

Adaptogenic effects of some medicinal plants: integration of traditional and modern concepts

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What is an adaptogen?

- The word *adaptogen* is used to refer to a natural herb product that increases the body's resistance to stresses such as trauma, anxiety and bodily fatigue
- In the past they have been called rejuvenating herbs, rasayanas, or restoratives.

Adaptogens....

Adaptogens reduce the intensity and negative impact of the stress caused by

- mental tension
- emotional difficulties
- poor lifestyle habits
- disease and infection
- pollution and other factors

Adaptogen...history

- Knowledge about **adaptogens** dates back thousands of years to ancient India and China, but serious scientific study did not begin until the late 1940s
- In 1947, **Dr. Nikolai Lazarev** defined an adaptogen as an agent that allows the body to counter adverse physical, chemical, or biological stressors by raising nonspecific resistance toward such stress, thus allowing the organism to “adapt”

Israel Breckham (1968)

- An adaptogen is nontoxic to the recipient
- An adaptogen produces a nonspecific response in the body—an increase in the power of resistance against multiple stressors including physical, chemical, or biological agents
- An adaptogen has a normalizing influence on physiology, irrespective of the direction of change from physiological norms caused by the stressor

Adaptogens...today

- Agents which reverse/prevent stress effects
- Important therapeutic moieties with complex mechanisms
- Both synthetic and herbals
- Herbal agents safer and equiactive
- Adaptogens attenuate anxiogenic responses, influence CNS and immune systems/functions

Stress

- Concept of stress in biology and medicine – Hans Selye(1936)
- Any external/internal stimulus which alters the physiological milieu
- Ability to cope/adapt crucial for survival
- Complex neurochemical pathways in CNS
- Concept of an integrated stress system - Triad of responses

CNS and stress...

- The CNS is crucial for the stress response
- Complex neurotransmitter mechanisms / interactions proposed
- The limbic areas are particularly sensitive to stress inputs
- Catecholamines (NE) and corticosterone are basic components of the stress response
- Neuroendocrine –immune axis crucial

Stress ...contd.

- Stress response : depends on nature/intensity of stressor
- Highly interactive phenomenon – multisystem involvement viz. CNS, Neuroendocrine, Immune , Cardiovascular, Musculoskeletal etc.
- Armed forces constantly exposed to emotional/environmental stress

Herbal Drug Research

- Emerging area of research in pharmacology and medicine – globally
- New drug development from herbal sources has been a thrust area in recent years
- Effective alternative/complimentary therapy in several diseases
- Safety profile mostly being well documented
- Scientific methodology being adopted to delineate molecular mechanisms (eg. systems biology approach)
- Interactions between traditional and modern medicine

Traditional and modern medicines : complimentary roles

- Reverse pharmacology
- Modern biological approaches
- Explore novel molecular mechanisms
- Systematic preclinical toxicity studies
- Clinical Trials and Pharmacovigilance
- Validation of herbal drug effects
- Golden Triangle Project (GTP) in India

Reverse Pharmacology

- Experimental evaluation of clinically observed findings, seen specially with herbal agents
- Reverse pharmacology as an alternative path for new drug development
- Reverse pharmacology correlates herbal (traditional medicinal) drug action
- A practice which was successfully employed in the past (eg. Reserpine) and is being more scientifically implemented now

Adaptogens

- **Adaptogens** have a normalizing effect on the body and are capable of either toning down the activity of hyperfunctioning systems or strengthening the activity of hypofunctioning systems
- It is claimed that **adaptogenic herbs** are unique from other substances in their ability to balance endocrine hormones and the immune system, and they help the body to maintain optimal homeostasis

Ayurveda ...branches

- Eight branches
- **Rasayana** : an important component
- Refers to therapeutic regimens
- It deals with conservation, transformation and revitalization of energy
- Rasayana describes herbal preparations that promotes a youthful state of physical and mental health and happiness

Rasayana

- Rasayana herbs have high levels of both safety for daily use and effectiveness –across all age barriers
- They are normalizers of disrupted physiological homeostasis (? **Hans Selye`**s concept of Stress)
- Rejuvenators or immunomodulators
- Some similarity with modern day **adaptogens** – considerable overlap
- Integration of Ayurvedic concepts with scientific validation – the order of the day

Adaptogenic herbs

Adaptogens with a significant level of scientific research confirming their use include:

- **Ashwagandha or Indian Winter Cherry** (*Withania somnifera*)
- **Tulasi or Holy Basil** (*Ocimum sanctum*)
- **Guduchi/Giloi or Heart leaved moonseed** (*Tinospora cordifolia*)
- **Yastimadhu or Licorice** (*Glycyrrhiza glabra*)
- **Amla or Indian Gooseberry** (*Emblica officinalis*)

Ocimum sanctum (Tulsi)

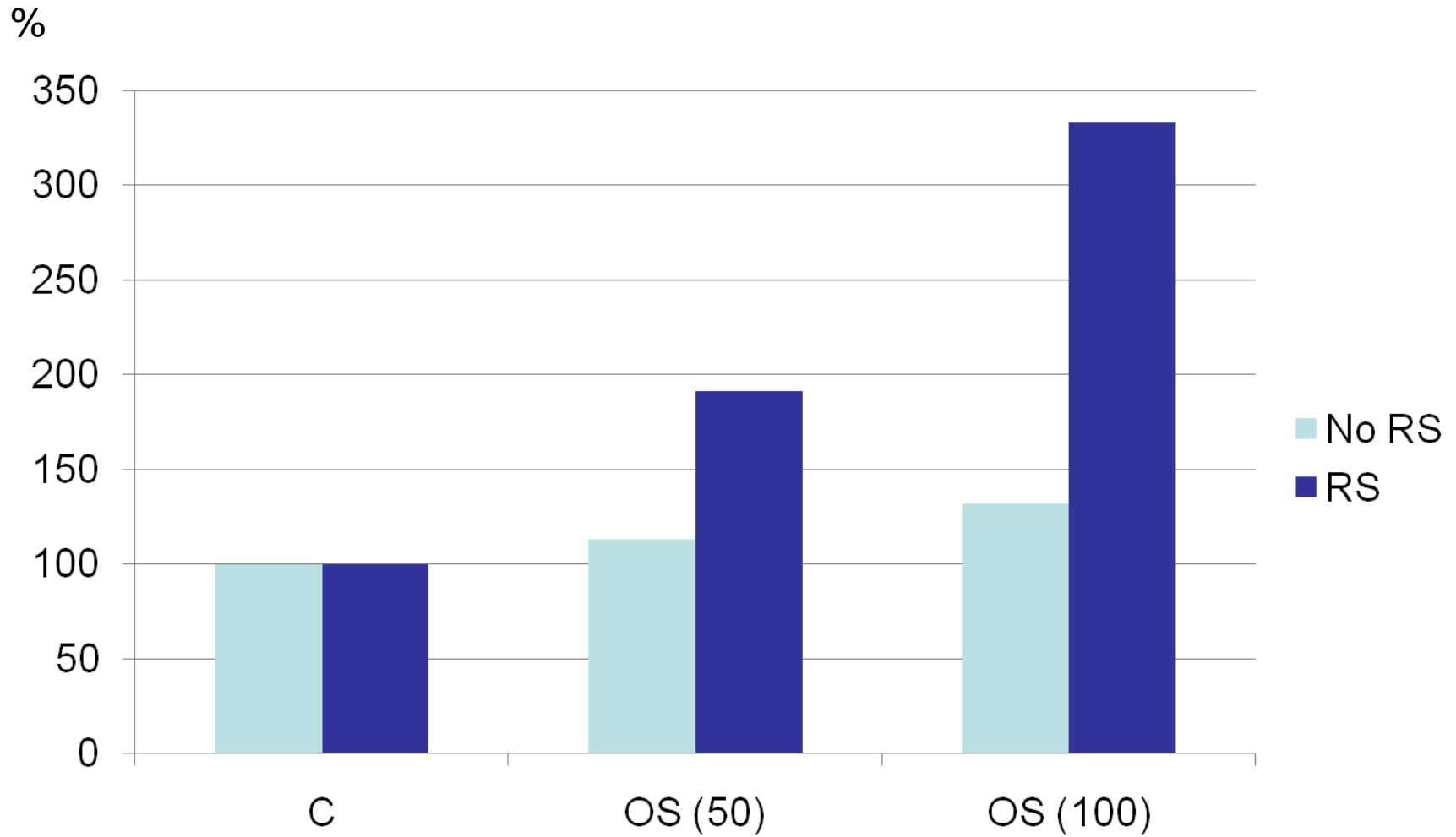
- *Ocimum sanctum* (Holy Basil) or Tulsi
- Most common and revered plant in the Indian household
- Healing herb with sacred implications in this part of the subcontinent
- In Ayurveda : role in enhancing immune and metabolic function and in respiratory disorders

Effects of *Ocimum sanctum* (OS) on anxiety-like behavior and plasma corticosterone in rats

Treatment (mg/kg)	OAE in the EPM (%)	OAT in the EPM (%)	Corticosterone (ug/dl)
Controls	28.7 ± 6.0	15.0 ± 2.8	23.6 ± 3.9
RS	9.0 ± 2.2 *	4.8 ± 1.0 *	41.6 ± 6.6 *
OS (50) + RS	17.2 ± 5.2 a	7.0 ± 2.2	33.0 ± 8.1
OS (100) + RS	30.3 ± 4.4 a	12.4 + 1.9 a	25.6 ± 3.3 a

* p < 0.05 (vs. no RS) ; a. p < 0.05 (vs. RS)

Effects of *O.Sanctum* (OS) on EPM activity in normal and stressed rats



Effects of *O. sanctum* on stress gastric ulcers

Treatment (mg/kg)	Mean Ulcer number	Mean Ulcer severity (mm)
Controls	0.6 ± 0.2	0.2 ± 0.04
RS	7.8 ± 1.6 *	2.8 ± 0.6 *
OS (50) + RS	4.8 ± 1.2 a	2.0 ± 0.6
OS (100) + RS	2.1 ± 0.3 a	0.8 ± 0.2 a

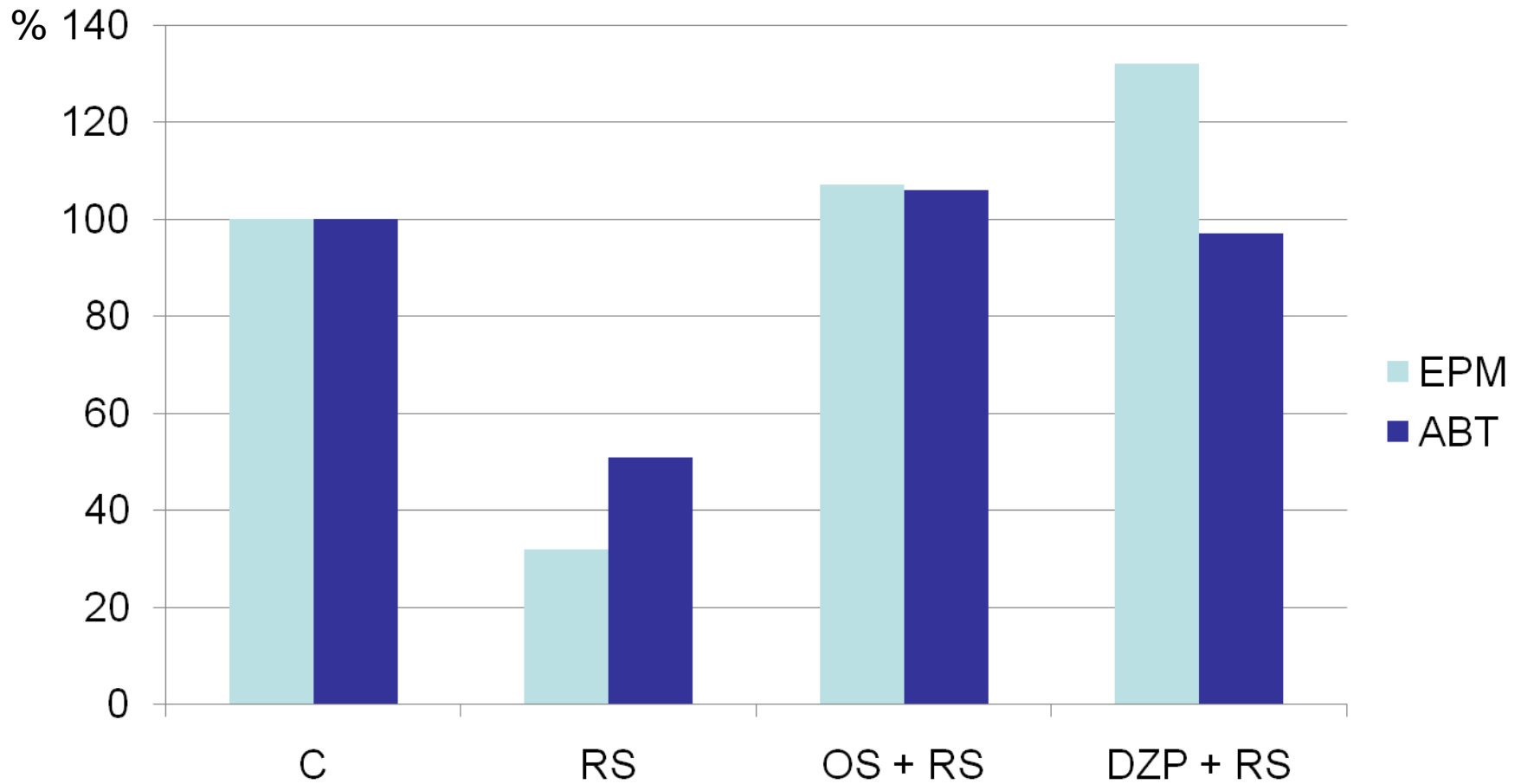
* $p < 0.05$ (vs. no RS) ; a. $p < 0.05$ (vs. RS)

Effects of *O.sanctum* on adaptive immunity

Treatment (mg/kg)	Antibody titre (-log2)	DTH response (%)
Controls	6.6 ± 0.6	20.2 ± 3.5
RS	3.4 ± 0.4 *	12.6 ± 5.0 *
OS (50) + RS	5.0 ± 0.6	19.6 ± 6.6 a
OS (100) + RS	7.0 ± 1.0 a	22.7 ± 4.2 a

* p < 0.05 (vs. no RS) ; a. p < 0.05 (vs. RS)

Effects of *O. sanctum* (OS) and diazepam (DZP) on stress responses



OS and stress responses

- OS leaf extract reversed RS induced neurobehavioral suppression in the elevated plus maze test
- The herbal extract lowered RS-induced elevations of corticosterone
- The severity of stress – induced gastric erosions were attenuated by OS
- Stress-induced suppressions of adaptive immunity were also reversed by this agent

Azadirachta indica (AI) - Neem

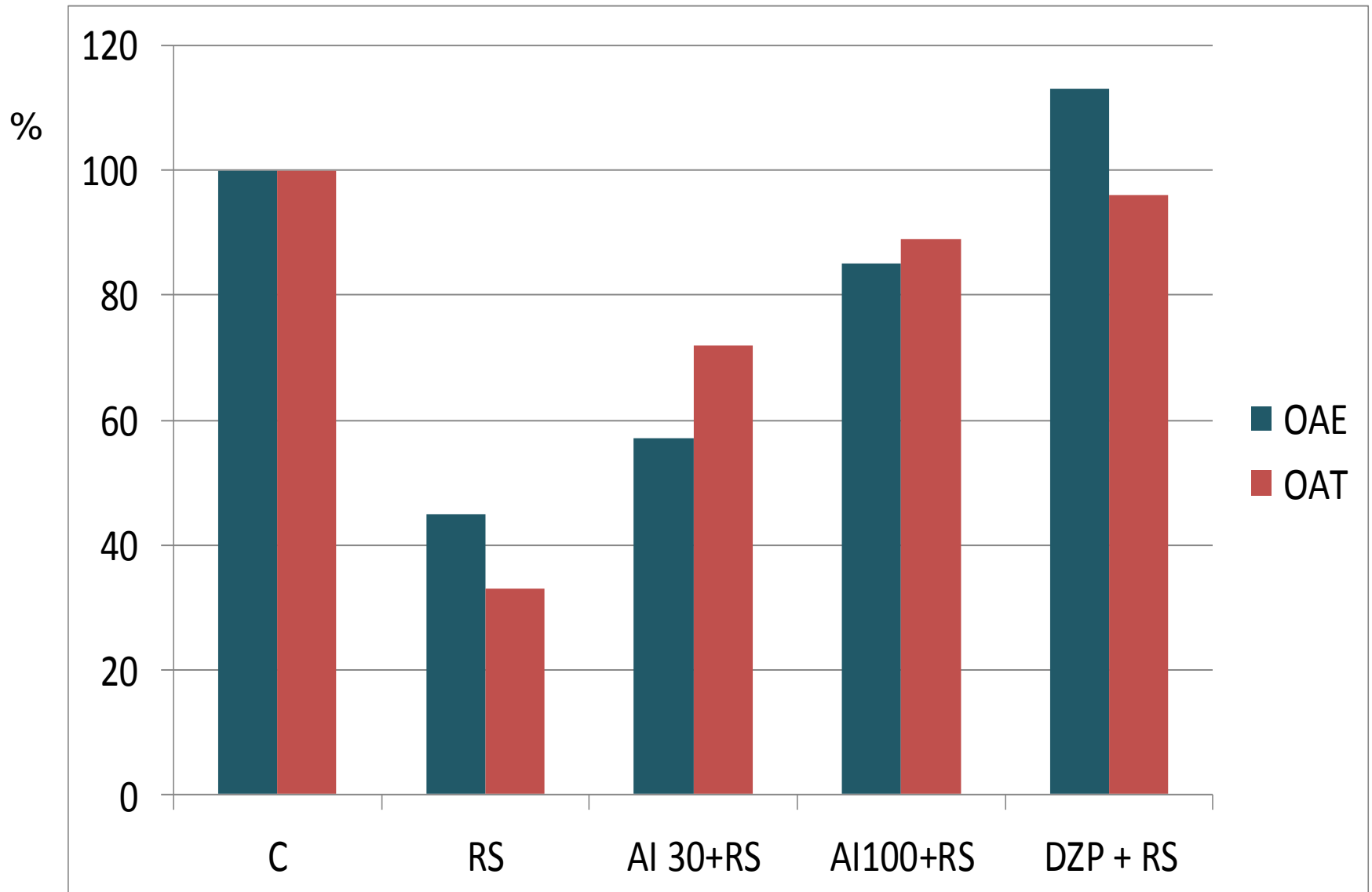
- Indian lilac, *Azadirachta indica* A. Juss (Latin)
- Highly esteemed, widely prevalent tree in Indian subcontinent (Wonder tree)
- In Ayurveda : Sarva Roga Nivarana
- Releases large amounts of oxygen (photosynthesis) as compared to others
- Air purifier
- All parts of the plant are beneficial (root, seeds, bark, stem, leaf, flower)

Effect of *Azadirachta indica* (AI) leaf extract on stress-induced anxiety in rats

Treatment (mg/kg)	Elevated Plus Maze (%)	
	OAE	OAT
Vehicle (no RS)	33.0 ± 6.2	10.6 ± 1.2
RS	14.5 ± 3.0*	3.0 ± 0.8*
AI (30) + RS	19.0 ± 5.1	7.7 ± 3.2
AI (100) +RS	28.1 ± 6.7 ^a	9.5 ± 2.8 ^a
DZP(1) + RS	44.8 ± 2.6 ^a	11.9 ± 4.0 ^a

* p < 0.05 (vs. no RS) ; a. p < 0.05 (vs. RS)

AI and stress-induced anxiety

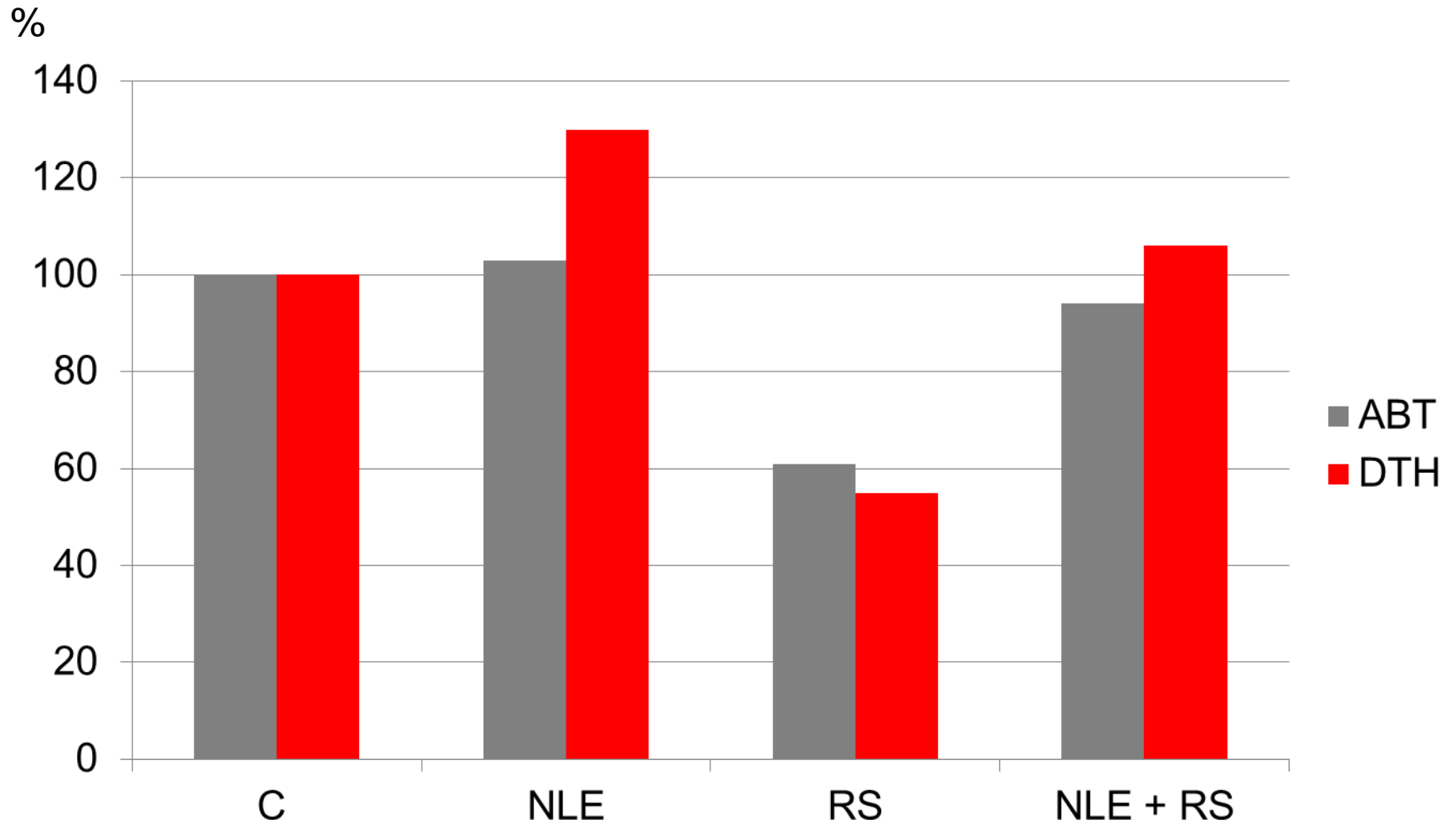


Effects of Azadirachta indica (AI) Leaf Extract on Immune responses in normal and stressed rats

Treatment (mg/kg)	Antibody Titre (-log2)	DTH response (% change)
Vehicle (no RS)	6.7 ± 0.5	33.0 ± 4.6
AI (100)	7.0 ± 0.3	40.0 ± 6.0
RS	4.1 ± 0.5*	18.4 ± 2.5*
AI (100) +RS	6.3 ± 0.3 ^a	27.7 ± 3.2 ^a

* p < 0.05 (vs. no RS) ; a. p < 0.05 (vs. RS)

AI and Immune responses



Stress, Immunity and AI

- Immunized rats showed higher antibody titres after AI treatment (no RS)
- RS suppressed antibody responses which was attenuated by AI pretreatment
- RS also suppressed cell mediate immune responses (footpad thicknes test)
- AI reversed RS-induced suppression of CMI
- AI also potentiated IgG and IgM levels in normal animals

Dopamine (DA) and stress

- **DA** : an important neurotransmitter in CNS
- The role of DA as stress modulator is reported
- DA agonists protect whereas, DA antagonists aggravate stress responses
- DA is also involved in the effects of other agents/transmitters
- Possible role of DA in anti-stress effects of other agents not clearly defined

Effects of dopamine depletors and receptor blockers on adaptogen effects on stress (RS) markers

Treatment (mg/kg)	Antibody Titre (-log2)	Gastric Ulcers (mm)
Vehicle (no RS)	6.7 ± 0.5	0.04 ± 0.02
RS	3.8 ± 0.4*	2.8 ± 0.6*
OS + RS	6.0 ± 0.6 ^a	1.0 ± 0.2 ^a
AI + RS	5.8 ± 1.0 ^a	0.6 ± 0.3 ^a
α-MT + OS + RS	4.0 ± 0.4	3.6 ± 0.8
Hal + AI +RS	4.8 ± 1.2	3.0 ± 0.3

* p < 0.05 (vs. no RS) ; a. p < 0.05 (vs. RS)

Withania somnifera

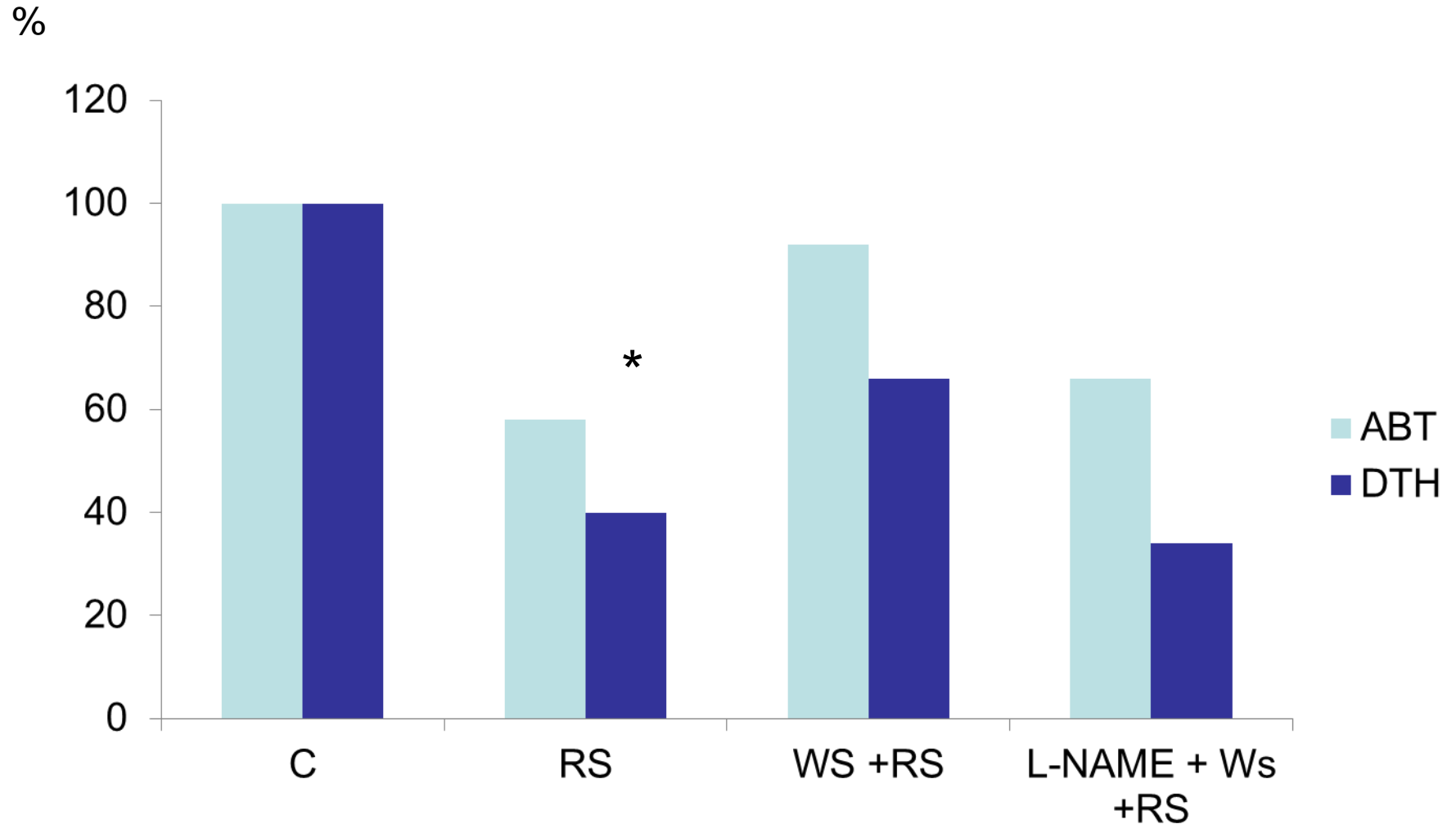
- Ashwagandha (Ayurveda) or Indian Ginseng
- Used for over 4000 years in Ayurveda
- Multifaceted medicinal properties
- Adaptogen, aphrodisiac, immunomodulator
- In Stress, Anxiety, Exhaustion, Amnesia, Insomnia
- Root extract has withanolides (active component)
- Preclinical/clinical studies showed efficacy in neurobehavioral disorders

Effect of *W. somnifera* (WS) root extract on adaptive immunity in normal and stressed (RS) rats

Treatment (mg/kg)	Antibody titre (-log2)	DTH response (%)
Controls (no RS)	7.8 ± 0.8	72.9 ± 8.5
RS	4.6 ± 0.6 *	29.0 ± 5.0 *
WS (100)	8.0 ± 1.3	68.0 ± 4.9
WS (400)	8.7 ± 1.8	87.7 ± 11.6
WS (100) + RS	5.0 ± 1.0 *	42.2 ± 6.2
WS (400) + RS	7.2 ± 0.7	48.8 ± 9.9

* P < 0.05 (vs controls)

WS –NO interactions on adaptive immunity



Effects of *W. somnifera* (WS) on cytokine levels in stressed (RS) rats

Treatment (mg/kg)	IL-4 (pg/ml)	IFN- γ (pg/ml)
Controls (no RS)	62.2 \pm 5.1	193.5 \pm 14.3
RS	30.2 \pm 3.9*	143.7 \pm 10.0*
WS (100) + RS	36.4 \pm 4.1	187.3 \pm 9.0
WS (400) + RS	43.3 \pm 2.9	215.3 \pm 7.5
WS (100) + L-Arg + RS	57.7 \pm 2.5**	243.5 \pm 11.9**
WS (400) + L-NAME + RS	25.0 \pm 2.7	118.6 \pm 5.2

Effects of *Withania somnifera* (WS) and NO modulators on oxidative stress markers in brain homogenates during stress (RS)

Treatment (mg/kg)	NO _x (nM/mg prot)	MDA (mM/mg prot)	GSH (μmol/g tissue)
Controls	27.9 ± 3.3	6.5 ± 0.9	23.1 ± 5.0
RS	12.3 ± 2.3 *	12.7 ± 2.2*	16.6 ± 3.7
WS (100) + RS	15.0 ± 1.5	9.2 ± 0.6*	19.4 ± 3.4
WS (400) + RS	20.1 ± 3.3	5.6 ± 0.7	21.7 ± 7.6
L-Arg + WS (100) + RS	28.6 ± 3.2	2.9 ± 0.4*	31.8 ± 6.8
L-NAME + WS (400) + RS	10.0 ± 1.4 *	15.5 ± 1.1 *	12.5 ± 3.0 *

* P < 0.05 (vs controls)

Summary and Conclusion

- OS (Tulsi) and AI (Neem) leaf extracts and WS (Ashwagandha) root extracts attenuated stress (RS) induced anxiety, immune suppression and gastric ulceration
- Pretreatment with DA depletors / blockers prevented these anti-stress effects of OS and AI, whereas, NOS inhibitor blocked RS attenuating effects of WS
- The results are suggestive of the role of DA and/or NO in the anti-stress effects of the adaptogens
- Such integrated studies are conducive and essential for herbal drug development

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Recent Advances in Herbal Drug Research and Therapy

Traditional systems of medicine are fast emerging as viable alternatives to modern medical science. Further, in recent years the emphasis on botanicals as source for drug discovery and development has been realized globally. Added to this, the safer profile of herbal drugs combined with their low costs make them ideal targets for newer drugs. As in the modern system of medicine, viz. allopathy, herbal drugs form an inseparable part of the management of various disorders. The concept of scientific validation of the basis of traditional uses of herbal medicines has given birth to a new concept of reverse pharmacology, and interactions between traditional and modern systems of medicine are being increasingly encouraged. Recent Trends in Herbal Drug Research and Therapy showcases some of these crucial and emerging issues relating to herbal drugs. This compilation is a judicious combination of research and conventional aspects on the subject of herbal drugs, their pharmacology and therapeutic applications. Some very relevant general and systemic pharmacological as well as toxicological aspects have been highlighted by some of the leading experts in this field. The book will be of interest to students, scientists, teachers and other health professionals in the area of pharmacology, toxicology and allied health sciences.

Spread in 26 chapters the book broadly focuses on:

- Standardization and quality control of herbal drugs
- Regulatory issues like ethics and pharmacovigilance with herbals
- Clinical research with herbal drugs
- Herbogenomics
- Herb-drug interactions
- Potential therapeutic uses of herbal drugs focusing on various systemic disorders of cardiorespiratory, endocrinal, neuropsychiatric, gastrointestinal systems and cancer
- Herbal drugs and environmental toxicology

Editors

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Thank You