UPMC LIFE CHANGING MEDICINE

University of Pittsburgh

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Ashwagandha - Scientific Findings on this Ancient Ayurvedic Herbal Medicine

Disclosures

- The University of Pittsburgh is pursuing intellectual property protection for this technology and Dr. Chengappa is listed as an inventor.

Ashwagandha

Sanskrit: "horse smell"

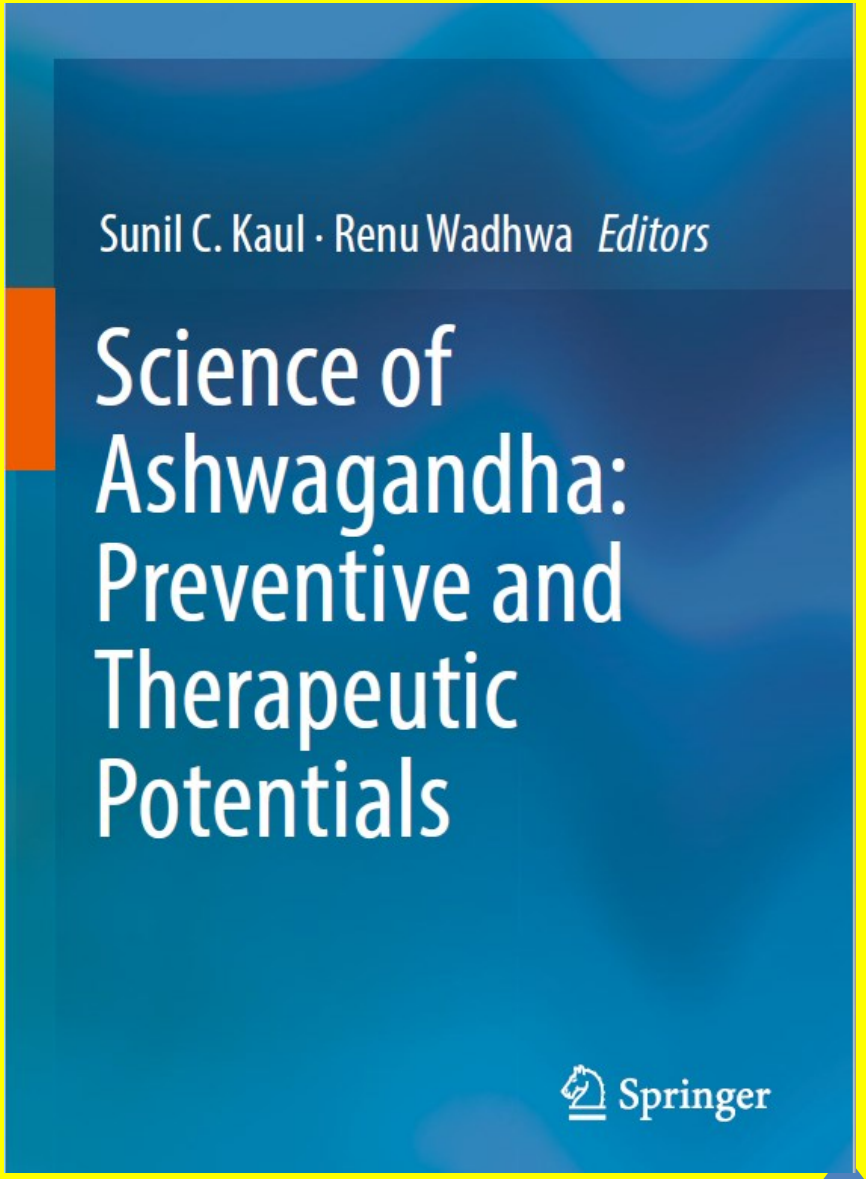
Vernacular Names

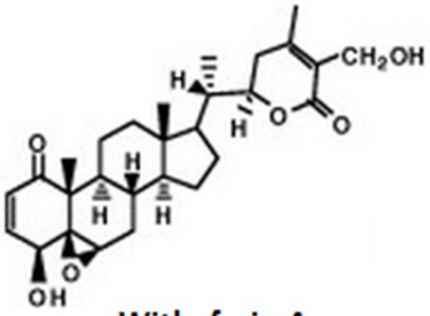
- Hindi: Punir, Asgandh
- Kannada: Pannaeru, Aswagandhi
- Gujrathi: Ghodakun, Asoda etc.
- Tamil: Ammukura, etc
- Punjabi: Asgandh, etc.
- Telugu: Pulivendram, Panneru – Gadda, etc.
- Marathi: Asgund, etc
- Rajasthani: Chiropotan

  Several Indian Language synonyms
- English: Winter Cherry

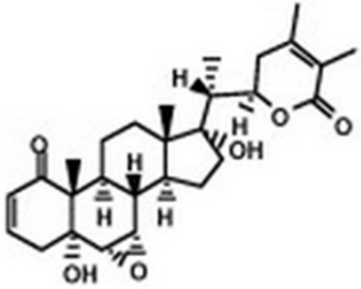
Ashwagandha – Potential Medicinal Claims

1. Rasayana – “adaptogen” (adapt to stressors) or “rejuvenator”
2. Treatment for arthritis
3. Anti-Stress, Anti-Anxiety, anti-depressant, OCD
4. Nootropic effects (cognition, dementia, stroke)
5. Schizophrenia, Bipolar
6. Anti-Parkinsonian
7. Rx of Various Cancer, immundmodulation, hematopoiesis
8. Others – hypolipidemic, cardiovascular, drug addiction, anti-bacterial, etc.

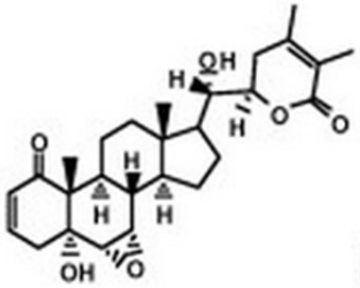

Sunil C. Kaul · Renu Wadhwa Editors
Science of Ashwagandha: Preventive and Therapeutic Potentials
Springer



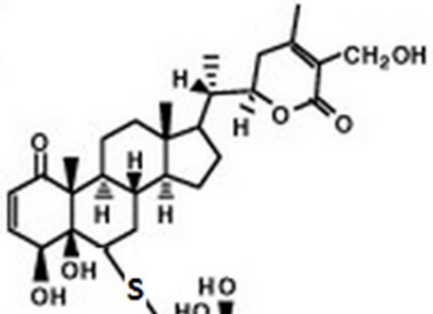
Withaferin A

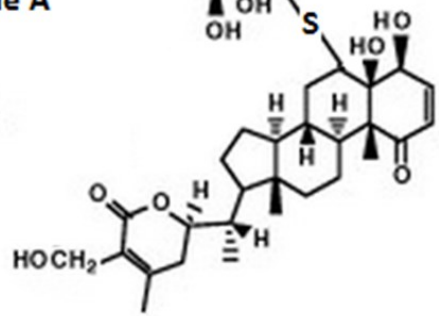


Withanone

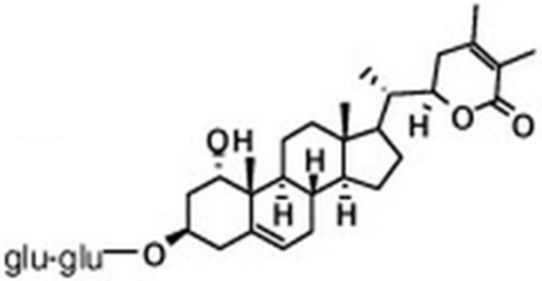


Withanolide A

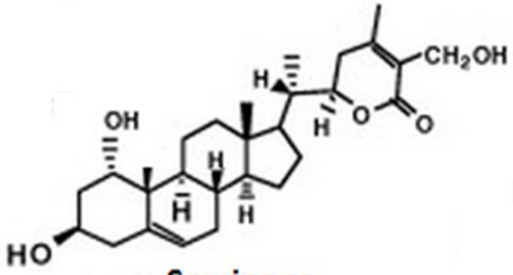




Ashwagandhanolide



Withanoside IV



Sominone

Modern Laboratory Based Animal Studies

Possible Targets of Action	Animal Data References
Immune – Inflammatory Processes	Durg et al. 2015 (Review) Anbalagan & Sadique, 1981, 1985, Begum & Sadique, 1988, Aggarwal et al. 1999, Nashine et al. 1995, Jayaprakasam & Nair, 2003, Khan et al. 2006, Subbaraju et al. 2006; Singh et al. 2007, Malik et al. 2007, Kour et al. 2009, Mulabagal et al. 2009,
Hypercortisolemia/Anti-Stress/Thyroid Promoting/Anxiolytic/Weight Loss	Ghosal et al. 1988, Panda and Kar, 1997, 1998, Bhattacharya et al. 2003, Khan & Ghosh, 2010
Antioxidant Potential	Durg et al. 2015 (Review), Ghosal et al. 1988, Bhattacharya et al, 2003, Kumar & Kumar, 2008, Ahmed et al. 2013,
Pro-Cholinergic Actions	Schliebs et al. 1997, Choudhary et al. 2004, Konar et al. 2011, Grover et al. 2012,
Decreased Glutamatergic Toxicity/Neuroprotective Effects/Anti-dyskinestic Potential	Jain et al. 2001, Naidu et al. 2006, Kumar & Kumar, 2009, Kataria et al. 2012
Synaptic, Dendritic and Axonal Reconstruction	Kuboyama et al. 2005, 2006, 2014 (Review). Tohda & Joyashiki, 2009, Joyashiki et al. 2011
Clearance of B-Amyloid, Decrease in B-Amyloid Neurotoxicity	Sehgal et al. 2012, Kurupati et al. 2013

Ashwagandha and Diabetes

Recent Review

Durg, Bavage and Shivaram. Phytotherapy Research. 2020. 34:1041-1059

Invitro Studies n = 6

Preclinical Studies n = 13

Clinical Trials n = 5

Ashwagandha and Diabetes

Invitro and Animal Data:

↓ Blood Glucose – 30%

↓ Glycosylated Hemoglobin

↓ Insulin Resistance

↑ Insulin Secretion

Lipid profiles (cholesterol) Improve

Oxidative stress markers improve (> 50%)

Ashwagandha and Diabetes

Human Studies

1. Andallu & Radhika 2000. 3 Gm/day root powder. 12 patients – observational study ↓ blood sugar – 1 month (Pre-diabetic patients and borderline cholesterol elevations)

2. Agnihotri et al. 2013. n = 25, placebo controlled 400 mg ↓ triglycerides, ↓ blood sugar – 1 month (People with schizophrenia who gained a lot of weight and borderline blood sugar increases)

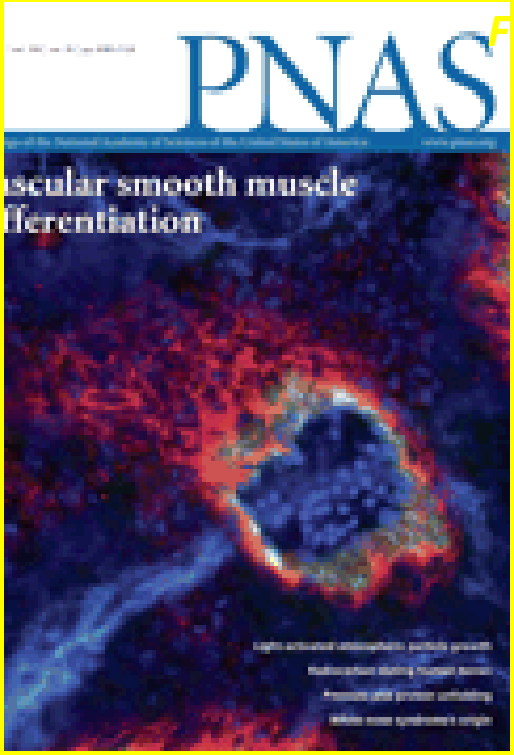
3. Nayak et al. n = 55, placebo controlled, 6 weeks, 600 mg fasting blood sugar, post-prandial blood sugar and glycosylated hemoglobin all ↓ in Ashwagandha group > control. (People with established Type 2 diabetes mellitus)

Ashwagandha and Diabetes

Human Studies continued

4. Usharani et al. 2014 Placebo controlled, Withania – 500 mg, “Amla” = 500 mg, n = 30, 2 months. Both Ashwagandha and Amla improved endothelial function and improved cholesterol compared to placebo group

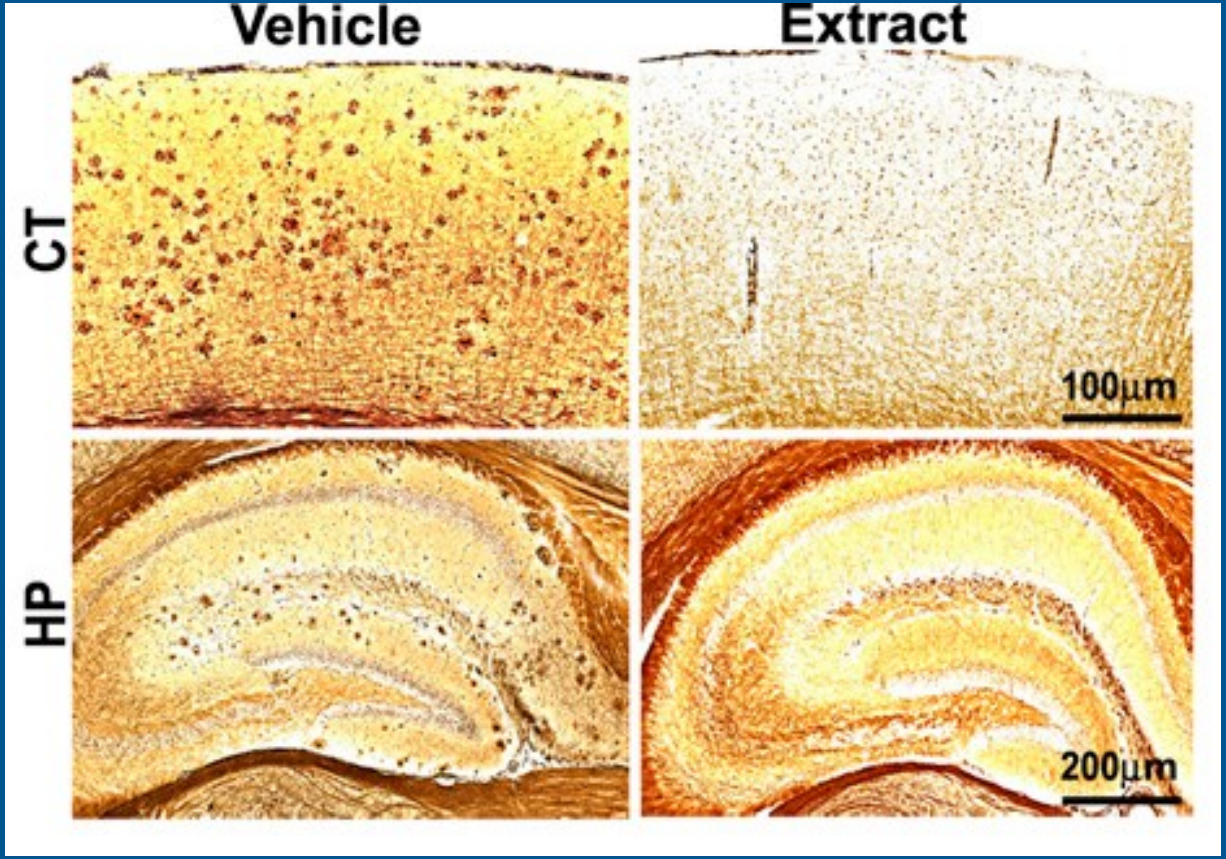
Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver



Vijayalakshmi Ravindranath

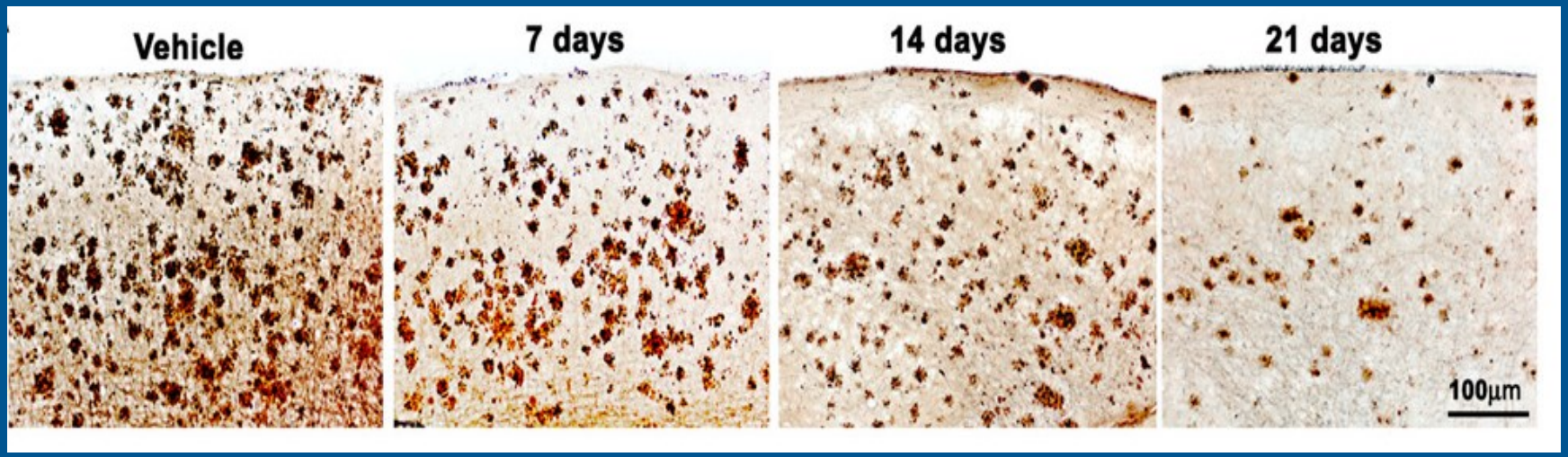
Division of Molecular and Cellular Neuroscience, National Brain Research Centre, Nainwal Mode, Manesar, Haryana 122050, India; Indian Institute of Science, Bangalore 560012, India

Reversal of amyloid pathology in female APP/PS1 mice



Sehgal et al. PNAS 2012
www.pnas.org/cgi/content/short/1112209109

Time course of clearance of AD pathology by WS in APP/PS1 mice.



www.pnas.org/cgi/doi/10.1073/pnas.1112209109
Sehgal et al 2012 PNAS

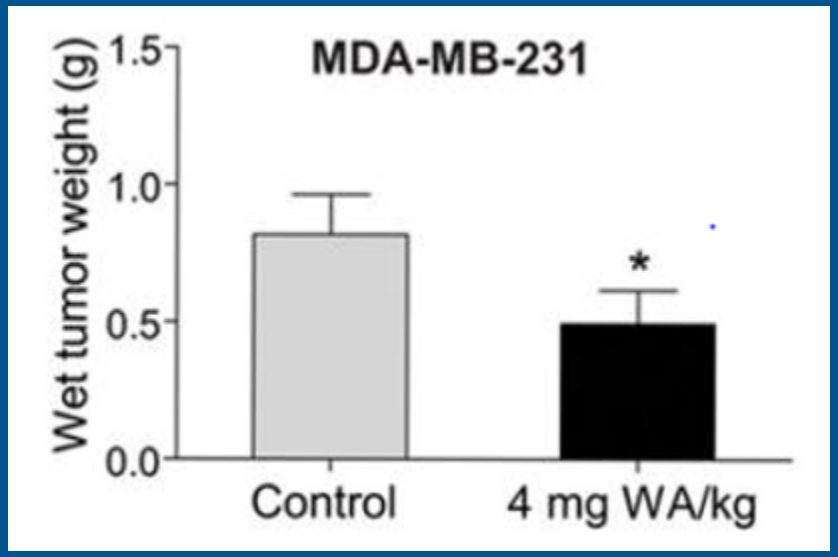
Science of Ashwagandha: Preventive and Therapeutic Potentials. 2017. Sunil C. Kaul, Renu Wadhwa *Editors*

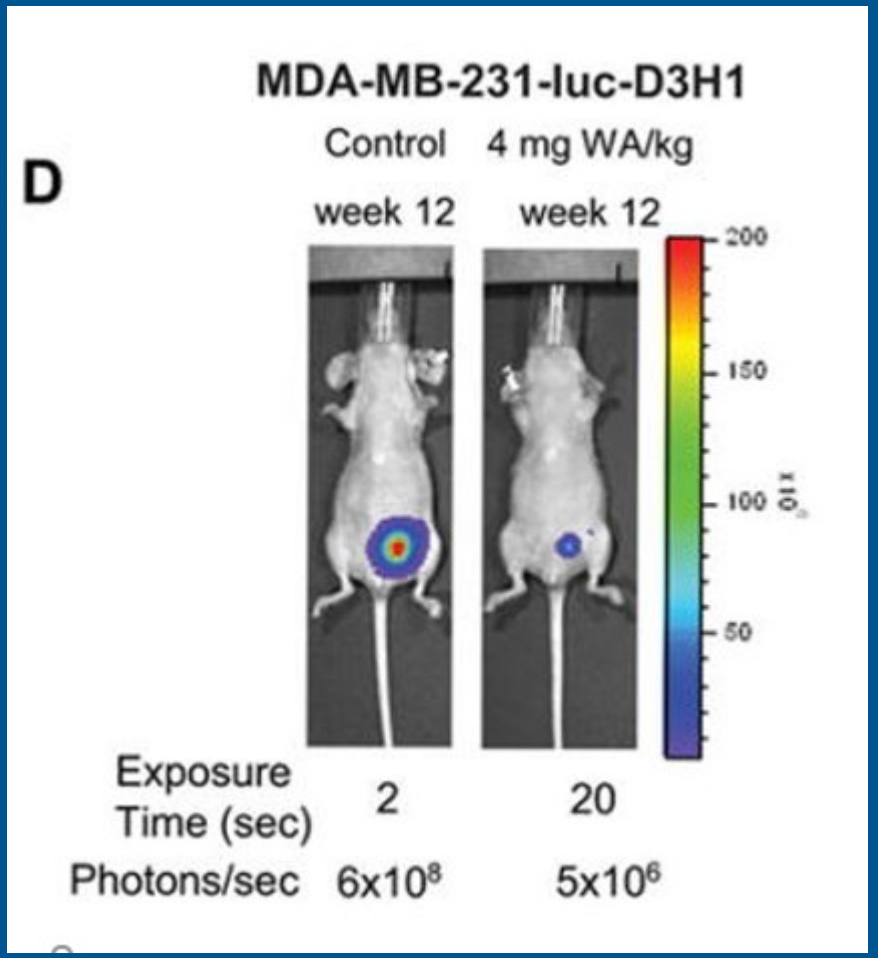
Animal Data in Cancer

- For Various Cancers – Breast, Melanoma, Bone, Blood, etc.
- Lots of Work – Many decades
- Different Laboratories in Various Countries
- Dr. Shivendra Singh's Group here at Pitt/UPMC
- Dr. Renu Wadhwa and Dr Sunil Kaul – Japan

Animal Data in Cancer

Effect of WA administration on growth of MDA-MB-231 cells s.c. or orthotopically implanted in female nude mice

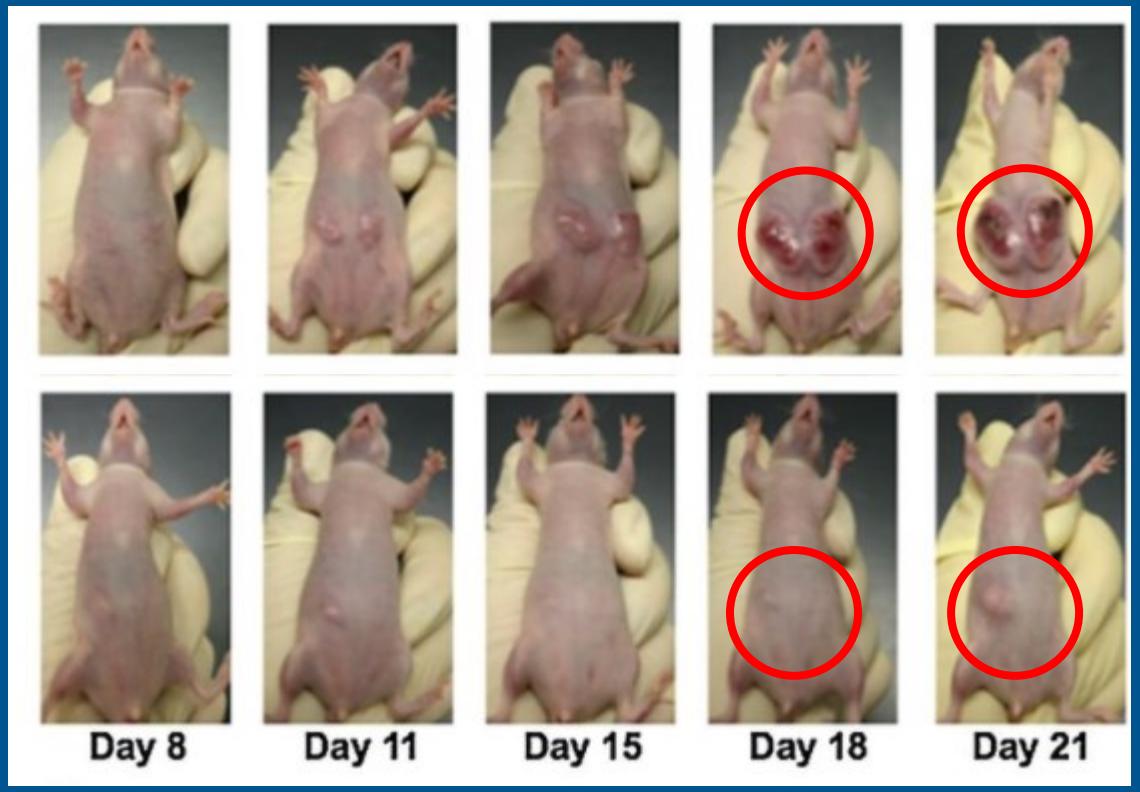




Silvia D. Stan et al. Cancer Res 2008;68:7661-7669

Dr. S. Singh's Lab Hillman-UPMC

Dr Kaul and Dr Wadhwa's Laboratories in Japan – showing an Ashwagandha extract that restricts metastases in an animal model



Gao R, et al. Withanone-rich combination of Ashwagandha withanolides restricts metastasis and angiogenesis through hnRNP-K. Mol Cancer Ther. 2014;13(12):2930-2940

Human Clinical Trials in Cancer

- Published: Biswal et al, 2013. Malaysia. 100 patients at various stages of Breast Cancer undergoing chemotherapy. Group that received 2 grams of Ashwagandha root powder three times daily added to chemotherapy **vs** chemotherapy alone experienced less fatigue, less pain, better emotional health and general quality of life

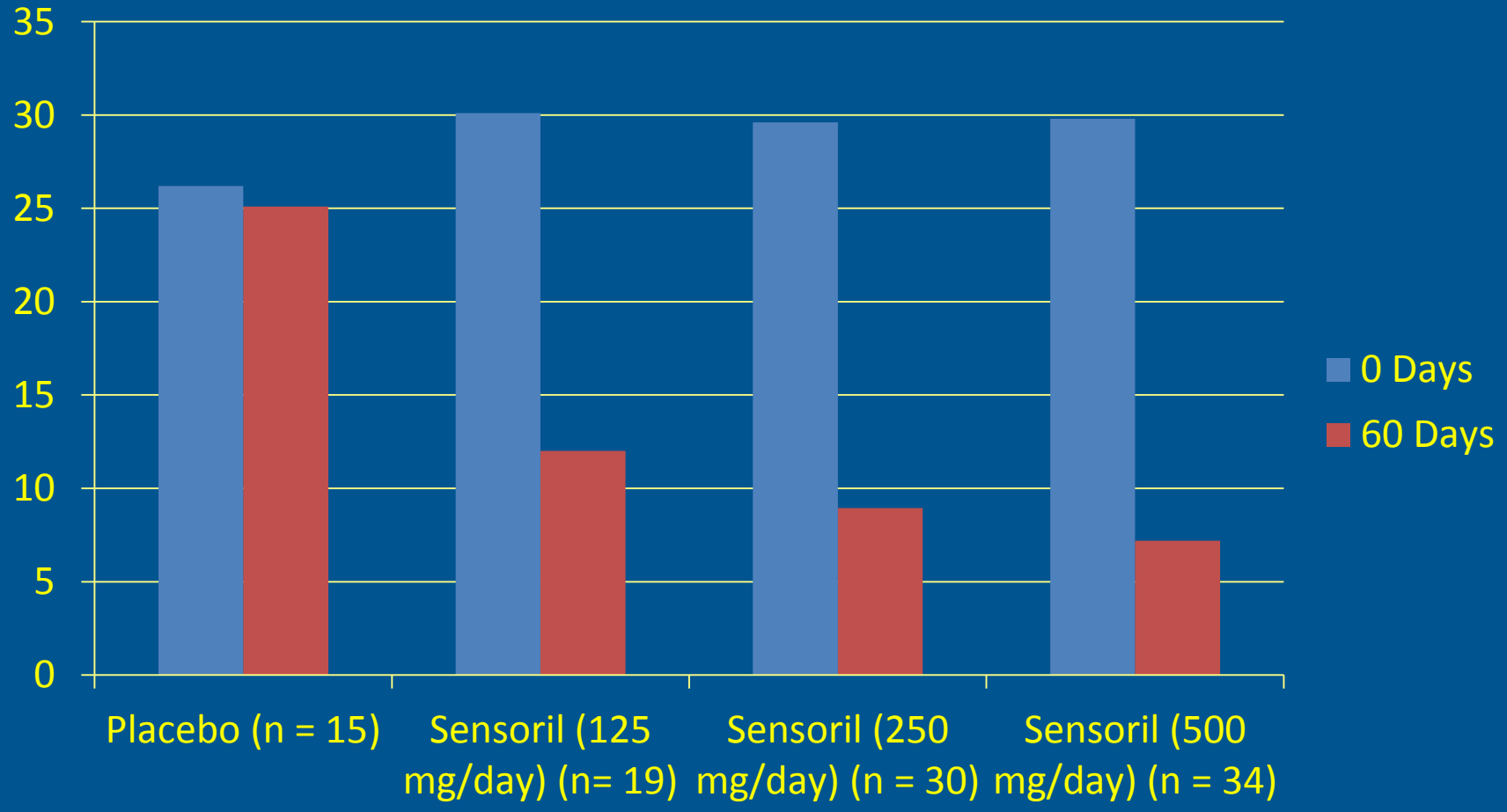
Human Clinical Trials in Cancer

- **Status not known**: Late stage Osteosarcoma, Tata Memorial Hospital, Mumbai (Dr. Manish Agarwal, PI) no update since 2012
- **Jan 2020** Sacramento, California (Dr. Stacy D'Andre, Sutter Health) Plan to study chemotherapy fatigue but randomized and placebo controlled (unlike Biswal et al) study in 80 patients undergoing chemotherapy for breast cancer

Clinical Trials in Psychiatry

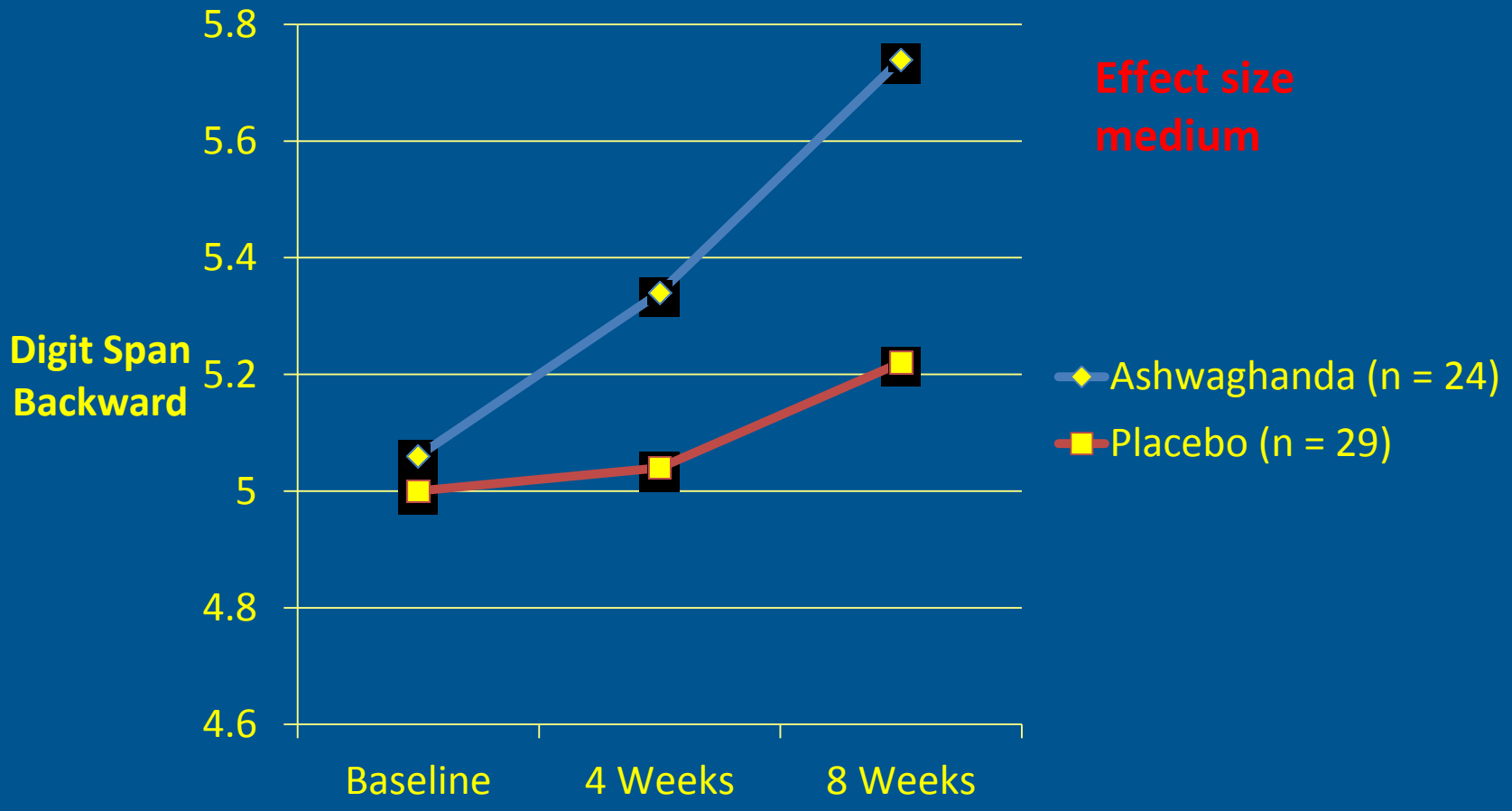
- Stress
- Anxiety
- Add on treatment in persons with Bipolar Disorder
- Add on treatment in persons with Schizophrenia
- Treatment for Insomnia

RCT of Ashwagandha and Placebo in "Stressed" Humans (modified HAM-A scores)



Auddy et al, 2008. J Nutraceutical Assn. of America 11;1:50-56

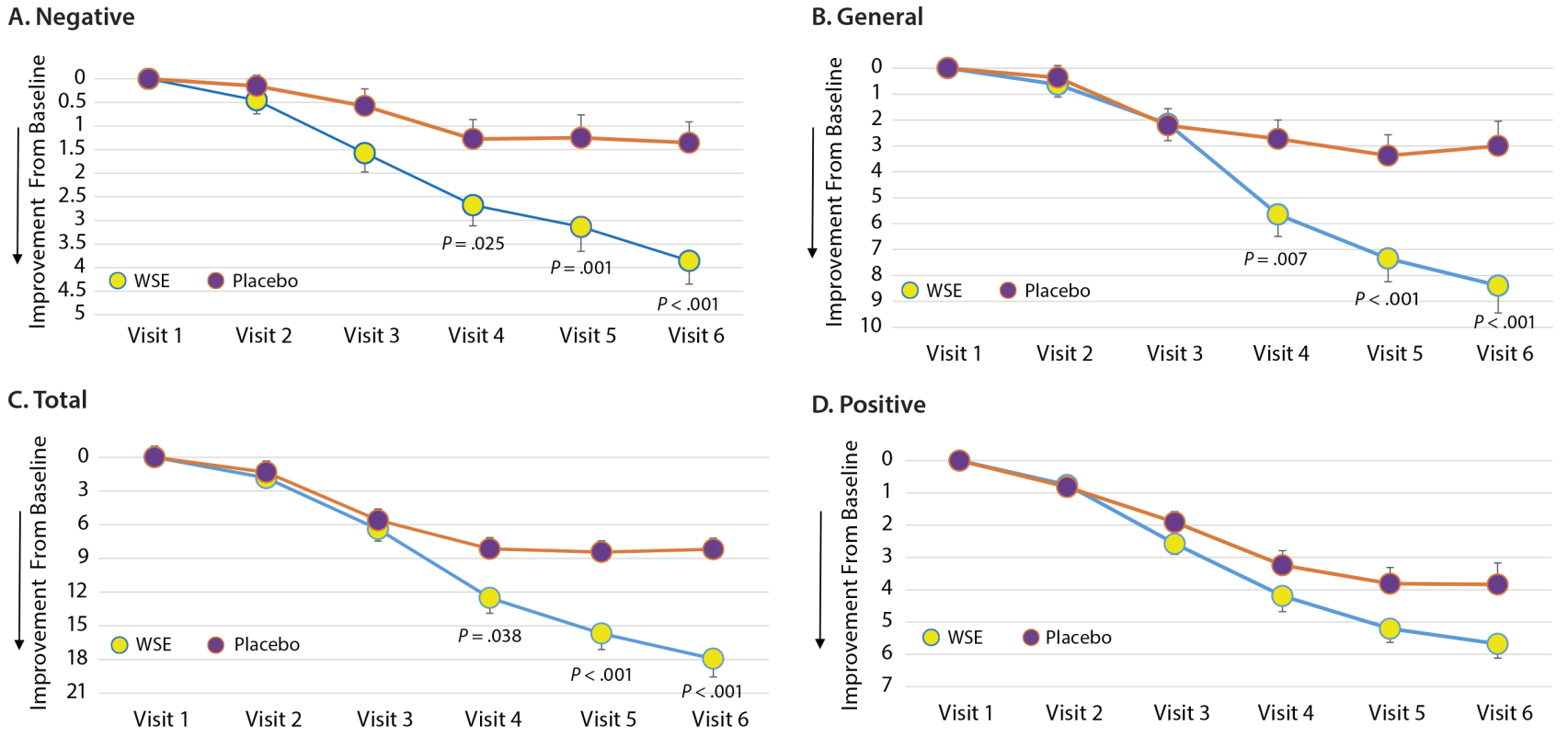
RCT of Ashwagandha for Cognitive Improvement in Persons with Bipolar Disorder



Chengappa KN, Bowie CR, Schlicht PJ, Fleet D, Brar JS, Jindal R. *J Clin Psychiatry*. 2013;74(11):1076-1083. doi:10.4088/JCP.13m08413

Adjunctive Use of a Standardized Extract of Withania somnifera (Ashwagandha) to Treat Symptom Exacerbation in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

Figure 1. Change in PANSS Negative, General, Total, and Positive Scores Relative to Baseline Values by Treatment[a] Group

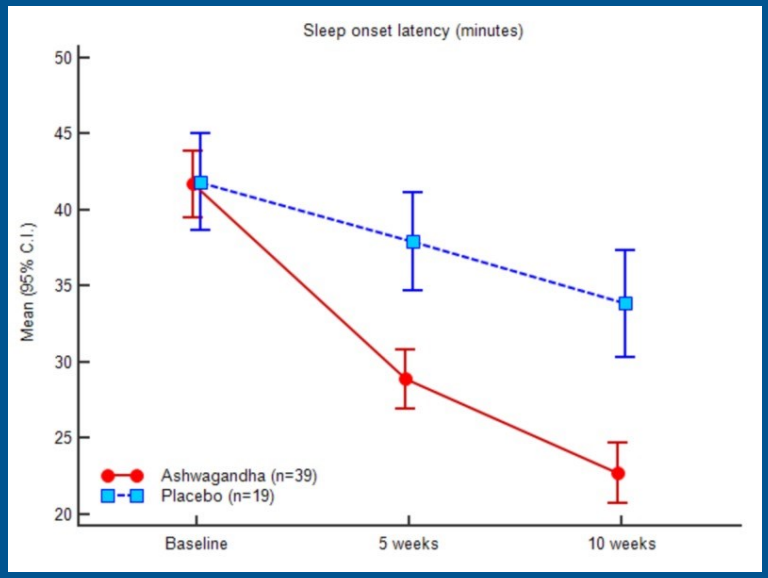


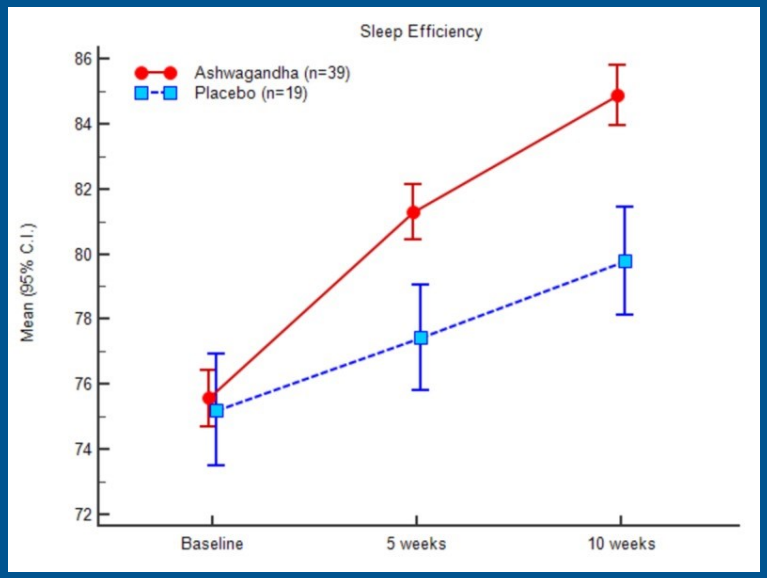
[a]Visit 1 = baseline, Visit 2 = randomization, Visit 3 = 2 weeks, Visit 4 = 1 month, Visit 5 = 2 months, Visit 6 = 3 months. Values are expressed as means; bars indicate standard error.

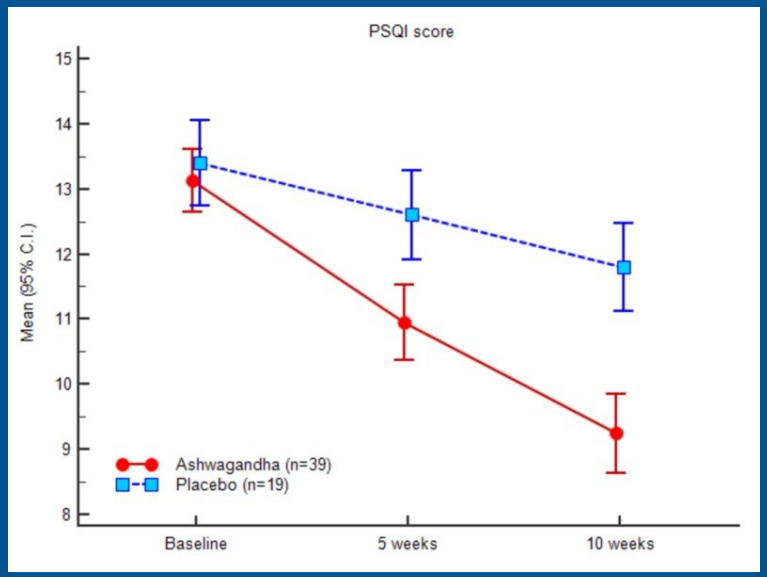
Abbreviations: PANSS = Positive and Negative Syndrome Scale, WSE = *Withania somnifera* extract.

Chengappa KNR, Brar JS, Gannon JM, Schlicht PJ.. *J Clin Psychiatry*. 2018;79(5):17m11826. Published 2018 Jul 10. doi:10.4088/JCP.17m11826

Efficacy and Safety of Ashwagandha (Withania somnifera) Root Extract in Insomnia and Anxiety: A Double-blind, Randomized, Placebo-controlled Study

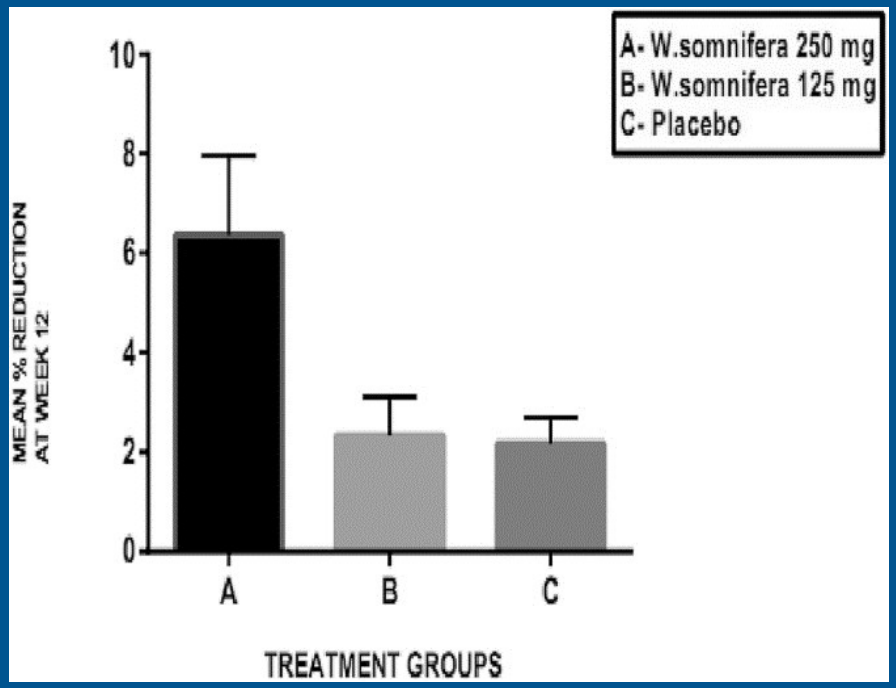




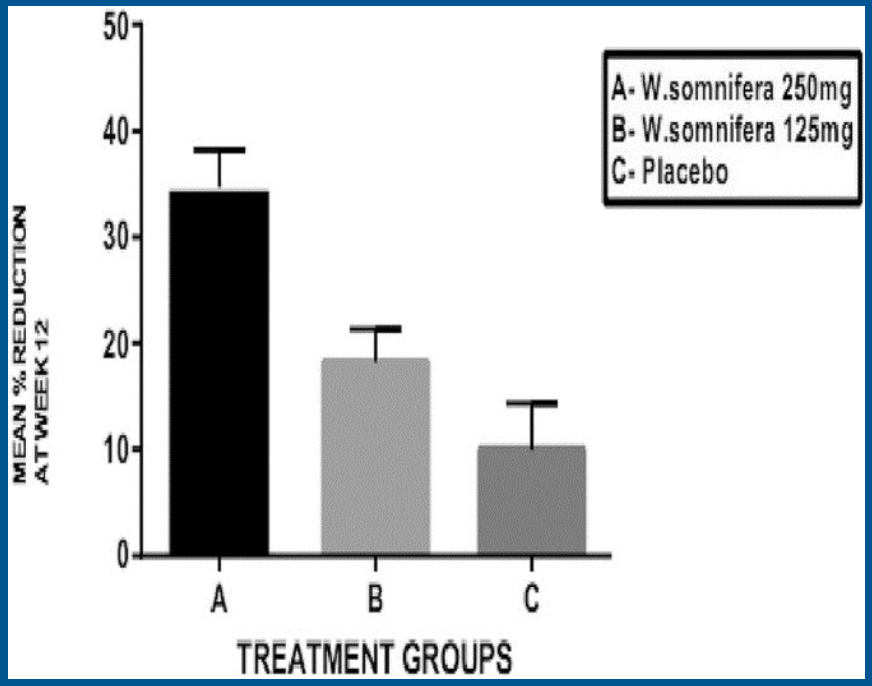


Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Cureus. 2019;11(9):e5797. Published 2019 Sep 28. doi:10.7759/cureus.5797

A randomized, double blind placebo-controlled study of efficacy and tolerability of Withania somnifera extracts in knee joint pain



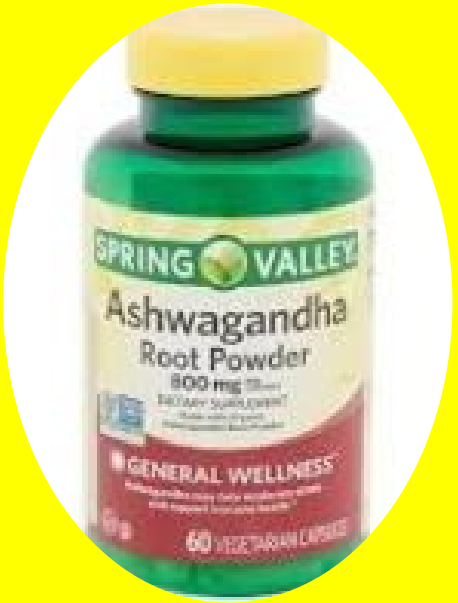
Mean percentage change in knee swelling index score at the end of 12 weeks.

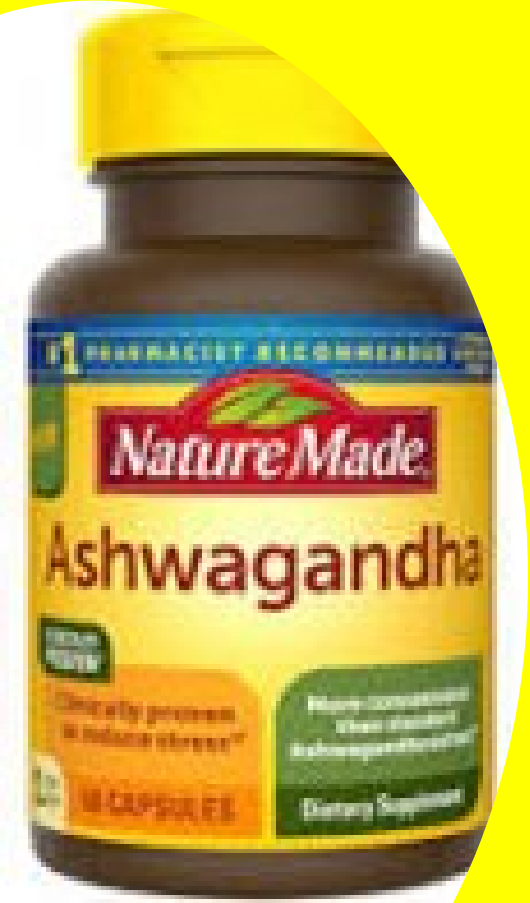


Mean percentage change in VAS – pain score at the end of 12 weeks.

Ramakanth GS, Uday Kumar C, Kishan PV, Usharani P. J Ayurveda Integr Med. 2016;7(3):151-157. doi:10.1016/j.jaim.2016.05.003

Sensoril Containing Products





Other Ashwagandha products (not Sensoril)

Standardization in Herbal Medicine

- Cultivation, Harvesting, Drying, Extraction
- Chemotype of plants (Wild vs. cultivated)
- Removal of impurities, toxic metals, microbial or fungal infestation
- Appropriate ratios of Bioactive constituents, Withanolides vs. Aglycones

Standardization of WSE (Sensoril)

- **Standardized and defined true bioactives:**
  - o **Withanolide glycosides (≥8%, w/w)**
  - o **Withaferin A (≤2%, w/w)**
  - o **Oligosaccharides (≥ 32%, w/w)**
  - X **Alkaloids (<0.1%, w/w)**
  - X **Polysaccharides (<10%, w/w)**

Many Ashwagandha extracts contain only Withanolide aglycones while Withanolide glycosides are important bioactive components

Issues in the Use of Herbs

1. Standardization - growing, harvesting, extraction
2. Chemotype specificity - cultivated vs wild plants
3. Standardization of preparations and batch to batch reliability
4. Basic Pharmacology – bioavailability, absorption, distribution, half-life, clearance
5. Bioactive vs Toxic moieties
6. Mechanisms of action
7. Safety and drug interactions
8. Controlled Trials

Some Final Thoughts on Herbal Medicines -1

- What is the right way to study them?
- Modern Allopathic medicines mostly are single chemical entities, occasionally combined with one or more other chemical entities
- Herbal Extracts by definition involve so many different bioactive, inactive and toxic chemicals, so “what” is doing “what” raises eyebrows in the scientific community?

Some Final Thoughts on Herbal Medicines -2

- How do we “standardize” these extracts such that each “batch” is the same or close to the same when it comes to having an effect on symptoms or functioning or some health related parameter?
- Intellectual Property: if none, then less incentive for companies or individuals to “innovate” etc.

Some Final Thoughts on Herbal Medicines -3

- Toxic impurities in products can lead to serious consequences for human health and an already skeptical public may be downright angry to continue to support such products
- Many Plants have provided us key medical breakthroughs and will likely continue to do so, and in my opinion, Ashwagandha is likely one such plant