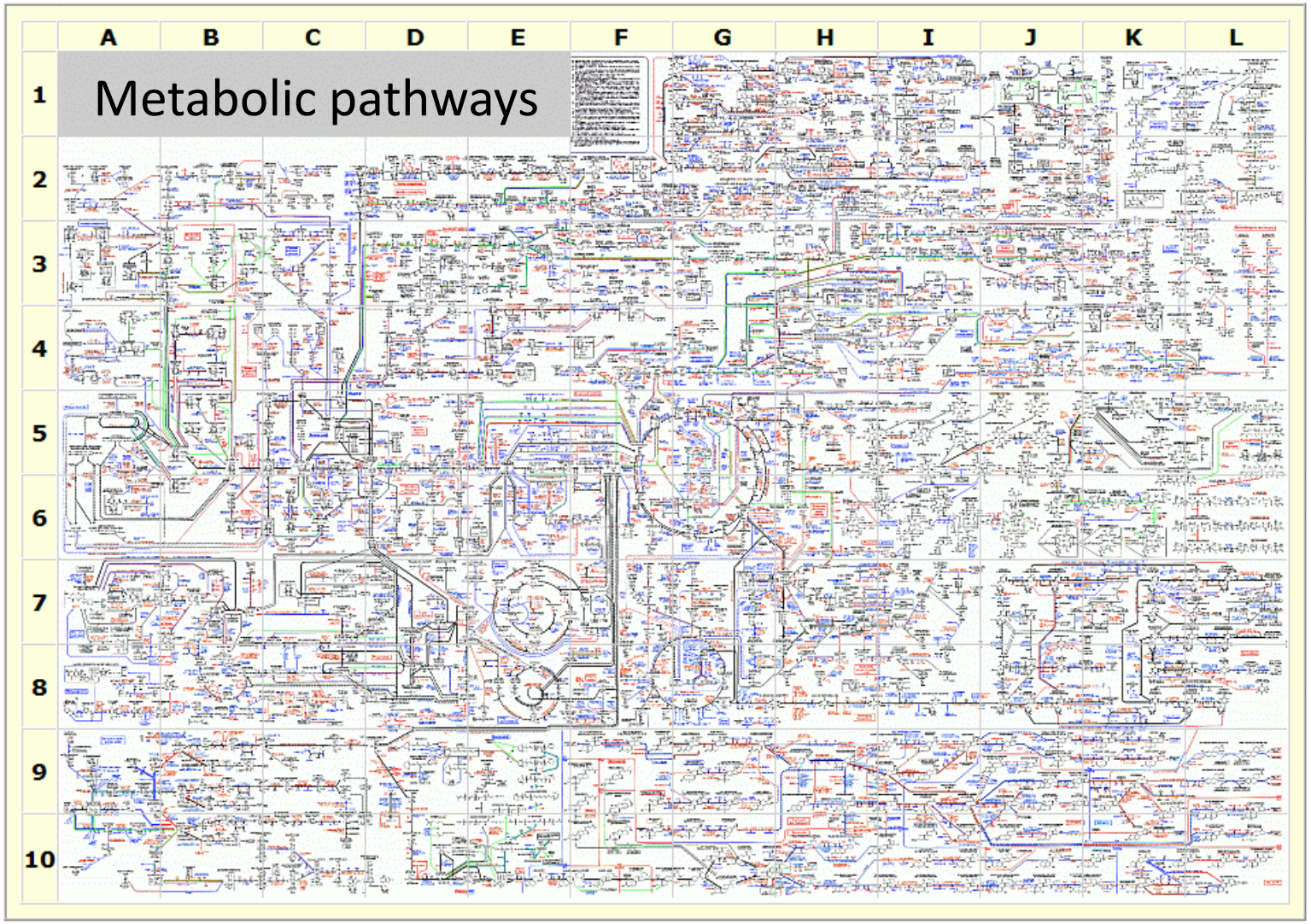
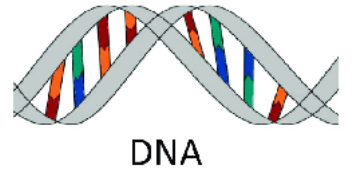
Molecular targets of pharmacological intervention

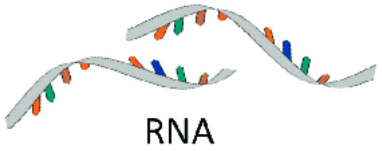


Panossian A.G. 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N.Y. Acad. Sci. 1401(1):49-64.

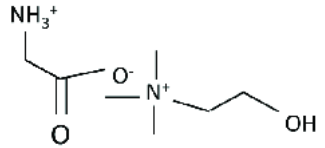
Molecular network-based cause–effect relationships concept




DNA


RNA


Proteins



Metabolites

Genomics

Transcriptomics

Proteomics

Metabolomics

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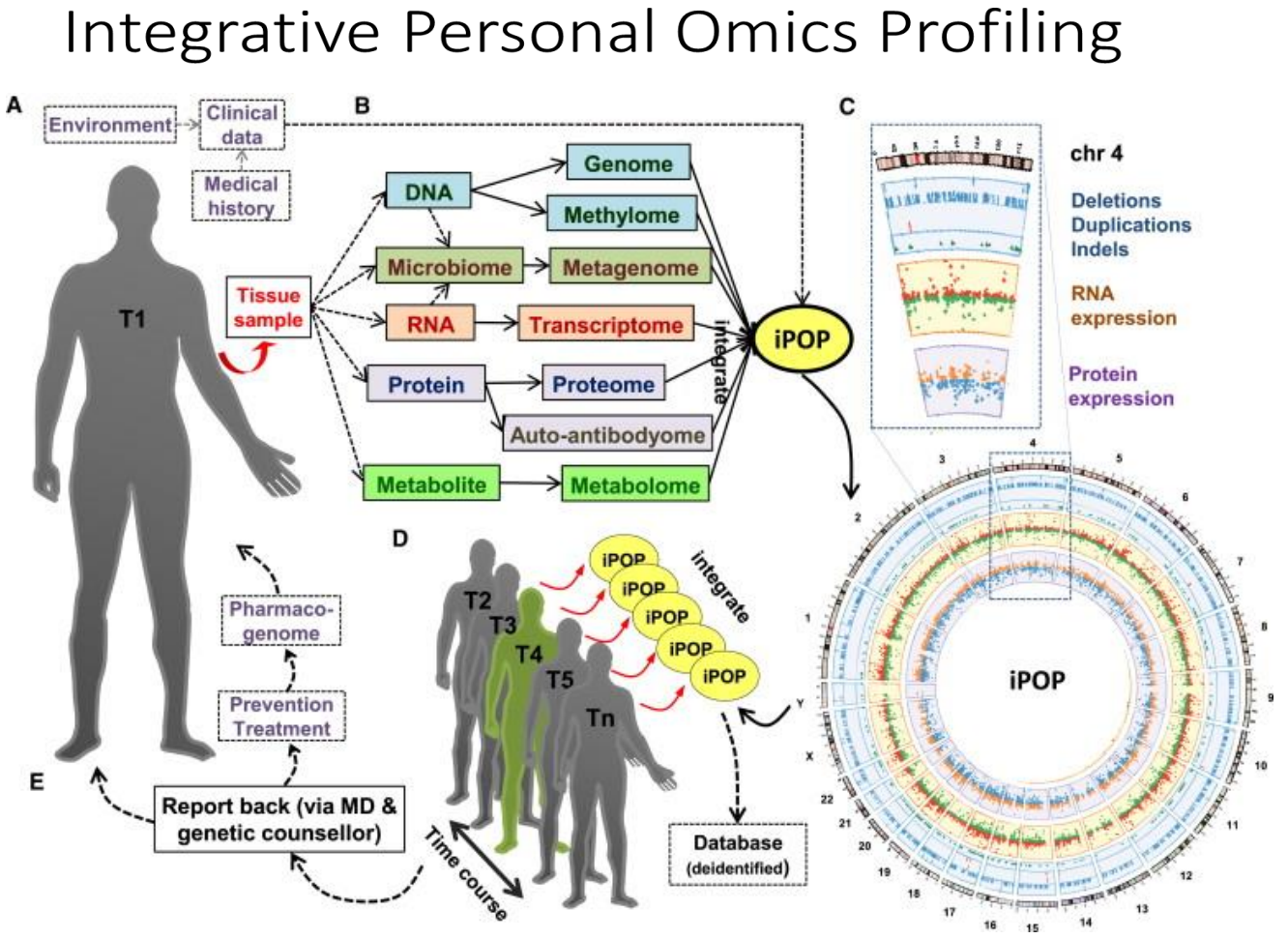
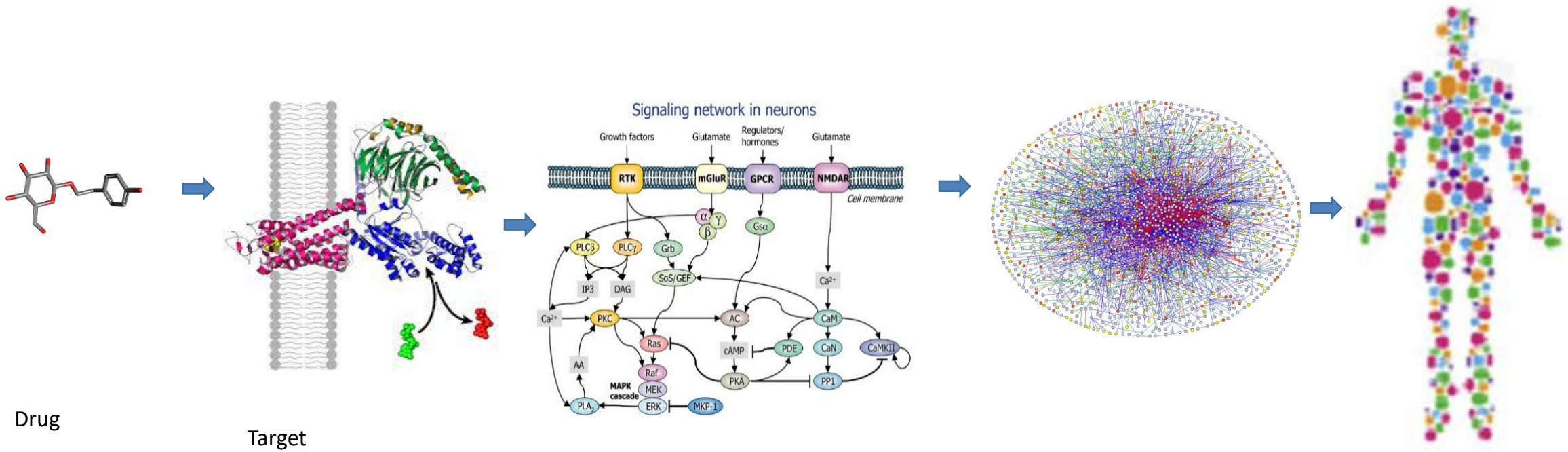
Molecular network-based cause–effect relationships concept

- **Genetic code determines our appearance, physiological and psychological properties: DNA → mRNA → protein (gene expression)**
- **We have the same set of DNA in all of our cells. BUT a liver cell is different from a muscle of brain cell because of differential gene expression**
- **How Integrative OMICS profiling changes in health and disease?**
- **How Integrative OMICS profiling changes after pharmacological intervention?**
- **The transcriptome was found as the most informative, Michael Snyder, 2012**



Molecular network-based cause–effect relationships concept

Current drug-discovery platform links drugs and targets with signaling pathways, molecular networks, and organism effects.



Drug

Target

Pathway

Protein Network

Effect

frontiers in NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 20 February 2013
doi: 10.3389/fnins.2013.00016

Synergy and antagonism of active constituents of ADAPT-232 on transcriptional level of metabolic regulation of isolated neuroglial cells

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journal homepage: www.elsevier.de/phymed

Mechanism of action of *Rhodiola*, salidroside, tyrosol and triandrin in isolated neuroglial cells: An interactive pathway analysis of the downstream effects using RNA microarray data

Alexander Panossian[a,*], Rebecca Hamm[b], Georg Wikman[a], Thomas Efferth[b]

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[b] Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany

Phytomedicine 50 (2018) 257–284

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Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology

Alexander Panossian[a,b,*], Ean-Jeong Seo[c], Thomas Efferth[c,*]

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Phytomedicine xxx (xxxx) xxx-xxx

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Effects of anti-inflammatory and adaptogenic herbal extracts on gene expression of eicosanoids signaling pathways in isolated brain cells

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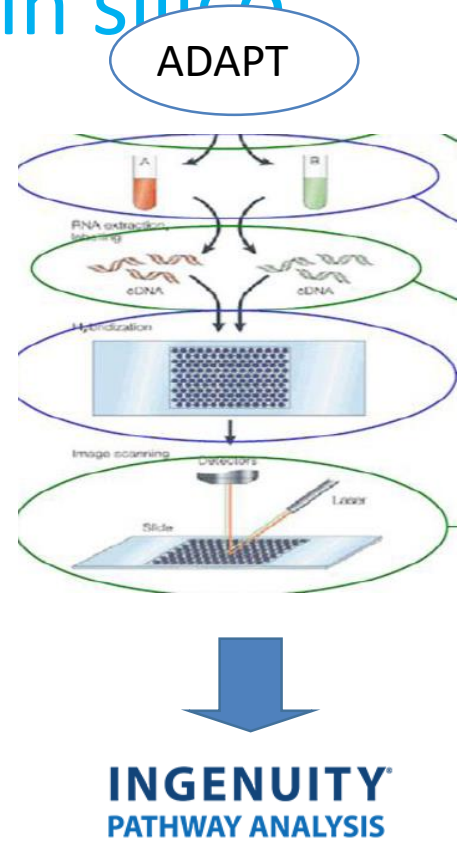
Assessment of adaptogens using systems pharmacology approach, molecular biology technologies and in silico models

- RNA Microarray or RNA sequencing technologies allows us to measure the level of gene expression for different cells, conditions, drug treatments, etc.
- Both methods provide differential gene expression profiling and degree of gene expression in fold changes compared to control.
- RNA sequencing data were analyzed using Ingenuity Pathway Analysis (IPA) software (QIAGEN Bioinformatics).
- IPA performs different calculations on transcriptomic datasets based on the Ingenuity Knowledge Base, a large gathering of observations with approximately 5 Mio findings manually curated from the biomedical literature or integrated from third-party databases.
- For obtaining information about the impact of test samples on cellular signaling pathways and networks, biological functions and diseases that are downstream of the genes, whose expression has been altered in a dataset.



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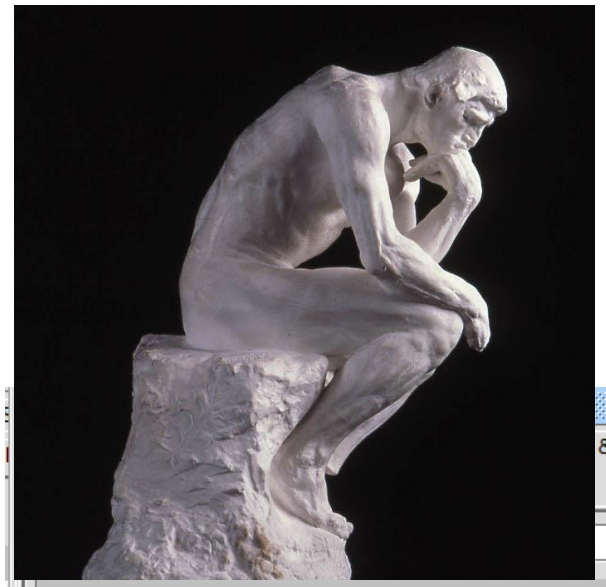
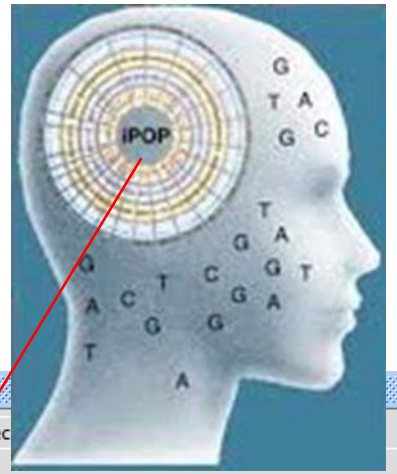
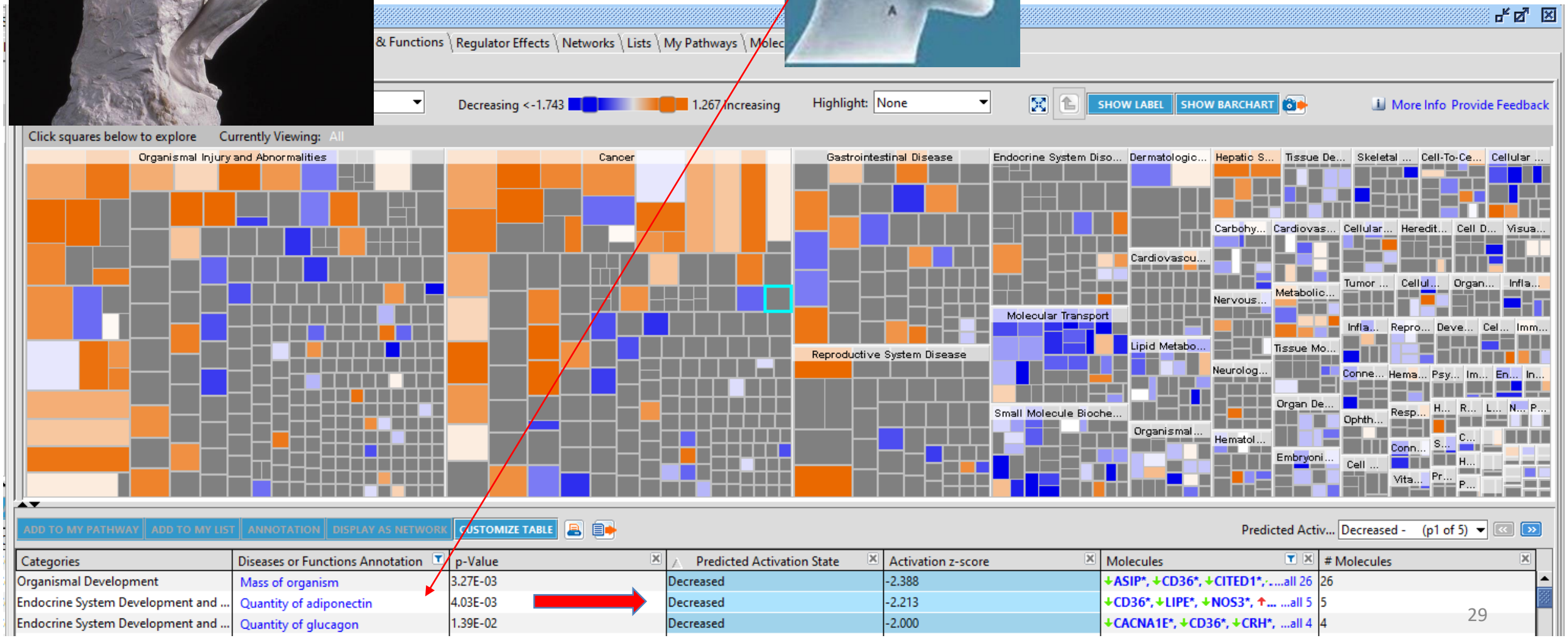


Withania low dose



"biological signature" – predicted effects on diseases and physiological functions



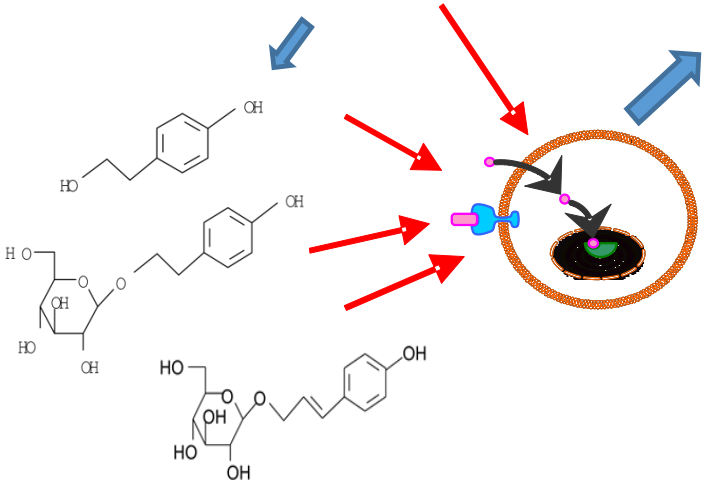
Categories	Diseases or Functions Annotation	p-Value	Predicted Activation State	Activation z-score	Molecules	# Molecules
Organismal Development	Mass of organism	3.27E-03	Decreased	-2.388	↓ASIP*, ↓CD36*, ↓CITED1*, ...all 26	26
Endocrine System Development and ...	Quantity of adiponectin	4.03E-03	Decreased	-2.213	↓CD36*, ↓LIPE*, ↓NOS3*, ↑... ...all 5	5
Endocrine System Development and ...	Quantity of glucagon	1.39E-02	Decreased	-2.000	↓CACNA1E*, ↓CD36*, ↓CRH*, ...all 4	4

Effect of Rhodiola SHR-5 on human genome: predictable effects on physiological functions and diseases

Radix Rhodiola

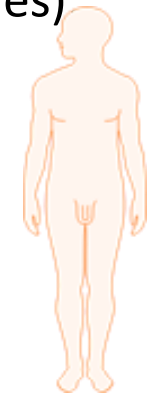
Microarray Data Analysis ➡ **Interactive pathways downstream effect analysis**

SHR-5 extract



Gene Expression profiling

- intracellular signalling pathways :
- molecular and cellular functions,
- physiological systems functions, associated with:
  - cardiovascular (72 deregulated genes)
  - metabolic (63 genes),
  - gastrointestinal (163 genes),
  - neurological diseases (95 genes),
  - endocrine (60 genes),
  - behavioral (50 genes), or
  - psychological disorders (62 genes).



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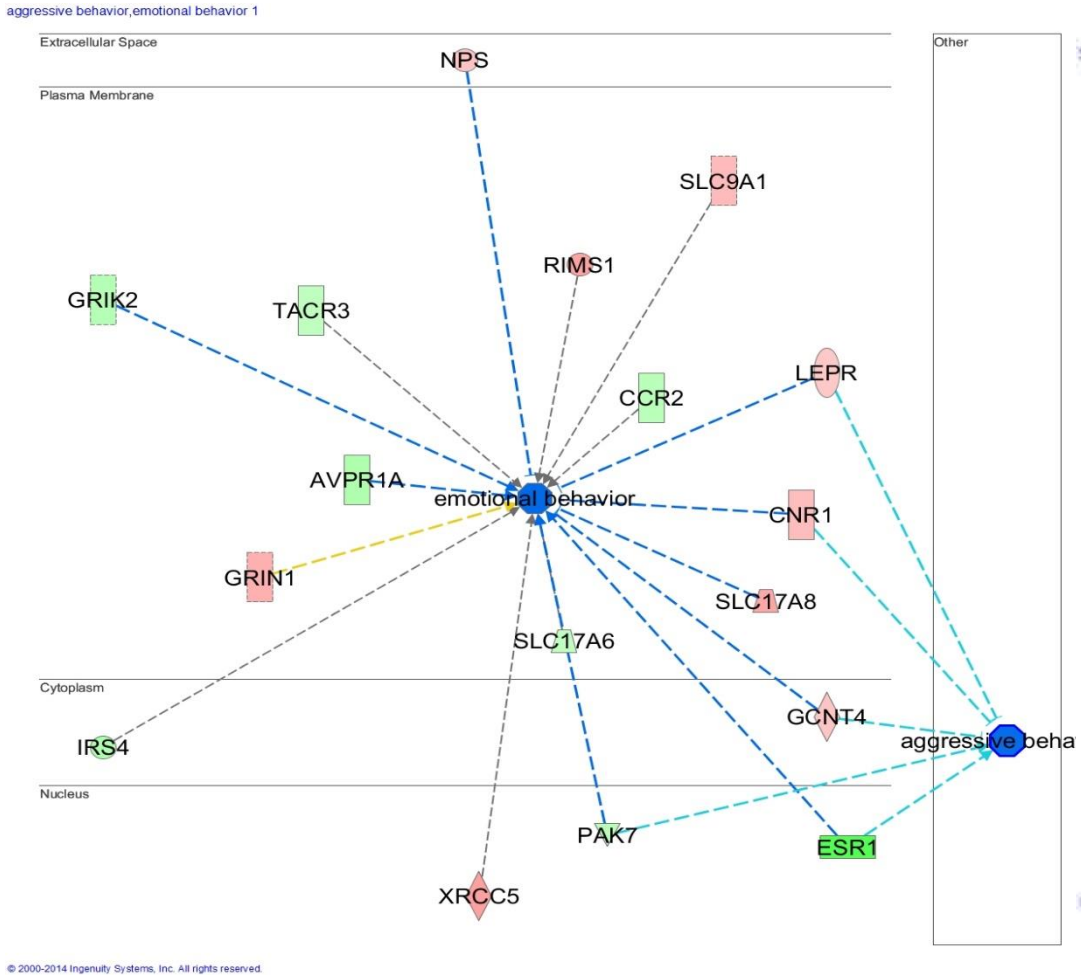
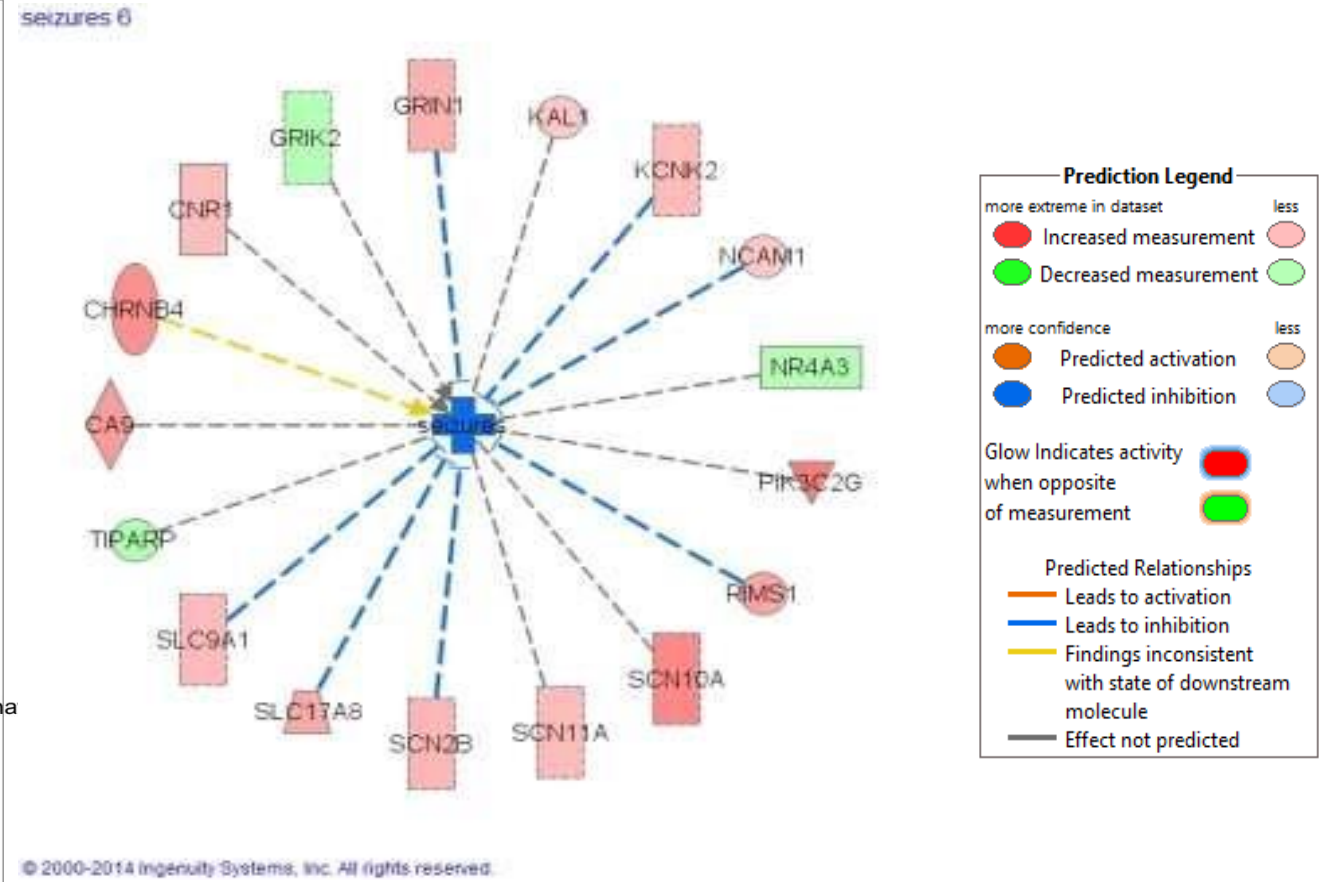
The effects of Rhodiola on molecular network associated with emotional behavior, aggression and seizures





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Eicosanoid Signaling

Rhodiola

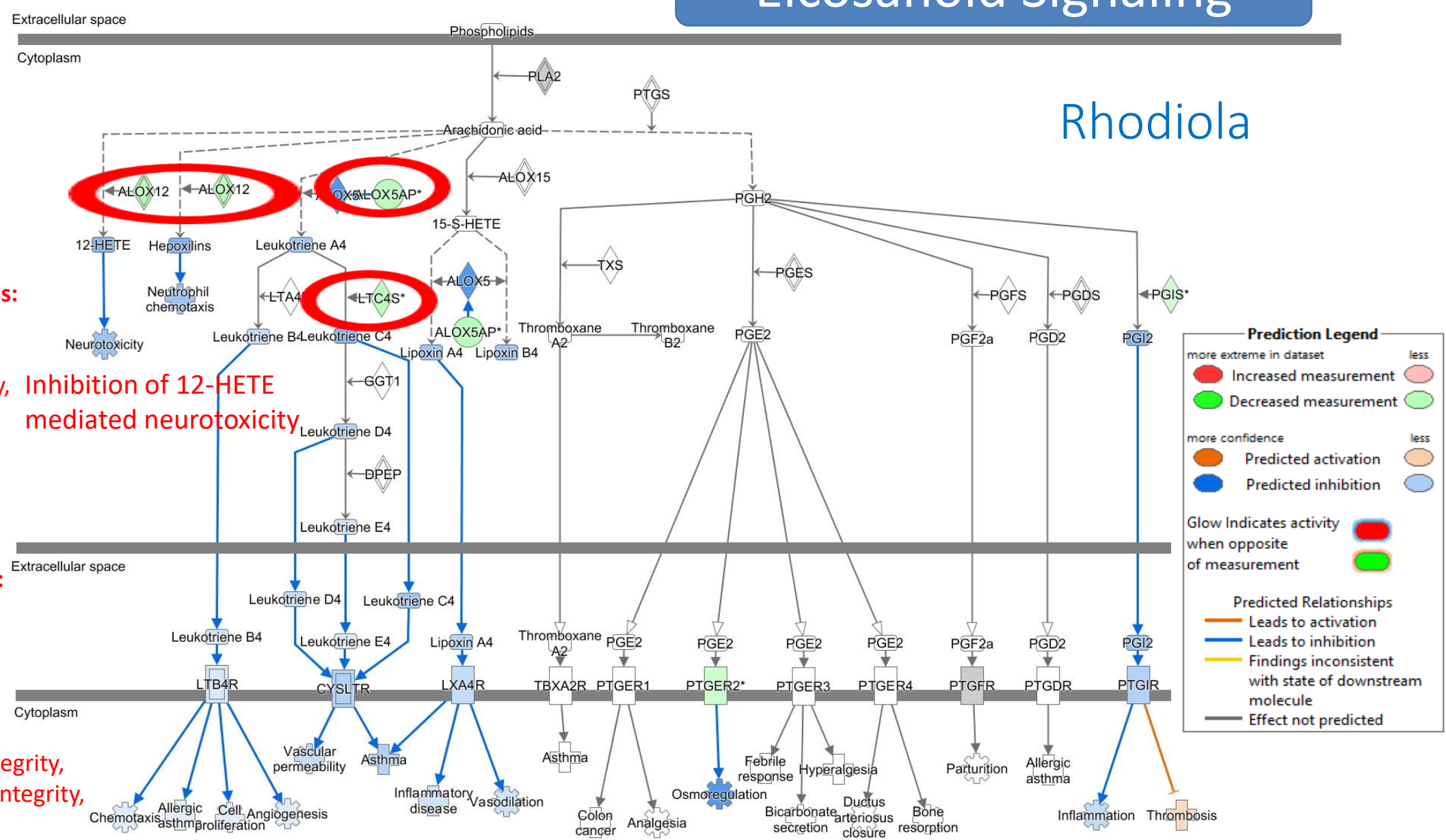
Inhibition of leukotrienes:

- **Asthma**
- vascular permeability,
- vasodilatation
- asthma
- chemotaxis
- inflammation
- allergic asthma

Inhibition of 12-HETE mediated neurotoxicity

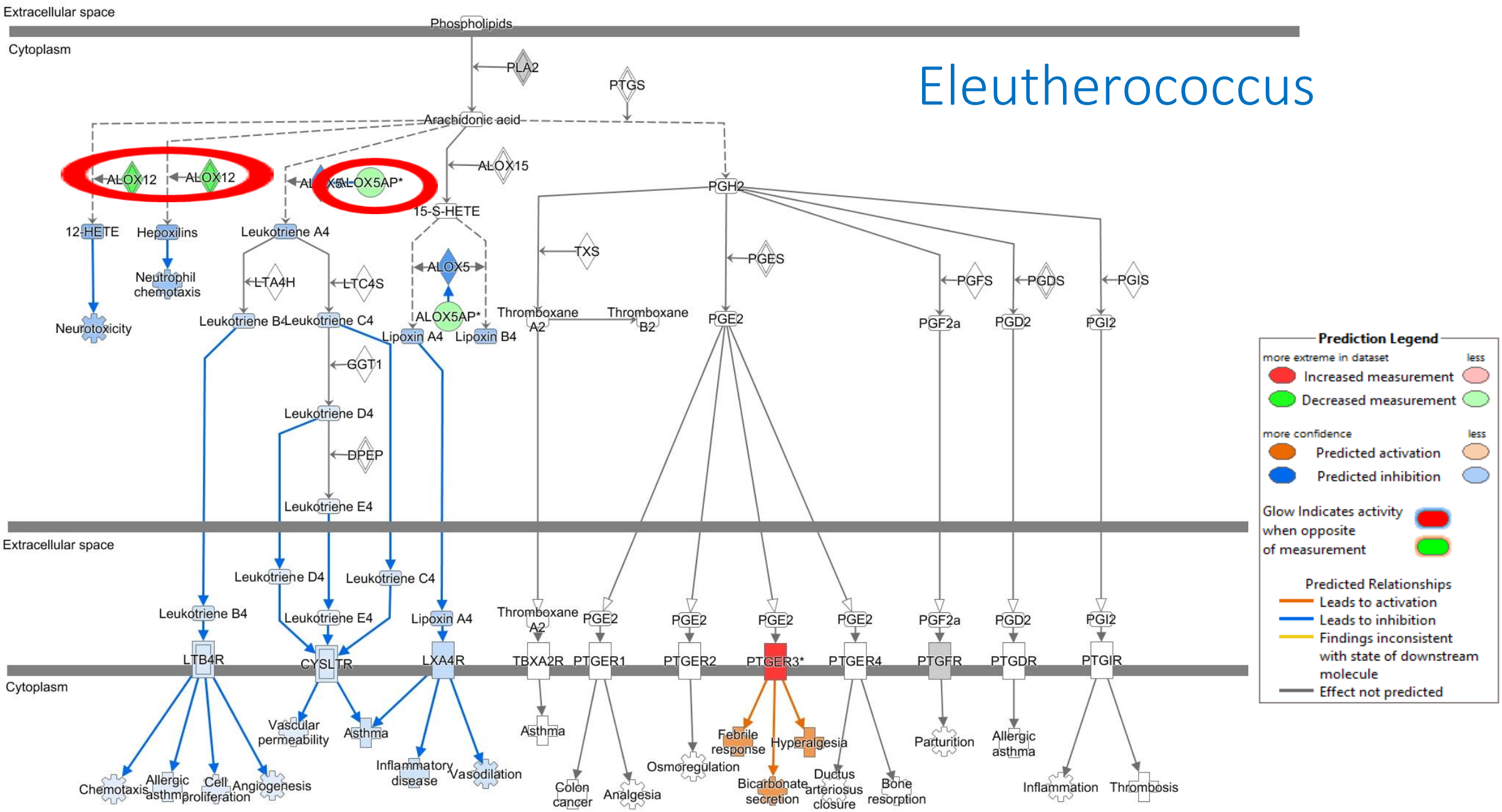
Inhibition of leukotrienes:

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



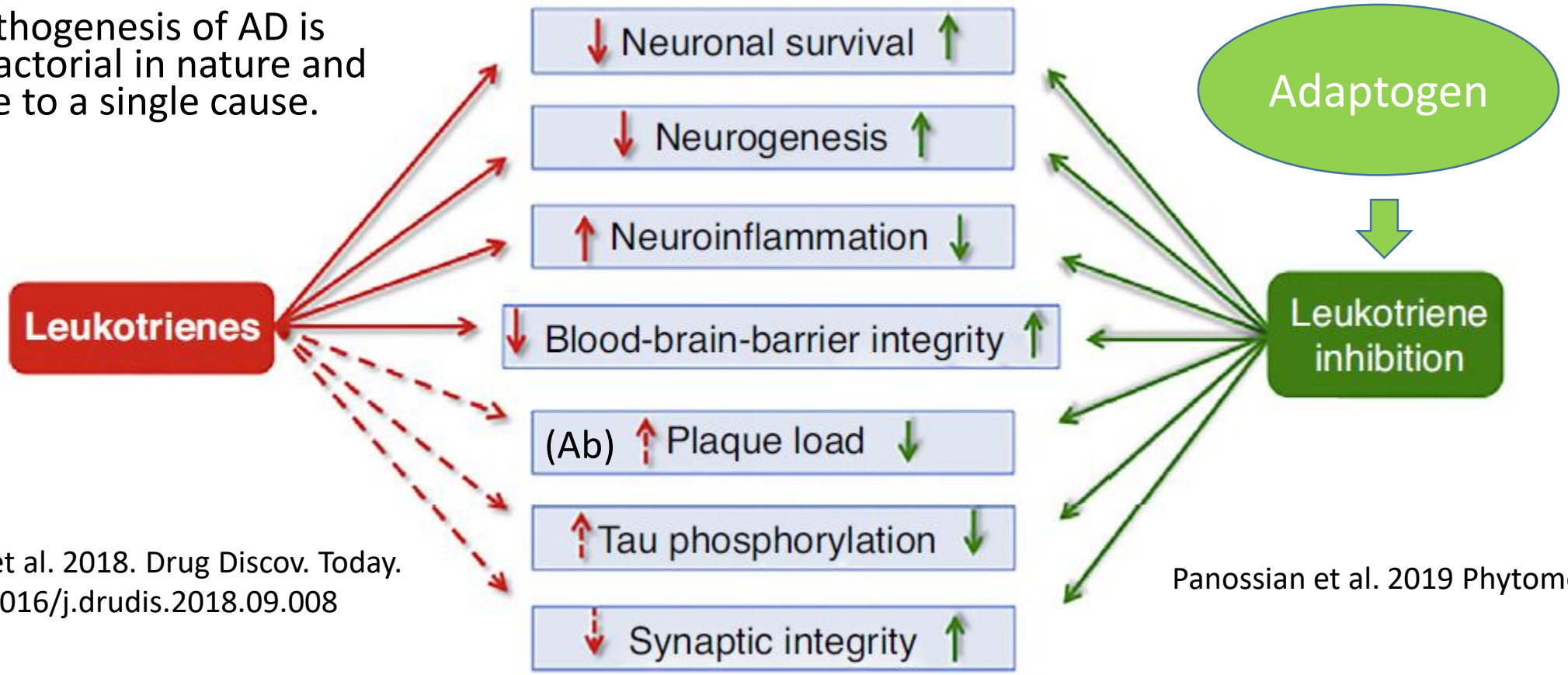
Eicosanoid Signaling : Adaptogens Dataset 2FC : Expr Fold Change

Eleutherococcus



Pleiotropic effects of leukotrienes in Alzheimer disease and leukotriene inhibition by adaptogens

The pathogenesis of AD is multi-factorial in nature and not due to a single cause.



Michael et al. 2018. Drug Discov. Today. DOI: 10.1016/j.drudis.2018.09.008

Panossian et al. 2019 Phytomedicine,

PHYTOMED

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**

PHYTOMED

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

PHYTOMED

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 Signaling and and degradation	MTNR1A,PLCD4, UGT2A3,CYP4X1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	MMP8,PIK3C2G,WNT16,TCF7L2
eNOS Signaling	PIK3C2G,CNGB3,ESR1

PHYTOMED

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	ESR1б MTNR1A - down regulated,
	Pain – inhibition	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

PHYTOMED

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

The effects of adaptogens 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

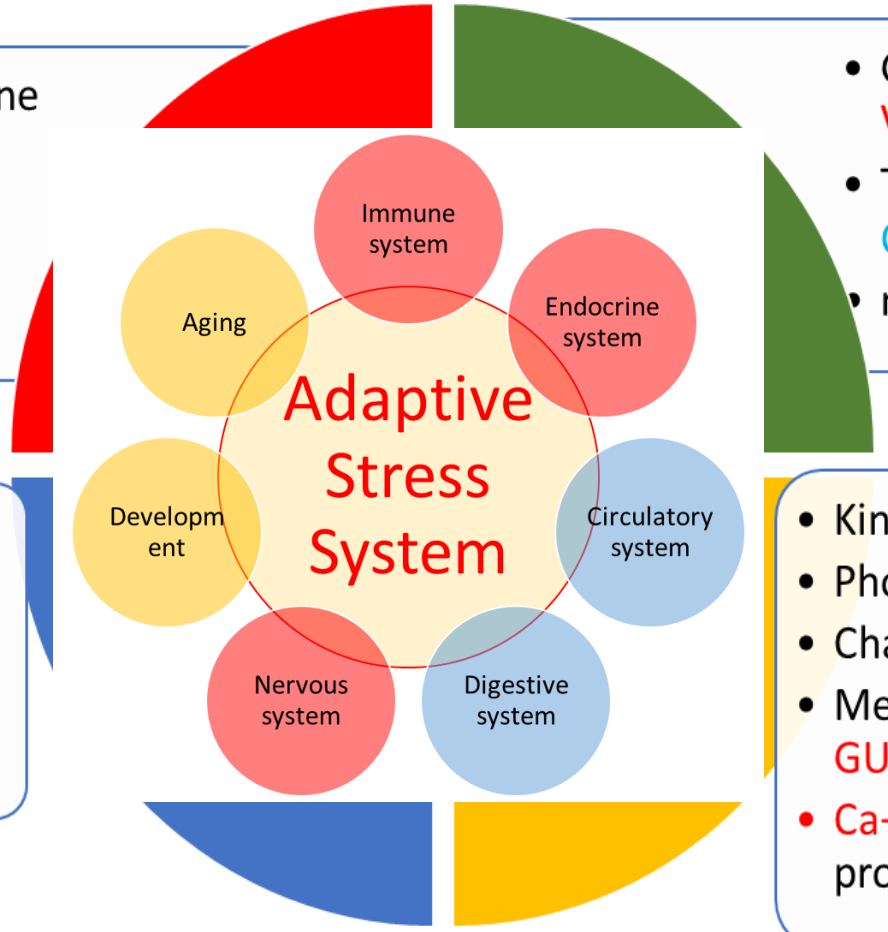
- Down regulation of cAMP
- Inhibition of ATP metabolism

PHYTOMED

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

Types of proteins regulated by adaptogens via regulation of genes expression

- CRH - corticotropin releasing hormone
- UCN - urocortins
- GNRH1 - gonadotropin releasing hormone



- G-protein coupled receptors CHRM4, VIPR2, etc.
- Transmembrane receptors TLR9, PRLR, CHRNE, etc.
- nuclear receptor RORA

- STAT5A
- FOS
- FOX06
- SCX
- Zinc finger proteins

- Kinases MAPK10, MAPK13, PRKCH, etc.
- Phosphatases PTPRD, PTPRR
- Chaperons HSPA6, STIP1
- Metabolic enzymes PDE9A, PDE3B, GUCY1A2, LDHD, CEL, AOC3, LIPE, etc.
- Ca+2 and K+ voltage-gated channels proteins, etc.

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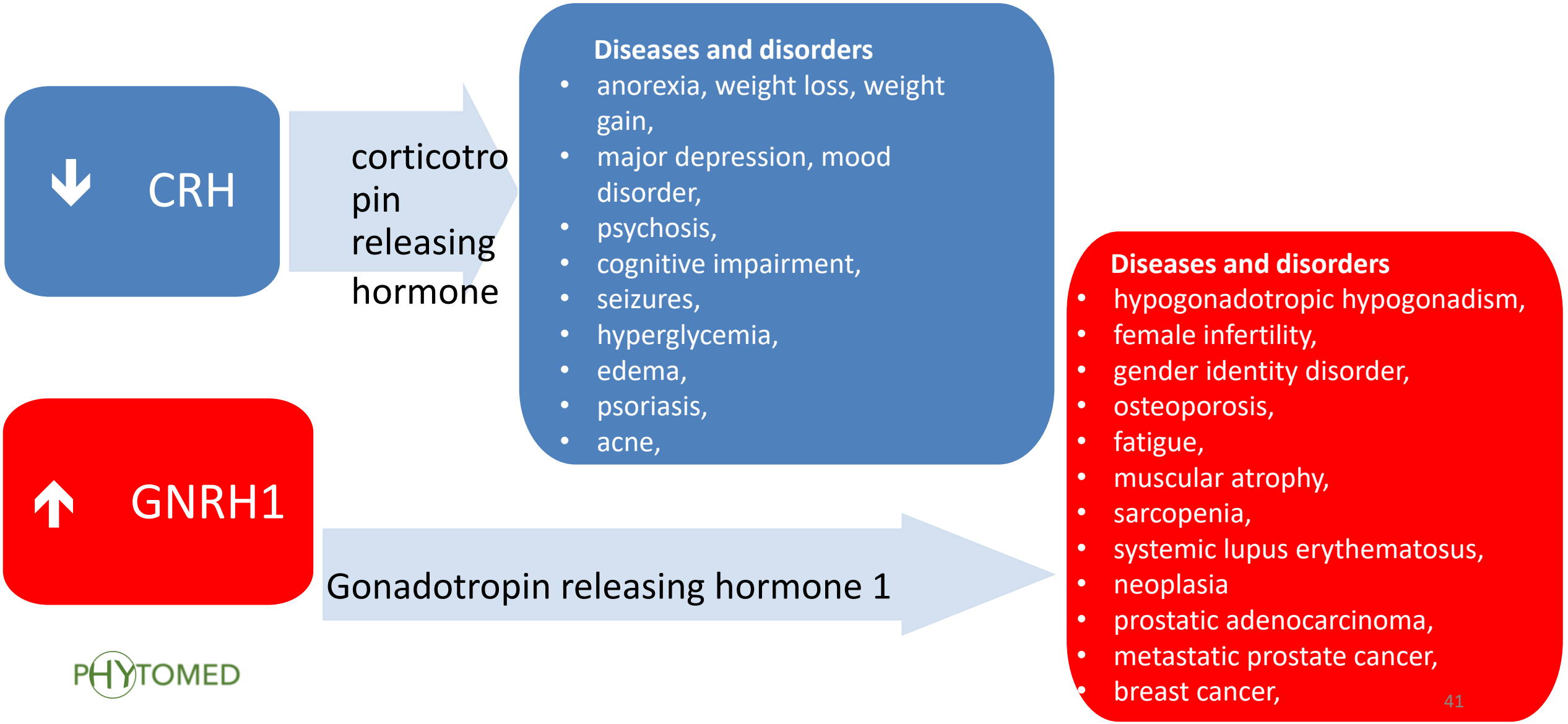
Effect of adaptogens on HPA axis hormones encoding genes expression



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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.

prolactin receptor

PRLR ↓

Transmembrane receptor

CHRNE ↓

cholinergic receptor

Diseases and disorders

- fatigue,
- insomnia,
- congenital myasthenic syndrome,
- familial infantile myasthenia type 1,
- major depression,
- schizophrenia,
- pain, pelvic and postoperative pain,
- nicotine withdrawal syndrome and
- nicotine dependence,
- chronic obstructive pulmonary disease,
- respiratory failure,
- acute respiratory distress syndrome,

Diseases and disorders

- Alzheimer disease,
- psychological disorder,
- myoclonus,
- psychomotor agitation,
- schizoaffective disorder,
- morbid obesity,
- bladder cancer,
- weight gain,
- malignant hypertension
- alcoholism,

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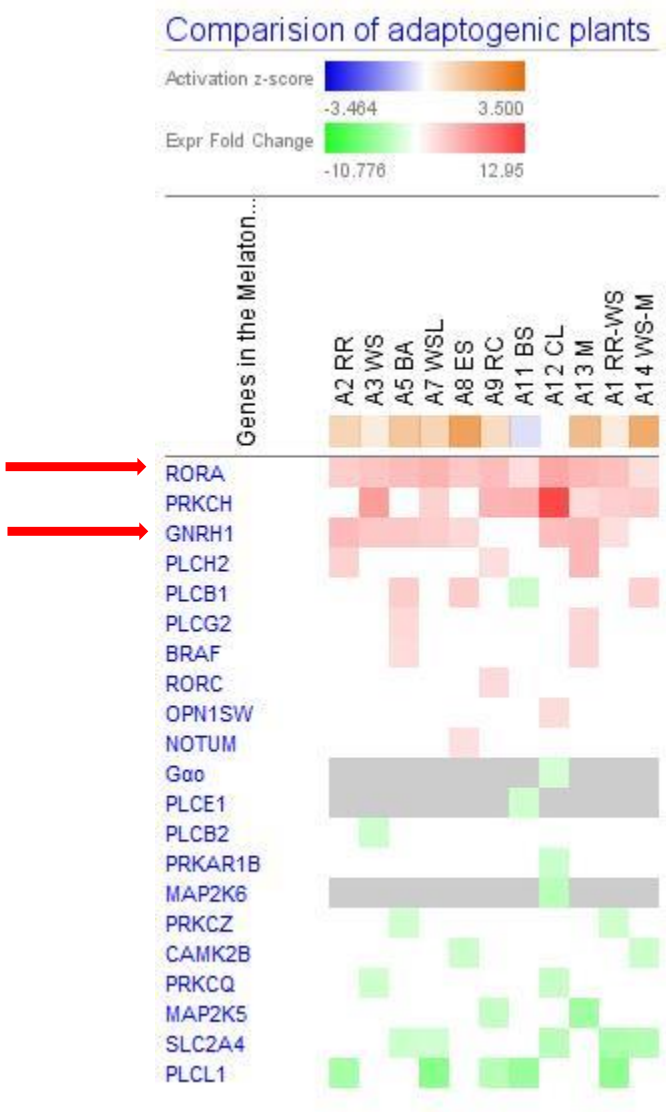
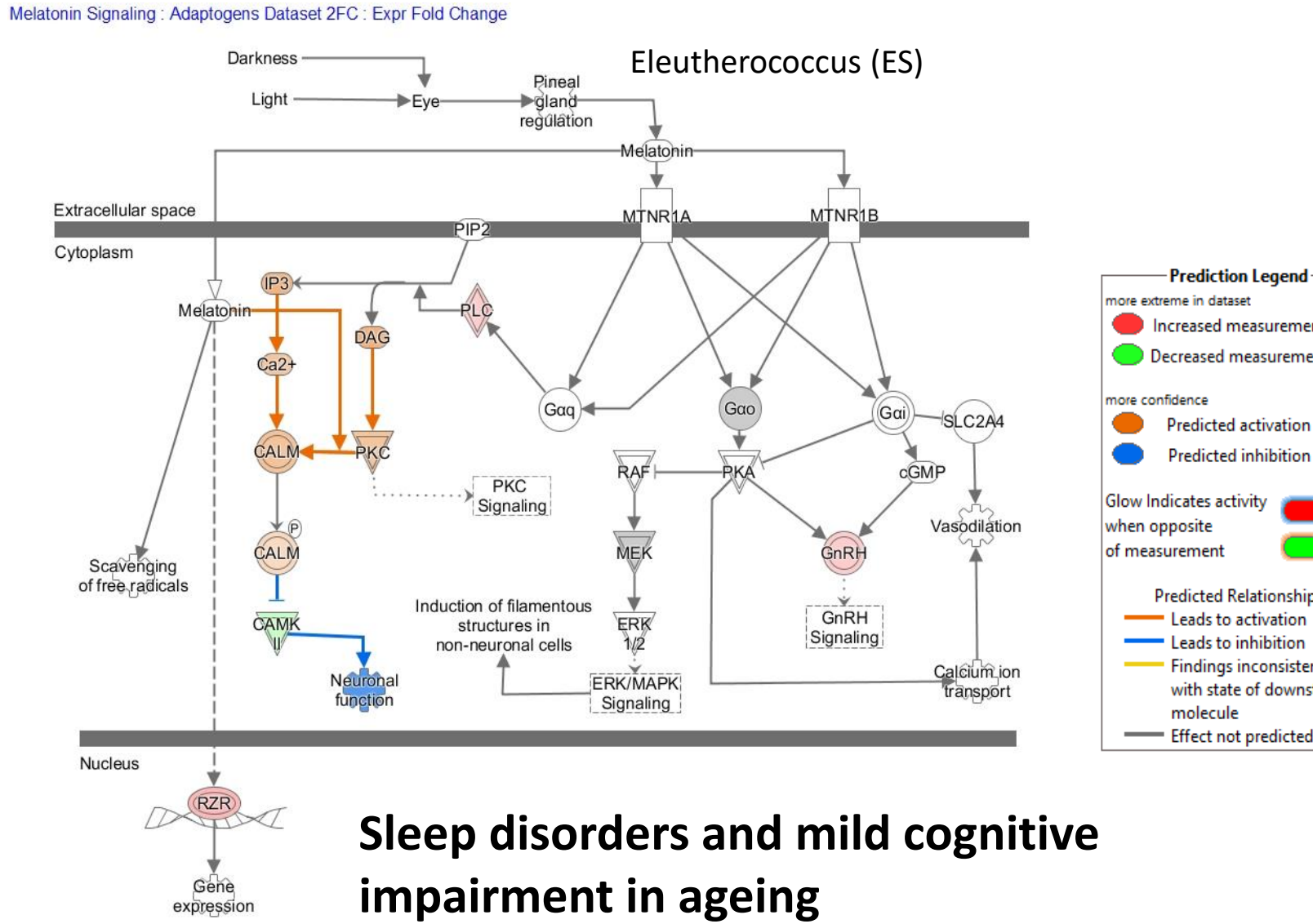
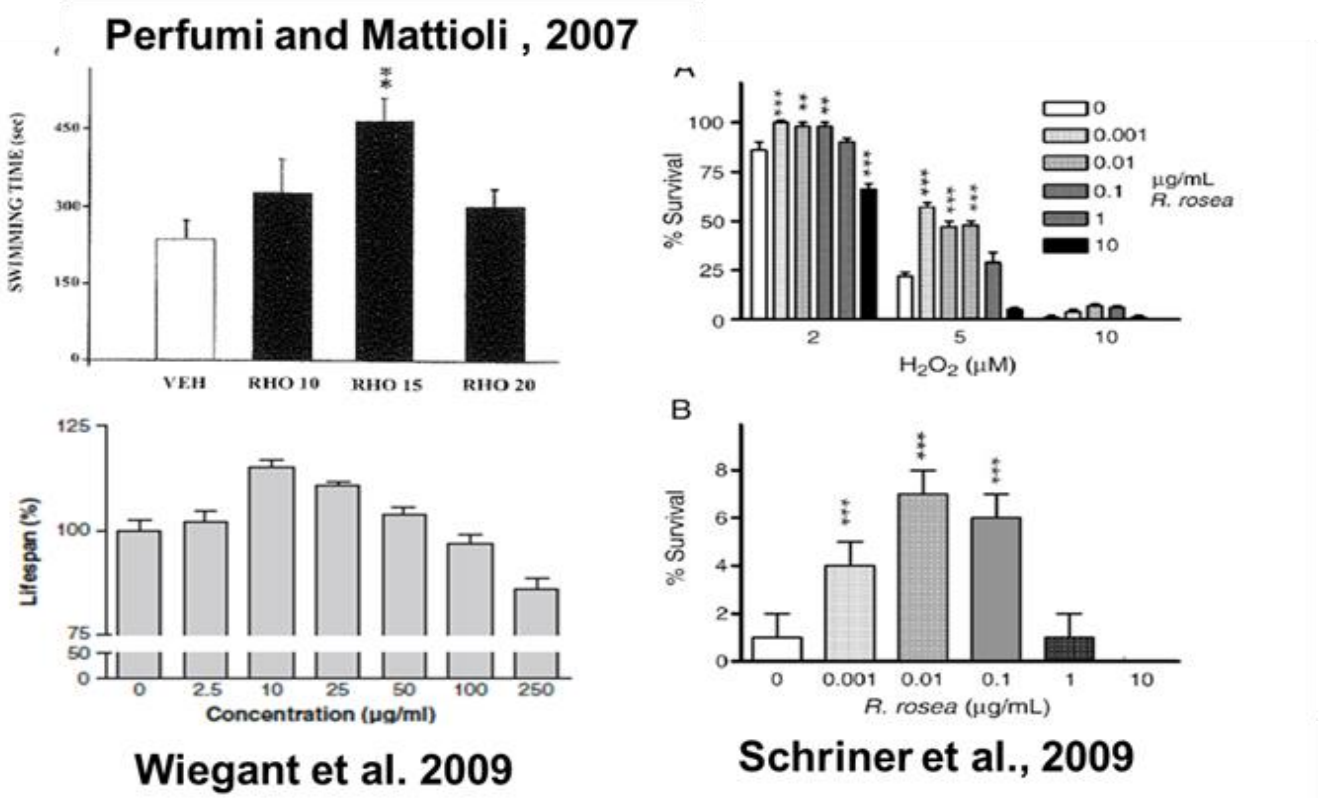
Gene maps of melatonin signaling pathway



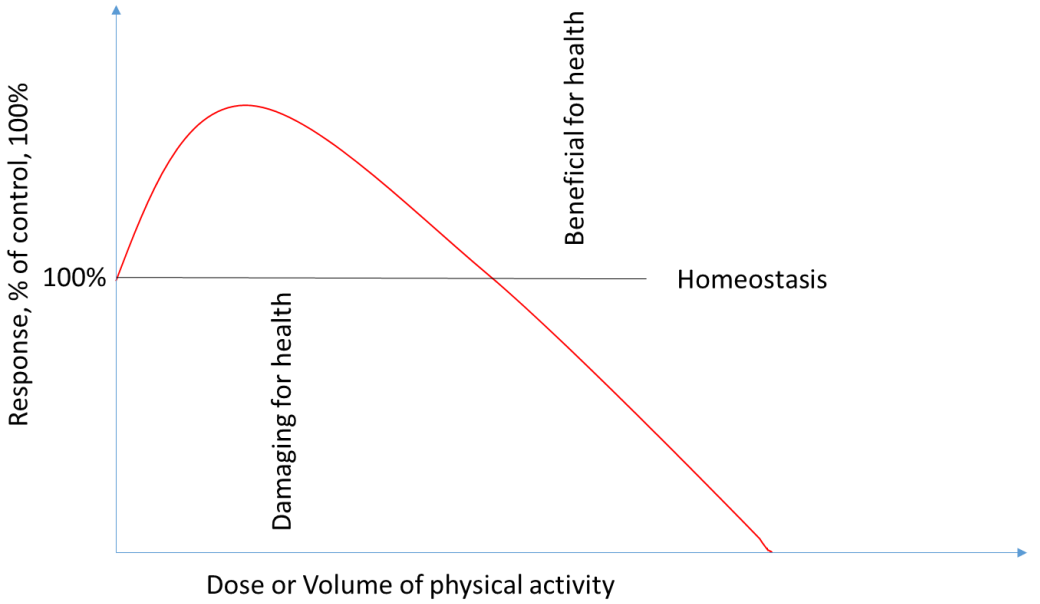


Sleep disorders and mild cognitive impairment in ageing

Biphasic dose-effect dependence in some of in vivo and in vitro studies of Rhodiola extracts



Adaptive (hormetic) stress response



Panossian et al., Molecular Chaperones as Mediators of Stress Protective Effect of Plant Adaptogens.
In: **Heat Shock Proteins and Whole Body Physiology** Heat Shock Proteins Vol. 5, Springer. 2010, pp. 351-364.

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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 cellular stress response pathways in humans .

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

PHYTOMED

Edward J. Calabrese

Hormesis – Biphasic dose-response

The term hormesis describe the process by which sublethal damage caused by small doses of a toxin would produce an exaggerated repair response in which the organism actually becomes stronger than it was previously.

"That which does not kill us makes us stronger."

Paracelsus

"*All things are poisons. It is only the dose which makes a thing poison*."

Friedrich Wilhelm Nietzsche

PHYTOMED

Mark Mattson

Adaptive stress response signaling

Adaptive stress response (hormesis) involves activation of intracellular and extracellular signaling pathways and increased expression of anti-apoptotic proteins, neuropeptides, antioxidant enzymes and defense response of an organism resulting in increased survival .

ADAPTIVE STRESS RESPONSE FACTORS

- exercise
- dietary energy restriction
- **nutrition and medication**
- cognitive stimulation / emotions
- toxins
- radiation
- temperature

MEDIATORS OF CELL ADAPTIVE STRESS RESPONSE SIGNALING SYSTEM

Receptors (GPCR, NTFR, TLR, IR) and ion channels
Enzymes (PLC, AC,GC) and second messengers (IP3, DAG, cAMP)
Kinases (PKC, PI3K, MAPK, PERK)
Transcription and nuclear factors (Nrf-2, FOXOs, CREB, NF-kB)

ADAPTIVE STRESS RESPONSE EFFECTORS

Free radicals, antioxidant enzymatic system

- superoxide dismutase
- catalase
- glutathione peroxidase
- glutathione

Protein chaperones, growth factors and defense response proteins

- HSP-70
- GRP-78
- BDNF
- VEGF
- bFGF

Mattson , 2007, 2008

PHYTOMED

Adaptive stress response, adaptive homeostasis and adaptogens

Adaptogens initiate 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.

In the context of responses of cells and organisms to stress, adaptogens act as “mild stress vaccines” and have beneficial effect in stress induced and aging related disorders.

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Adaptive stress response signaling regulated by adaptogens

ADAPTIVE STRESS RESPONSE FACTORS

- adaptogens

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, FOX06, SCX, Nrf-2, CREB, NF-kB, Zinc finger proteins

ADAPTIVE STRESS RESPONSE EFFECTORS

Free radicals, antioxidant enzymatic system

- superoxide dismutase
- catalase
- glutathione peroxidase
- glutathione

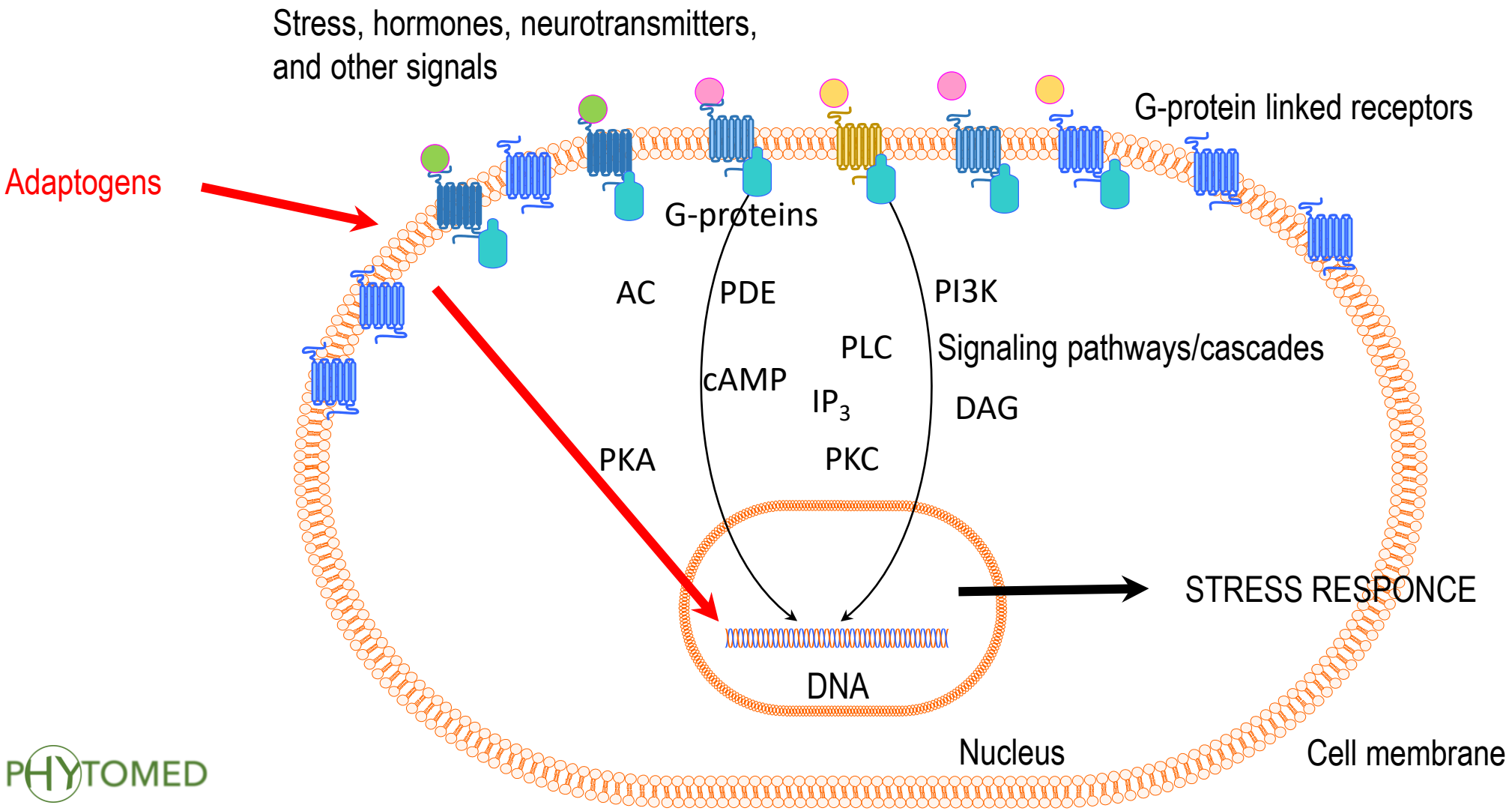
Protein chaperones, growth factors and defense response proteins

- HSP-70, HSPA6, STIP1, PDE9A, PDE3B, GUCY1A2, LDHD, CEL, AOC3, LIPE, etc.

Panossian et al., 2018

PHYTOMED

Adaptogens regulate genes encoding GPCR and key mediators of GPCR adaptive signaling pathways



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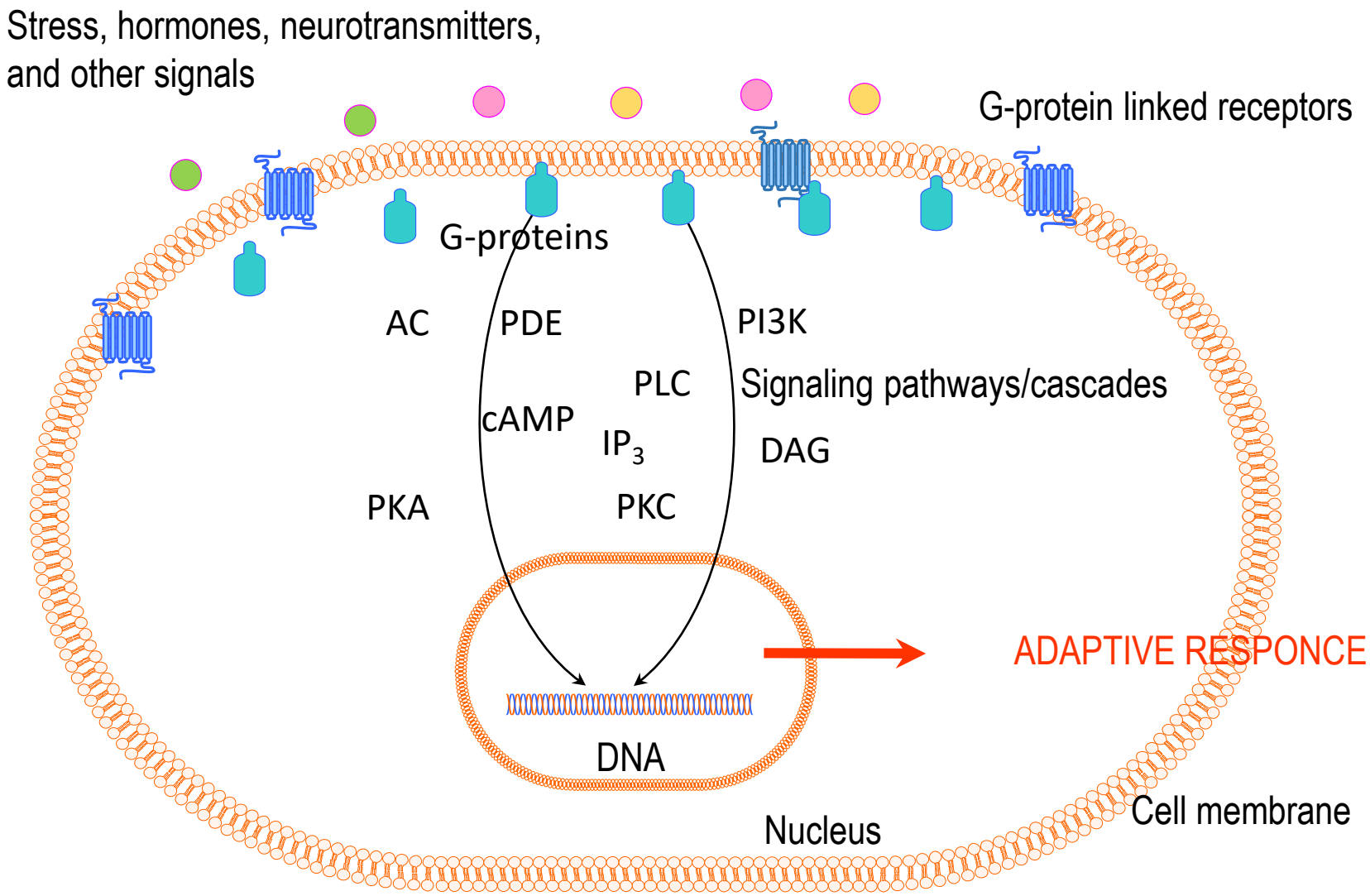
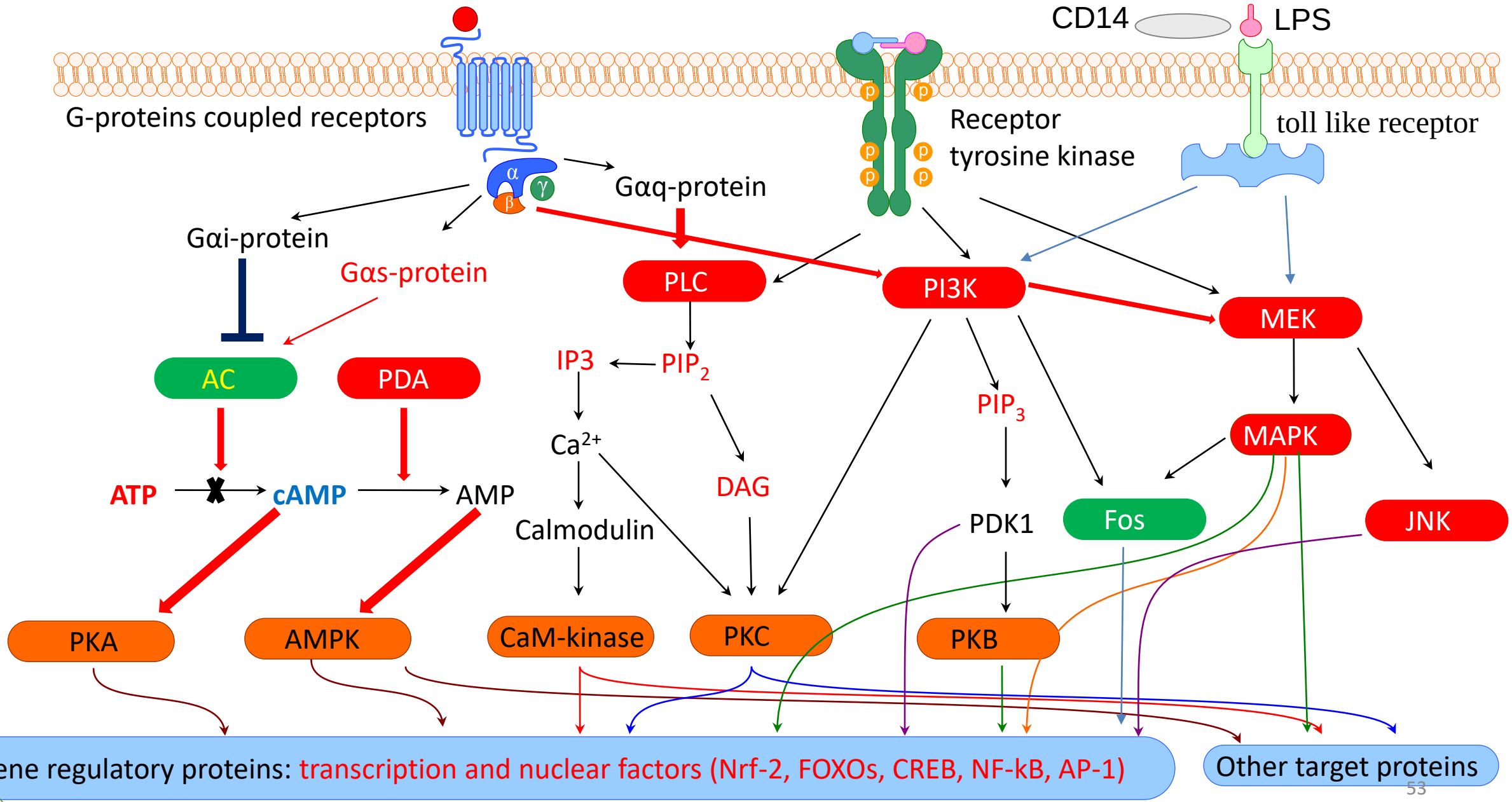
Adaptogens deregulate genes encoding GPCR and key mediators of GPCR adaptive signaling pathways



The effect of adaptogens on adaptive stress response signaling pathways



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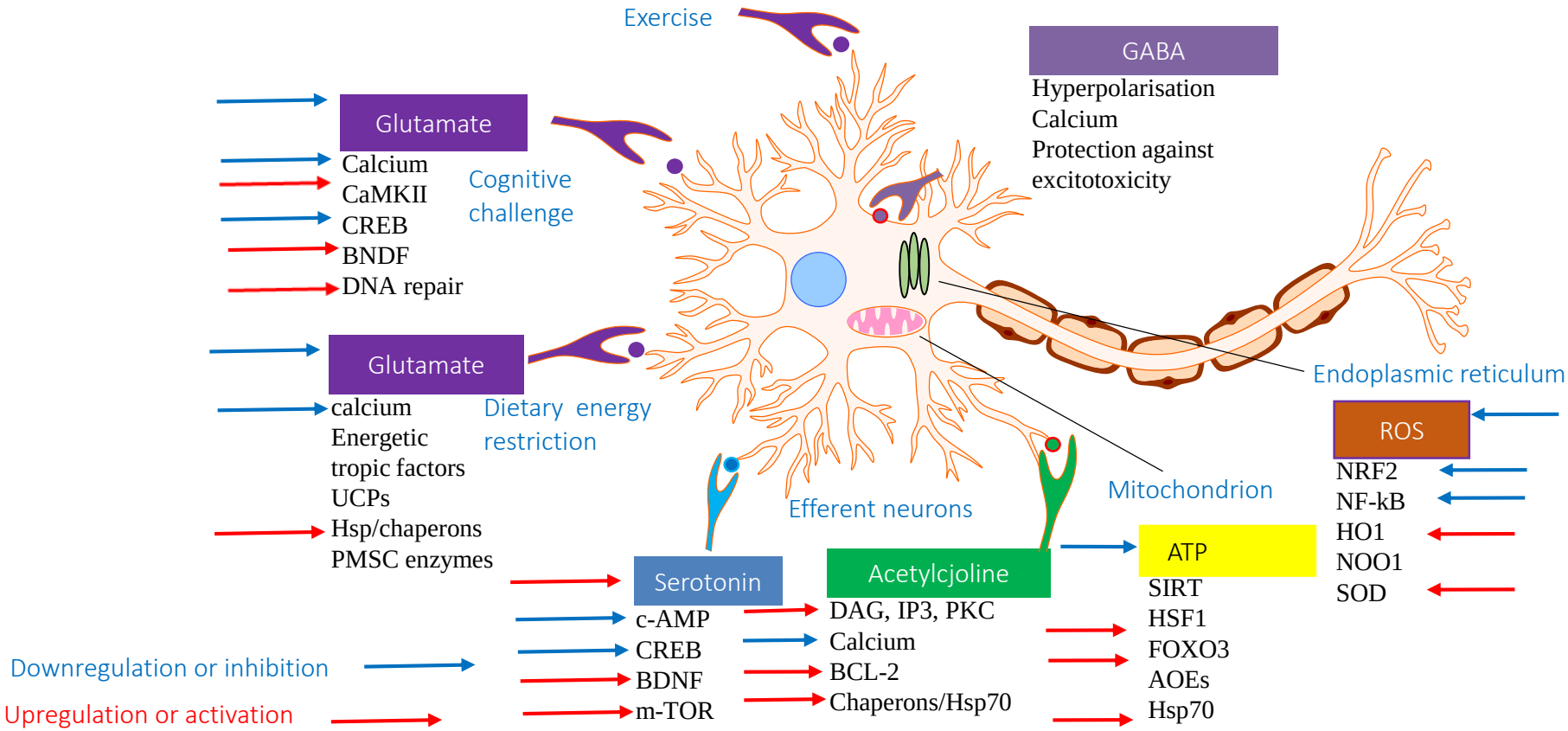
Effects of adaptogens on adaptive stress response signaling pathways that protect neurons against degeneration and promote synaptic plasticity.



A glutamatergic neuron in the hippocampus receiving excitatory inputs from neurons activated in response to exercise, cognitive challenges and dietary energy restriction.

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.

Conclusions

Adaptogens exert a polyvalent biological activity and provoke multiple effects at the transcriptional level of regulation of cellular metabolism and homeostasis.

There are many molecular targets for stress response modifiers since stress response and adaptation to environmental challenge are multistep processes that involve intracellular and extracellular signaling pathways at all levels of stress regulation.