Repurposing Cancer drug:Ginsenoside Rg3 ,the putative Epigenetics Modulator targeting NLRP3-Inflammasome in Alzheimer Dementia drug development

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ABSTRACT

Abstract:

Background: Recent evidence suggests tumor micro-environment in cancer shares with neurodegeneration in Alzheimer dementia (AD); however, conflicting findings emerge from epidemiological and cohort studies. Immune-genes in late onset AD overlap with oncogenes and late-onset psychoisis , highlighting Immunity-inflammation in cancer and AD and risk factors may converge at NLRP3 inflammasome signaling. We propose repurposing Ginsenoside-Rg3,the oncology drug towards AD therapeutics targeting Inflammasome-Interleukin interfacing with Epigenetics-Insulin resistance pathway, and leverage the translational pharmacology of Ginsenoside Rg3 (Dalian Pharm-Jilin-Vaatai Pharmaceuticals co, China) currently approved in FDA China for non-small-oat-cell-lung (NSOL) cancer for AD.

Methods: Our study is threefold : to search public clinical trial registries for drug platforms repurposing AD clinical trial from oncology drug leads targeting NLRP3 inflammasome-interleukin-cell death cascade, 2) to relate the translational pharmacology of Panax Ginseng and Ginsenoside Rg3/ginsenosides to the NLRP3-inflammasome link to NMDA-glutamate-regulated cognitive decline and Parkinsonism in later AD stage ; 3) to examine the cognitive and metabolic effects of Rg3-enriched Ginsana-115 (Boehringer-Ingelheim-Pharmaton, Switzerland) in treatment-resistant-schizophrenia (TRS)as related to prodromal AD.

Results: We fail to find any registered clinical trials of drug leads approved for cancer treatment hitting Inflammasome signaling to repurpose AD and Parkinson disease. RCT trials in AD have shown Panax Ginseng extracts to be efficacious in improving cognitive decline with few adverse events. Our Rg3 research group has found that in MPTP Parkinson disease model, Rg3 reduced motor deficits, antagonized Tumor-necrosis-factor, interleukin 1 & 6, and attenuated apoptosis. In TRS RCT trial we found Ginsana-115 at 200 mg oral dosage for 8 weeks significantly (p <0.05) improved facial memory cognitive domain within neuro-cognitive battery, decreased diabetes risk and Framingham cardiovascular risk compared with placebo control.

Conclusion: The favorable and consistent efficacy and safety of Rg3 cancer treatment, the promising translational and clinical findings of Rg3 in CNS and metabolic disorders, anchor our creative strategy for repurposing GinsengRg3 as approved oncology drug towards transitioning novel AD therapeutics. The first-of-kind disease-modifying NEURO-IMMUNE-INFLAMMATION-(NIM) drug platform will unravel AD risk factors, triggers and progression in clarifying the NLRP3 pivotal role in orchestrating immune-inflammation and innate and auto-immunity , interfacing with beta-Amyloid-Tau cascade and neurotransmitters-signal transduction-Insulin signaling

INTRODUCTION

Paradoxical Link of AD and related Dementia syndrome Risk and Cancer Epidemiological findings from Meta-analysis and Systematic review

1)A recent Meta-analysis search multiple data bases Embase, Global Health Ovid Medline and APA Psy-Info, corrected for Bias and heterogeneity, reports key findings

Lung and colon-rectal cancers show the largest risk reduction in all-cause-Dementia (ACD) and Vascular dementia (VaD). Lung cancer reduced AD risk by 17%, and melanoma reduced VaD risk by 27%.

ACD and AD patients had lower risks of lung (30%/36%), bladder (32%/34%), breast (26%/20%), and colorectal (31%/28%) cancers

Melanoma and colorectal cancers protect against risk in vascular dementia (VaD).

Prostate cancer survivors on androgen deprivation therapy (ADT) have higher risk of newly onset of ACD/AD , the impact depends upon staging of prostate cancer and duration of ADT.

Breast cancer patients on tamoxifen had a lower AD risk. Chemotherapy was linked to a reduced AD risk.

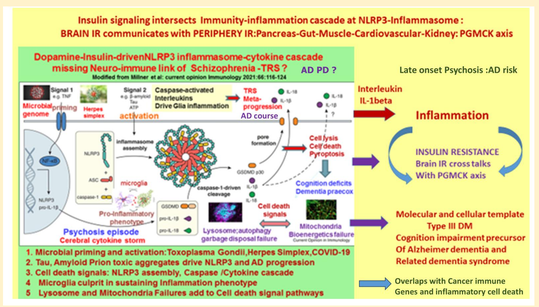
Alzheimer Dementia 2025 Feb 21(2) e14540. .

2)Melanoma and Parkinson Disease and PD-dementia reveals co-morbidity relationship Higher risk of melanoma in PD . PD carries higher risk of melanoma

Glioblastoma multiforme has been found to co-exist in advanced AD with likely AD risk.

3) An independent meta-analysis reviewing 19 cohort studies and 3 case control studies : total 9,630,435 individuals : cancer any type (n=13), prostate cancer (n-5), breast cancer (n=1) was conducted to decipher the link of cancer and AD.

Combining all studies indicate that cancer was associated with decreased AD incidence (cohort studies: random-effect hazard ratio 0.89; 95% CI, 0.79-1.00) (case control studies: random-effects odds raio:0.75, 95% CI 0.61-o.93)



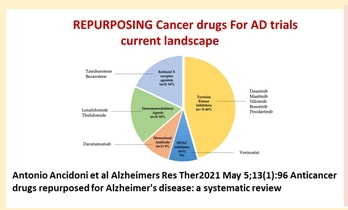
Tumor hijacks immune response to induce pyroptosis :
regulatory role of Inflammasome-interleukins

TMI: Tumor micro-Environment : immune cells network

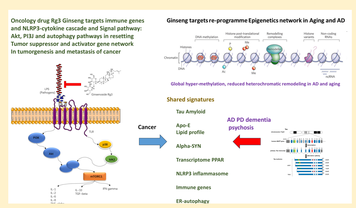
Cancer and PD/AD share inflammation-mediated cell death ?

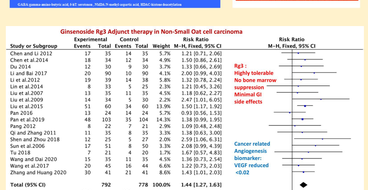
Adapted from Biorender Image and from Duan et al European Journal of Medicinal Chemistry15 November 2023 Article: 11575 Volume 260

RESULT:REPURPOSING ONCOLOGY drugs to AD therapeutics development



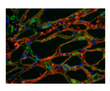
Antonio Ancidoni et al Alzheimers Res Ther2021 May 5;13(1):96 Anticancer drugs repurposed for Alzheimer's disease: a systematic review





The meta-analysis of Ginseng Rg3 in Lung cancer has unmasked the therapeutic target of angiogenesis beyond cancer to embrace changes in cerebral blood flow and energy metabolism in cognitive aging, vascular AD , PD, and cerebrovascular disease. VEGA Vascular endothelial Growth factor (VEGF) level, coupled with neuro-vascular unit in the brain, as indicative of altered angiogenesis, has been found VEGF levels were shown to be increased among subjects with mild cognitive impairment (J Alzheimers Dis. 2020;75(3):959-969. doi: 10.3233/JAD-191293) and angiogenesis activity was correlated with increased white matter hyperintensities.

Ginseng consumption showed a significant effect on increasing Mini-Mental State Examination scores (MD = 0.68; 95% CI: 0.03, 1.32; p = 0.04; I2 = 66%).
For Alzheimer's Disease Assessment Scale-Cognitive Subscale, a significant reduction in scores was observed in both the total (MD = −1.10; 95% CI: −1.82, −0.38; p = 0.003; I2 = 0%) and low-dose groups (MD = −1.09; 95% CI: −1.96, −0.22; p = 0.01; I2 = 0%).

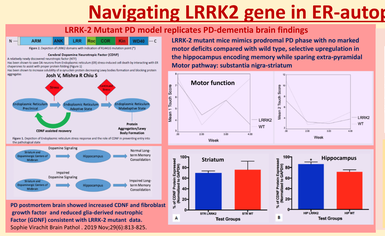


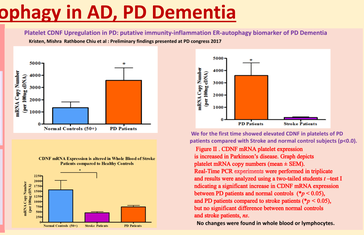
Computerized analysis of Angiogenesis
Adapted from Google.

CSF pTau181 showed positive associations with CSF angiogenesis factors (soluble vascular endothelial growth factor receptor 2 [sVEGFR2], VEGF-C, VEGF-D, placental growth factor [PLGF],Angiopoietin2, and Serpin E1),highlighting angiogenesis as a therapeutic target in vascular dementia, and AD and Cerebrovascular disorder.

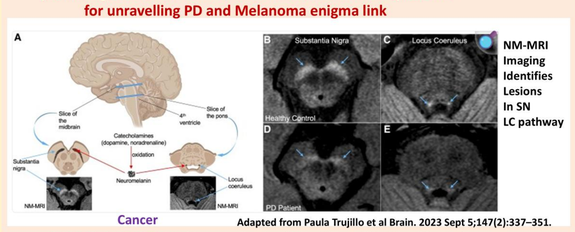
Treatment	Study Design	Diseases	Sample Size	Treatment Dosage and Rote	Outcomes	References
Sun ginseng-13S (ginsenoside complex)	Randomized, open-label trial	AD	40	From 1.5 g/day up to 4.5 g/day; oral administration	MMSE scores and ADAS scores were improved	Heo et al. [11]
Korean red ginseng (KRG) (containing 8.54% of ginsenosides)	Randomized, open-label trial	AD	31	4.5 g/day or 9 g/day; oral administration	CDR and ADAS scores were significantly improved	Heo et al. [44]
Panax ginseng powder (contains total 8.19% of ginsenosides)	Randomized controlled trial	AD	97	4.5 g/day or 9 g/day; oral administration	ADAS and the MMSE score show improvements during ginseng treatment	Lee et al. [45]
KRG	Randomized, double-blind, placebo-controlled trail	Healthy individuals	51	1000 mg/4 (500 mg/capsule × 2 capsules). oral administration	Gray matter volume in the left parahippocampal gyrus and the composite score of combined cognitive function were significantly increased	Namgung et al. [46]
HT1001 (consists of a mixture of important ginsenosides)	Randomized controlled trial	Schizophrenia	64	100 mg/day; oral administration	Visual working memory was significantly improved, extrapyramidal symptoms were significantly reduced	Chen et al. [48]
KRG (contained major ginsenosides)	Double-blind, randomized, placebo-controlled trial	Participants with high-stress occupations	63	500 mg of KRG powder per capsule; oral administration	Triglyceride levels were significantly increased, epinephrine level was decreased	Beak et al. [49]
Cereboost™ (10.65% ginsenosides)	Randomized, double-blind, placebo-controlled crossover	Healthy young adults	32	100, 200, or 400 mg/day; oral administration	Working memory was improved	Scholey et al. [50]
G115 (ginsenoside complex)	Double-blind, placebo-controlled, balanced crossover	Healthy young adults	27	200 mg/day; oral administration	Enhancing cognitive performance	Reay et al. [51]

Navigating LRRK2 gene in ER-autophagy in AD, PD Dementia





Dopamine-Norepinephrine-driven Neuromelanin NM Signaling promising biomarker for PD, AD & related Dementia syndrome for unravelling PD and Melanoma enigma link



Adapted from Paula Trujillo et al Brain. 2023 Sept 5;147(2):337–351.

Substantia Nigra-Striatum (dorsal and ventral) DA pathway : PD, AD and Psychosis
Locus coeruleus DA/NE pathway: PD , AD and Psychosis

Bifunctional relationship of PD and Melanoma: PD risks in melanoma , melanoma risk in PD
.*CYP2D6 or GSTM1, VDR, MC1R gene changes in both PD and melanoma
*Park, α-synuclein, LRRK2, DJ-1, PARK genes mutations in PD and melanoma
TRPM7 and p53 are additional genes altered in PD and melanoma.

Emerging evidence suggests DA/NE-NM connects to Immune Tumor Micro-Environment
Krasowska D et al Cancers (Basel). 2023 Nov 23;15(23):5541.

Rg3 ginseng in NM-toxin model of PD/AD

Figure 1 :Ginseng Rg3 improves Survival of DA neuron labelled with Tyrosine Hydroxylase (TH+) in vitro study in mesencephalon primary murine culture

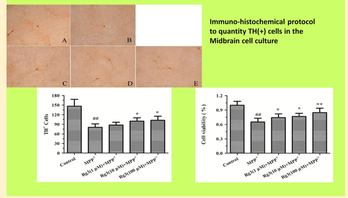


Figure 2 : Ginsenoside Rg3 improves motor function in MPTP PD mice
Effect of Rg3 on pole climbing time of PD mice

- MPTP mice exhibited longer pole climbing time in the standardized motor task compared with control group (P <0.01),

Motor findings in MPTP mice : no grab bar crawl, shaking, dragging and hind leg weakness.

* Ginsenoside Rg3 group significantly reduced pole climbing time (P <0.05 or P <0.01)

Group	Pole climbing time (s)
1.control group	8.9 ± 2.8
2.MPTP group	15.6 ± 5.9 ##
3.MPTP + Ginsenoside Rg3 (5 mg / kg) group,	11.1 ± 3.6 *
4.MPTP + Ginsenoside Rg3 (10 mg / kg) group,	10.6 ± 4.2 **
5. MPTP + Ginsenoside Rg3 (20 mg / kg) group,	10.1 ± 3.0 **

- Compared with the control group: ## P <0.01;
- compared with MPTP group: * P <0.05, ** P <0.01.

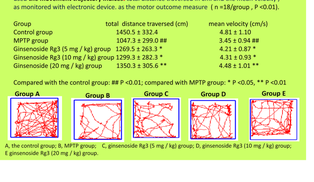
Funded by Stanley Medical Research Institute, USA; Michel J Fox Foundation, USA, OMH Ontario; CIHR Canada

Figure 3 Ginsenosine Rg3 ameliorates motor deficits in MPTP PD model
dose dependent Rg3 effects on total distance and average velocity

*The MPTP mice displayed significant motor deficits compared with the normal control. We used **the movement trajectory indices**: total distance traversed in cm. and the mean velocity , as monitored with electronic device. as the motor outcome measure (n =18/group , P <0.01).

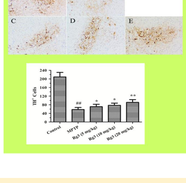
Group	total distance traversed (cm)	mean velocity (cm/s)
Control group	1450.5 ± 332.4	4.81 ± 1.10
MPTP group	1047.3 ± 299.0 ##	3.45 ± 0.94 ##
Ginsenoside Rg3 (5 mg / kg) group	1269.5 ± 263.3 *	4.21 ± 0.87 *
Ginsenoside Rg3 (10 mg / kg) group	1299.3 ± 282.3 *	4.31 ± 0.93 *
Ginsenoside (20 mg / kg) group	1350.3 ± 305.6 **	4.48 ± 1.01 **

Compared with the control group: ## P <0.01; compared with MPTP group: * P <0.05, ** P <0.01



A, the control group; B, MPTP group; C, ginsenoside Rg3 (5 mg / kg) group; D, ginsenoside Rg3 (10 mg / kg) group; E ginsenoside Rg3 (20 mg / kg) group.

Figure 4 : Ginsenoside Rg3 effect on TH expression in striatum of MPTP mouse



*Tyrosine hydroxylase (TH+) expression was reduced in the striatum of MPTP mice compared with normal group. *Ginsenoside Rg3 treatment significantly enhanced TH+ expression in MPTP mice group (Fig. 7).
*Dose dependent effect of Rg3 on the mouse within the PD striatum TH expression (× 100). A, control group;
B, MPTP group;
C, ginsenoside Rg3 (5 mg / kg) group;
D, ginsenoside Rg3 (10 mg / kg) group;
E ginsenoside Rg3 (20 mg / kg) group.

Figure 5 : Ginseng Rg3 effect on TH (+) cells of Substantia Nigra of MPTP mice

*MPTP mice showed reduced TH positive cells in the substantia nigra compared with normal control

*Ginsenoside Rg3 significantly increased TH(+) cells in the substantia nigra of MPTP mice

Effect of Rg3 on the expression of TH in substantia nigra of PD mice (× 100).
A, the control group;
B, MPTP group;
C, ginsenoside Rg3 (5 mg / kg) group;
D, ginsenoside Rg3 (10 mg / kg) group;
E ginsenoside Rg3 (20 mg / kg) group.

Figure 6 Rg3 antagonizes MPTP-induced decrease in Dopamine turnover in the striatum

- We found MPTP mice showed impaired dopamine (DA) turnover : levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) were significantly decreased as compared with control group (P <0.01).
- Ginsenoside Rg3 at 10 mg/kg, 20 mg/kg significantly increased DA, DOPAC, HVA in the striatum compared with MPTP group (10 mg/kg P <0.05 , 20 mg/kg P <0.01)
- Effect of Rg3 on the mouse within the PD striatum DA, DOPAC, HVA content

	DA (μg / g)	DOPAC (μg / g)	HVA (μg /g)
Control group	10.23 ± 1.83	2.10 ± 0.27	1.65 ± 0.37
• MPTP group	3.77 ± 0.81 ##	0.85 ± 0.36 ##	0.94 ± 0.25
Ginsenoside Rg3 (5 mg / kg)	4.75 ± 1.54	1.06 ± 0.68	1.25 ± 0.44
Ginsenoside Rg3 (10 mg / kg)	5.89 ± 1.78 *	1.70 ± 0.95	1.67 ± 0.63 *
Ginsenoside Rg3 (20 mg / kg)	6.89 ± 1.23 **	2.31 ± 0.70 **	1.78 ± 0.51 **

- Compared with the control group: ## P <0.01; compared with MPTP group: * P <0.05, ** P <0.01. n=6/group.

Typical HPLC profile of DA indices DA, DOPAC and HVA levels

Figure 7: Rg3 blocks MPTP-induced decreased mRNA PPARγ levels in the striatum

Figure 7: Ginsenoside Rg3 effects on PPARγ mRNA levels in the striatum of MPTP PD mice.

- We found that MPTP significantly decreased PPARγ mRNA level in the striatum as compared the control group (P <0.01)
- Compared with MPTP group, ginsenoside Rg3 enhanced PPARγ mRNA in MPTP PD mice (P <0.05 or P <0.01)

P <0.01 compared with control ; * P <0.05, ** P <0.01, (n = 9). compared with MPTP group:

PPAR-gamma : Peroxisome proliferator activated Receptor : transcription complex at cross talks of inflammation and immunity in Cancer and Dementia

Figure 8: Ginsenoside Rg3 blocks MPTP-induced elevated TNF-α levels in striatum

*MPTP group showed elevated pro-inflammatory cytokines TNF-α
*Ginsenoside Rg3 at 3 dsoages antagonized MPTP-induced elevated TNF-α mRNA level in the striatum
P <0.01 compared with control group
* P <0.05, ** P <0.01, (n = 9) compared with MPTP-treated group

Figure 8 : Differential effect of Ginsenoside Rg3 on MPTP-induced IL-1β & Il-6 mRNA

Ginsenoside Rg3 effect on MPTP-induced elevated pro-inflammatory **Interleukins IL-1β & Il-6.**
* MPTP mice had higher levels of mRNA levels **IL-1β & IL-6** in striatum compared with control
* Ginsenoside Rg3 antagonized MPTP-induced elevated IL-1β mRNA levels
* Ginsenoside Rg3 had no effect on MPTP-induced increased level of IL-6 mRNA
* ## P <0.01 compared with control ; * P <0.05, ** P <0.01, (n = 9). compared with MPTP group:

Figure 10 : Ginsenoside Rg3 restores MPTP-induced Decline in BDNF mRNA levels in striatum

*MPTP mice showed significant decline in Brain derived neurotrophic factor :BDNF mRNA in the striatum , compared with normal control (P <0.01).
*Ginsenoside Rg3 mice dose dependently restored MPTP-induced reduction in BDNF mRNA
P <0.01 compared with control group ; compared with MPTP group:
* P <0.05, ** P <0.01 compared with MPTP group (n = 9).

RCT trial of Ginsana-115 in schizophrenia :Dementia Praecox

Probabilities Matrix of Insulin resistance (IR) correlation with Core Schizophrenia symptom cluster: SANS and PANSS

	SANS-anhedonia	SANS-Inattention	PANSS-Positive symptom
Log-Insulin resistance	0.020	0.002	0.054

Significant correlation of log-IR and schizophrenia symptoms
Negative symptom SANS subscale: Anhedonia and Inattention
Positive symptom of PANSS scale.

Correlation Matrix of Insulin resistance (IR) and Cognitive Measures
U PENN R-Gur /Computerized neurocognitive measures

	Abstractmemory-dependent task	Attention and working memory	Delayed memory Facial recognition
Log IR Inversely related to Cognitive measures; higher IR results in worse Cognitive performance *Statistically significant P < 0.05	* r= 0.33	* r=0.34	*r= 0.40

The correlation IR with Neurocognitive measures and Positive & Negative symptoms in TRS echoes the emerging role of Brain Insulin Signaling/ inflammasome in AD

Transforming
AD PD Dementia
Therapeutics landscape

from Repurposing Oncology dynamics

NIM neuro-immune modulators Drug Platform coupled NLRP3INFLAMMASOME signaling Signaling

Driven by Dopamine, NE Norepinephrine Insulin

Epigenomics regulation

PRECISION MEDICINE VISION

Ginsana-115 effect on IR, BMI and Body Weight

	Baseline Week 0	Post-Ginseng Week 8	Statistics Paired t-test
Insulin Resistance (mmol.mU-1.L -2)	4.31 +/- 1.03	*3.41 +/- 0.7	P < 0.05
BMI:	32.1 +/- 2.0	30.5 +/- 1.9	P > 0.05
Body weight lb.	197 +/- 13.8	30.5 +/- 1.9	P > 0.05

Ginsana-115 effect on FRS (Framingham CV-Metabolic Risk score)

group	baseline	8 weeks	Paired t-test, 2-tailed	Percent change
Combined 200 mg (N=8) and 100 mg (N=6) ginseng groups (total N=14)	8.3 (SD=8.6)	6.3 (SD=6.6)	t=2.4, Significant at P < 0.05 (p =031)	24.1% reduction
Placebo group N=14)	6.2, SD=6.8	5.2, SD=5.0	t=1.8, p>.05, not significant	16.1% reduction

Framingham CV Risk Score is derived from HEART STUDY The composite Framingham score comprises of:
1. Age 2. Gender 3. Smoking history 4. Hypertension 5. Diabetes history 6. Lipid profile: low LDL, high HDL 7. BMI (Body mass index)

Table Neurocognitive Changes in Patients on ginseng 100mg first versus placebo first : change from week 0 to week 8, in z-score

Neuro-cognition (z-scores)	Ginseng 100mg (N=11) Baseline mean (SD)	Change by week 8 (SD)	CI for the delta (change)	Placebo(N=11) Baseline mean (SD)	Change by week 8 (SD)	CI for the delta (change)	Ginseng vs placebo t value	P value, 2-tailed	effect size r_{pb}
Total index	.072 (.495)	-.003 (.372)	-.263 – .269	.079 (.609)	.186 (.255)	-.369 - .003	-1.323	.203	.30
SPATIAL PROCESSING Abstraction /flexibility Emotion Processing Sensori-Motor Attention	.151 (.784) -.234 (.957) .015 (.920) .195 (.727) .036 (.396)	-.045 (.635) .173 (.672) -.018 (.599) .041 (.529) -.008 (.572)	-.409 - .500 -.624 - .278 -.385 – .421 -.396 – .315 -.401 – .417	.068 (.912) .230 (.851) .266 (1.030) .234 (.535) .119 (.396)	.082 (.754) .336 (.589) -.111 (.682) -.150 (.374) -.003 (.328)	-.589 - .416 -.425 -.732 - .059 -.347 - .570 -.118 - .418 -.232 - .238	-.416 -.606 .341 .944 -.023	.682 .551 .737 .357 .982	.10 .13 -.08 -.21 .01
Facial Memory	-.102 (.754)	-.044 (.534)	-.315 - .403	-.269 (.999)	.581 (.607)	-1.016 - -.148	-2.516	.021	.50*
Verbal Memory	192 (.321)	-.171 (1.200)	-.635 - .977	-.094 (.797)	.275 (.405)	-.565 - .015	-1.163	.267	.25
Reaction Time	0.328 (.868)	-0.313 (.291)	.069 - .556	.086 (.783)	-.387 (.352)	.116 - .658	.472	.644	.12

Legend: * indicates p<.05, 2-tailed; CI = confidence interval

Ginseng effects on Between-Subject psychiatric rating scales changes (Wk0-Wk8) GINSANA 200 mg versus placebo

	Ginseng 200mg (N=10) Baseline mean (SD)	Change by week 8 (SD) W8-W0	CI	Placebo (N=11) Baseline Mean (SD)	Change by week 8 (SD) W8-W0	CI	Ginseng vs Placebo t value	P value	effect size r_{pb}
SANS Total	46.7 (14.4)	16.0 (12.1)	7.3 - 24.7	55.4 (17.1)	-7.8(14.6)	-2.0 - 17.6	-1.38	0.181	.30
flat AFFECT	13.3 (9.0)	-5.8 (4.4)	2.7 – 8.9	13.5 (7.4)	-1.5 (4.9)	-1.8 - 4.8	-2.1	0.05	.43*
alogia	6.0 (5.5)	-3.2 (3.2)	.9 - 5.5	8.2 (4.6)	-0.5 (4.3)	-2.4 - 3.5	-1.6	0.129	.34
avolition	10.1 (3.6)	-2.2 (2.4)	.5 - 3.9	11.0 (2.6)	-1.0 (3.0)	-1.0 - 3.0	-1.0	0.327	.23
anhedonia	14.2 (6.7)	-3.3 (4.4)	.1 - 6.5	17.4(5.1)	-2.1 (5.3)	-1.4 - 5.7	-.56	0.580	.13
inattention	3.1 (2.9)	-1.5 (2.5)	.3 - 3.3	5.1 (3.6)	-2.6 (3.5)	-.3 - 5.0	.85	0.405	-.19
PANSS Total	62.6 (9.3)	8.0 (11.1)	1 - 15.9	73.8(15.2)	-6.8(14.7)	-3.2 - 16.8	-.21	.840	.05
Positive	10.5 (3.0)	-0.9 (1.9)	-.4 - 2.2	11.3 (5.3)	-1.8 (3.6)	-.6 - 4.3	.72	.481	-.16
Negative	18.9 (5.1)	-3.4 (4.2)	.4 - 6.4	22.5 (7.7)	-1.8 (5.0)	-1.5 - 5.2	-.78	.445	.18
General	33.2 (6.7)	-3.7(8.02)	-2.0 - 9.4	40.0 (7.1)	-3.2(10.3)	-3.8 - 10.1	-.13	.900	.03
BPRS	34.5 (8.7)	-5.2 (5.1)	1.5 - 8.9	40.1(10.8)	-2.1 (7.5)	-2.9 - 7.1	-1.1	.287	.24
HAMD	18.9 (8.8)	-6.5 (6.4)	1.9 - 11.1	24.4 (9.9)	1.7(10.2)	-8.6 - 5.1	-2.2	.042	.45*
QLS	59.8(22.2)	9.8 (14.8)	-21.2 - 1.6	48.0 (19.3)	1.8 (19.2)	-17.0 - 15.8	1.1	.305	-.26