Review

A Critical Review to Identify the Domains Used to Measure the Effect and Outcome of Adaptogenic Herbal Medicines

Sophia E. Gerontakos[a,*], David Casteleijn[a,b], Alexander N. Shikov[c], and Jon Wardle[a,d]

[a]Australian Research Centre in Complementary and Integrative Medicine, Faculty of Health, University of Technology Sydney, Ultimo, NSW, Australia; [b]Endeavour College of Natural Health, Fortitude Valley, QLD, Australia; [c]St Petersburg State Chemical Pharmaceutical University, St. Petersburg, Russia; [d]National Centre for Naturopathic Medicine, Southern Cross University, Lismore, NSW, Australia

Background: Phytoadaptogens are considered to be herbal medicines with a multi-target effect that strengthen organ systems compromised by stress. Although animal and laboratory studies have identified numerous molecular targets associated with adaptogenic activity, the non-specific characteristic of these herbal medicines has meant there is no known methods to accurately determine efficacy of adaptogens in humans. This critical review of the evidence aims to identify domains which have been used to measure the effect of adaptogens in humans, in order to create pathways for translating laboratory, animal, and clinical studies on adaptogens into practical applications in the future. **Methods**: EMBASE, AMED, PubMed, Cochrane Library, and WHO ICTRP databases were searched for randomized trials which examined known physiological actions of adaptogens. **Results**: Twenty-four studies were identified and critically appraised using the Jadad scale. The findings identified three broad categories of outcome measures, including cognitive, mood and biological measures. **Conclusions**: There was a great heterogeneity in data making it difficult to draw conclusions as to the most effective measurement tools to capture the holistic activity in humans. Cognitive measures hold promise as a reliable measurement tool when used in conjunction with other relevant tools. Further investigation is necessary to determine the most appropriate and diverse tools to measure the complex multi-target action of adaptogens.

*To whom all correspondence should be addressed: Sophia E. Gerontakos, 15c/40 Annerley Rd, Mater Hill, QLD, 4102, Aus; Tel: +61 424 465 919; Email: s.gerontakos@gmail.com; ORCID iD:0000-0003-3423-414X.

INTRODUCTION

Phytoadaptogens (often referred to as "adaptogens") are a class of herbal medicine commonly used by herbalists to assist in reducing the negative impact that chronic stress has on health [1]. The most recent definition describes phytoadaptogens as stress response modifiers that non-specifically increase an organism's resistance to various stressors (physical, chemical, and biological), thereby promoting adaptation and survival [2]. They are considered to strengthen organ systems compromised by stress and normalize body functions in the face of stress [3].

The term "adaptogen" dates back about 70 years to investigations into a synthetic compound (dibasol) found to have this effect by a Russian toxicologist, N. V. Lazarev [4]. It was later defined more precisely and attributed to herbal medicines by herbalists Brekhman and Dardymov [5] who noted that the concept had been preceded by folk medicine of long standing. The herbalists defined this action as having a non-specific response therefore increasing the power of resistance against multiple stressors, having a normalizing effect, irrespective of the nature of the pathology, and being non-toxic [5]. Both the original definition and the more recent definitions derived from laboratory findings are relatively vague with no specific or measurable domains that could be used to standardize the concept by regulatory bodies. The vague nature of adaptogen definitions may relate to the deficit of current clinical research due to there being a vast array of possible approaches to measuring a non-specific and poorly understood herbal action, and no consensus having been reached on the most appropriate approach.

In the 1960s, the Union of Soviet Socialist Republics (USSR) drove a targeted research direction into the study of plant adaptogens with extensive research (over 1000 studies) being published, primarily on *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. over the following 20 years [6]. Due to security measures within the former USSR these papers published in Russian journals and conference proceedings were not accessible to the public, were never translated, and have mostly remained inaccessible to Western researchers. Given the modernity of the term adaptogen, there is no discussion of adaptogens within traditional texts in the context of the current terminology. However, herbal medicines with adaptogenic qualities have a long history of traditional use in many cultures and various parts of the world [2]. Herbs exhibiting adaptogenic qualities – and subsequently recognized as adaptogens today – were often listed as tonics traditionally [4]. As such, the cross-over of herbal concepts "tonic" and "adaptogen" may represent the link between traditional use and modern terminology. Prior to the "birth" of the adaptogenic term and concept by Laz-

arev, some of the herbs considered to have adaptogenic qualities were traditionally described as tonics, which can be seen in the State Pharmacopoeia of the USSR [4].

To date, the concept of adaptogen has primarily been studied from physiological, pharmacological, and toxicological perspectives [6-9]. The latter laboratory data has been reviewed in 2017, identifying a range of key molecular and regulatory targets involved in adaptogenic activity including stress hormones such as cortisol and neuropeptide Y (NPY) and key mediators of the adaptive stress response including nitric oxide (NO), heat shock proteins (HSP), and the FOXO transcription factor [2]. Further, at least 88 of the 3516 genes identified as being regulated by adaptogens were closely associated with adaptive stress response and adaptive stress-response signaling pathways (ASRSPs), including neuronal signaling related to corticotropin-releasing hormone, cAMP-mediated, protein kinase A, and CREB; pathways related to signaling involving CXCR4, melatonin, nitric oxide synthase, GP6, Gαs, MAPK, neuroinflammation, neuropathic pain, opioids, renin–angiotensin, AMPK, calcium, and synapses; and pathways associated with dendritic cell maturation and G-coupled protein receptor–mediated nutrient sensing in enteroendocrine cells [10]. The pharmacological data builds on the identified need for well-designed clinical trials to demonstrate the efficacy of these traditional medicines by examining the contemporary understanding of the multi-faceted mechanism of action of adaptogens. Panossian [2] proposes that the multi-target action and shared use of receptor sites exhibited by adaptogens is an example of network pharmacology, and the typical reductionist pharmacological paradigm of one receptor-site for one drug does not apply to these medicines, an argument that has been echoed by the European Medicines Agency (EMA) [3]. An accepted clinically validated tool to measure this complex phytotherapeutic activity has not yet been developed.

While there is some research on individual aspects of certain adaptogenic herbs and some adaptogens are listed in internationally recognized traditional texts [11,12] modern evidence is lacking on adaptogenic activity and the knowledge base underpinning the use of adaptogens by Western herbalists is unclear. Knowledge translation from the former USSR data to the broader research world has commenced with two English language reviews examining in detail (from a laboratory perspective) two herbal medicines considered in Russia to be classical adaptogens [13,14], adding to the body of experimental data available. Traditional applications of a number of adaptogenic plants are also discussed in a review of medicinal plants of the Russian Pharmacopoeia [4], adding some traditional evidence to the body of knowledge Western researchers have collated on adaptogens. However, there remains a paucity of well-designed human clinical

trials and a lack of understanding of the adaptogenic concept overall.

The process of defining the term adaptogen has been ongoing over many decades and there remains some confusion. In 2008, EMA published a reflection paper on this topic to establish the scope and interpretation of the term "adaptogen" to assess the feasibility of the acceptance of the term into pharmacological and clinical terminology for herbal and medicinal products [3]. The EMA review concluded that clinical data is insufficient, and the concept needs further clarification, also noting the necessity to work towards developing the tools to differentiate between herbal concepts (for example tonic and adaptogen) to facilitate standardization of these concepts. The US Food and Drug Administration (FDA) does recognize adaptogen as a functional term [15]. However, the term is recognized by the FDA as a "structure or function" claim on the basis that it is not a recognizable health or disease claim [15], echoing EMA comments on the unsuitability of the term (thus far) for clinical terminology. As such, there is a need for researchers to focus on identifying a relevant method to measure this action, that translates from laboratory to practical applications.

The majority of the earlier studies are either published in Russian and difficult to access and/or animal and *in vitro* studies. Given the complexity of the mechanism of action of adaptogens, animal and *in vitro* studies offer limited insight into the action and effect of adaptogens in humans. However, the expansiveness of the Russian literature needs to be considered in discussions of the contemporary understanding of phytoadaptogens. Russian health-regulatory authorities regard the term "adaptogen" as a functional term [13] and they have classified a number of herbal medicines including *Panax ginseng* C.A.Mey, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. and *Aralia elata var. mandshurica* (Rupr. & Maxim.) J.Wen (syn. *Aralia mandshurica* Rupr. Et Maxim), *Schisandra chinensis* (Turcz.) Baill., *Oplopanax elatus* (Nakai) Nakai as classical adaptogens [13].

Despite some examples of adaptogen being used as a functional term, there appears to be a gap in knowledge translation between traditional understanding and use of adaptogens and clinical data, and between laboratory data and practical applications. In order for researchers to corroborate the practical use with modern evidence, more human clinical studies are needed. For this to proceed, a consensus on the most appropriate method of measuring the activity of adaptogens needs to be reached. The first step in achieving this is to identify those methods which have been used to date and analyze their efficacy and accuracy. A review of laboratory and animal studies [2] as well as other pre-clinical studies [16,17] have identified molecular targets and stress-related parameters relevant to measuring adaptogenic activity. The purpose of this review is to identify the domains that have been used to measure the effect and outcome of adaptogenic herbs in humans. It is the first review to analyze the methods of measurement of adaptogens used in human studies. An analysis of this data is necessary in order to determine the body of knowledge available, and which methods are the most suitable to give accurate insight into the activity of medicinal plants considered to be adaptogens. This is the preliminary work necessary to facilitate the translation of the body of laboratory and experimental data on adaptogens into practice, and to create valid methods of measuring adaptogenic activity to move forward with future clinical studies in this area of herbal medicine.

METHODS

A database search was conducted to identify randomized clinical trials from the database's inception to March 18th 2018 to identify domains that have been used to measure the effect and outcome of adaptogenic herbs in humans. On March 18th 2018, the following databases were searched: EMBASE (via OVID), AMED (via OVID), PubMed, Cochrane Library, and WHO ICTRP. Search terms (MeSH) were employed for: known physiological actions of adaptogens (*adaptation, physiological/; stress, physiological/*); herbal medicine (*phytotherapy/; plants, medicinal/; herbal medicine/; plant extracts/*); specific herbal medicines which were identified as adaptogens in traditional texts (*rhodiola/; withania/; eleutherococcus/; panax/; ginseng.mp.; schisandra/* and *astragalus plant/; astragalus membranaceus/*); as well as a keyword search for the term adaptogen (*adaptogen.mp*). The search strategy is outlined in Table S1 (Appendix A). All articles were imported into Endnote [18], a bibliographic referencing software system. Twenty-two duplicates were identified and removed.

Articles were included if they were clinical trials reporting original research findings on individual herbal medicines with an adaptogenic action examining physical and mental endurance or physiological stress adaptation in healthy individuals. A data-extraction sheet was developed collaboratively between authors. This was pilot-tested on five randomly-selected included studies and agreed on by all authors. A critical analysis and narrative synthesis review was selected in order to capture those domains that have been used to date, to measure the outcome and effect of adaptogenic herbs. This method is considered most suitable where statistical meta-analysis is not feasible [19] and was implemented to critique the body of knowledge available rather than to statistically analyze results and efficacy. Articles were excluded if they were not in the English language, were not clinical trials, or were examining combinations of herbal medicines in a single treatment. Figure 1 outlines the methodological
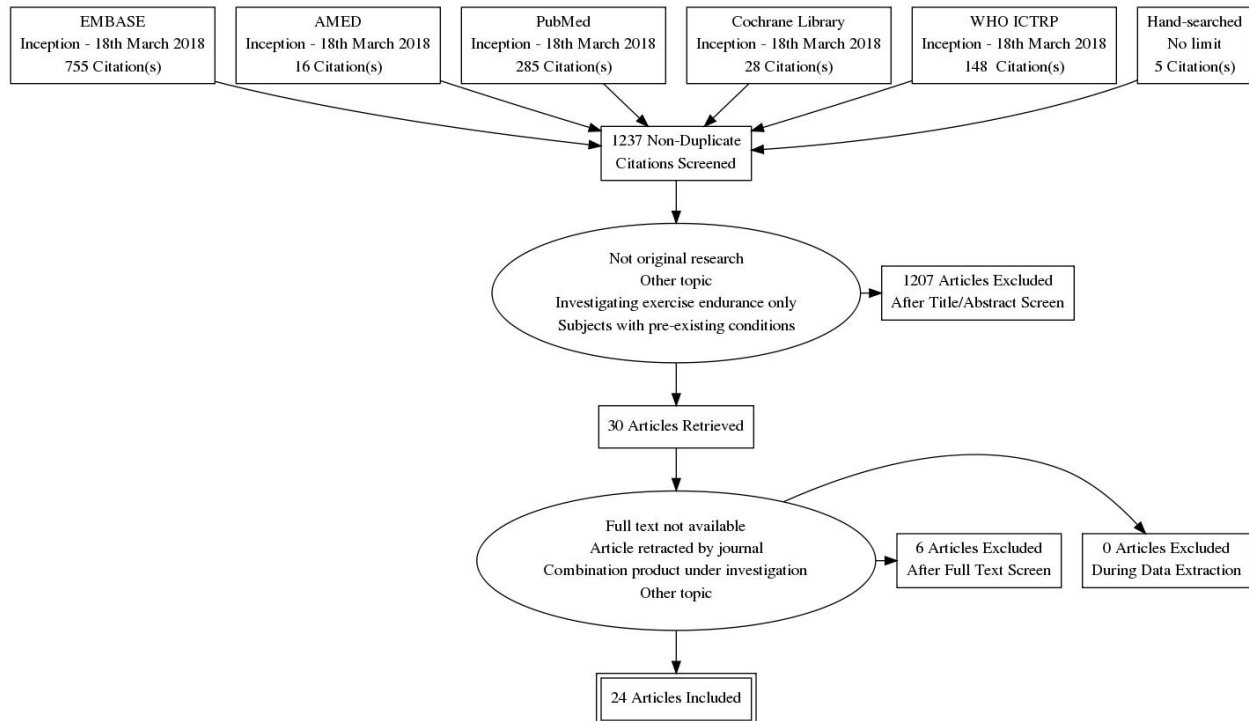
Figure 1. Process of article selection.

process of article selection. Articles were screened by title and abstract by one author (SG). Abstracts were analyzed by a second author (JW), and full texts agreed upon for selection. Bibliographic searching of included articles was also employed to identify additional material. Four additional articles were added at this stage. A summary of the characteristics of included articles is displayed in Table S2 (Appendix A).

Critical Appraisal Analysis

On the basis of the review being limited to randomized controlled trials and that the majority of studies being reviewed predate the development of reporting guidelines, the Jadad Scale [20] was selected to assess the quality of each included study. The Jadad Scale is a simple, reliable, and validated tool for assessing scientific rigor of reports [20]. This tool has been used elsewhere [21,22] and contains one question on reporting of withdrawals, and two questions each on randomization and blinding where inappropriate methods can attract a negative score. Although not as detailed as other scales, the Jadad scale has advantages in the simplicity of assessment questions and ease of assessment performance, which is important when comparing trials of considerable heterogeneity, particularly when much of the literature predates established reporting standards. The Jadad scores focus on blinding, randomization, and appropriate description

of withdrawals including point deduction where this has been inadequate, allows sufficient simplicity whilst retaining the features most important to studies of this topic. Table S3 (Appendix A) demonstrates the populated critical appraisal tool.

RESULTS

A total of 24 articles were selected for review published worldwide between 1985 and 2014. Of the selected articles, 21 employed placebo-controlled methods, two were comparative parallel group studies, and one was an open-label study.

Trends of studies included those examining dose-dependent changes of herbal medicines with adaptogenic qualities ($n = 9$), those comparing one herb to another herb ($n = 3$) and those examining a single dose (of one herb or of one compared to another) ($n = 12$). A total of nine articles were examining acute dosing, two examining sub-acute (up to 8 days) dosing, eight investigating chronic dosing, and two articles undertook a comparison of acute versus chronic dosing. The herbs examined in the included articles were: *Panax ginseng* C.A.Mey. ($n = 9$), *Rhodiola rosea* L. ($n = 6$), *Ginkgo biloba* L. ($n = 3$), *Bacopa monnieri* (L.) Wettst. ($n = 2$), *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. ($n = 2$), *Bryonia alba* L. ($n = 1$), *Panax quinquefolius* L. ($n = 1$), *Paullinia cupana* Kunth ($n = 1$), *Piper methysticum* G.Forst. ($n = $

1), *Schisandra chinensis* (Turcz.) Baill. (*n* = 1), *Valeriana officinalis* L. (*n* = 1), and *Withania somnifera* (L.) Dunal (*n* = 1). The majority of studies used standardized extracts (*n* = 22) guaranteeing the content of active constituents and marker compounds of the extract, with two studies not sufficiently reporting on the extract used. Regarding safety, 12 studies did not report on adverse events and toxicology, eight studies reported no adverse events were observed, and three studies reported a minimal number of mild adverse events including headache and gastro-intestinal disturbance relating to *Rhodiola rosea* L. and *Panax ginseng* C.A.Mey. No serious adverse effects were reported in any studies.

A significant proportion (58%) of the selected articles scored lower than 4 on the Jadad Scale (*n* = 14). Fifteen articles failed to describe the double-blinding methods, 15 articles failed to report the number of withdrawals, and nine articles did not describe the randomization methods. Three articles were of a superior standard with a score of 5. Results of critical appraisal on individual articles is displayed in Table S3 (Appendix A).

Articles reported three broad areas for outcome measures: cognitive tests (predominantly Cognitive Demand Battery (CDB) or tailored version) (*n = 15*), mood measures (*n = 11*), and biological measures (*n = 7*). Most of the articles included more than one of these measures or a combination of all three. Statistical significance was regarded as a *p* value of less than 0.05.

Outcome Measures

A tailored Cognitive Drug Research (CDR) computerized assessment battery or CDB was utilized in 12 articles to assess the effects of specific herbs on cognitive function and mental endurance in stressful situations. Seven of those studies used the Bond-lader Visual Analogue Scale (BL-VAS) [23-29] and two used other mood measures [30,31] in conjunction with the CDR battery. Six of those studies were examining *Panax ginseng* C.A.Mey. [24-27,29,32]. Similar cognitive tests (though not specifically CDR battery) were used in four articles examining *Rhodiola rosea* L. [31,33-35]. Five studies that used a tailored CDR battery also used biological measures [23,30,35-37]. These included blood pressure (BP) and heart rate (HR), salivary or serum cortisol testing, or a combination of both. Three studies used biological measures only [38-40], three studies used mood measures only [41-43], and two studies used mood measures in conjunction with a biological measures [44,45]. Table 1 outlines the outcome measures used across studies.

Cognitive Measures

The CDR system is a reliable and validated set of computerized testing designed to assess cognitive func-

tion [46]. The CDR battery includes the tests described in Table 2. The studies utilizing this outcome measure have used these tests, or a tailored version including a selection of these tests.

Among the studies examining *Panax ginseng* C.A.Mey. using the CDR battery all found significant improvements in cognitive function in four or more independent and objective measures. One placebo-controlled, double-blind, crossover study examining different dosages found significant improvement in cognition (specifically quality of memory) at 400mg of ginseng, but no significant difference at 200mg or 600mg [26]. On the contrary, a decrement in speed of memory was found at 200mg dosage at the 4-hour time point. Another randomized, placebo-controlled trial found a significant improvement in cognitive function after acute dosing (one dose), but no significant improvement after 7 days of treatment [27].

One double-blind, placebo-controlled cross-over study used the cognitive measures (in the form of a Multitasking Framework (MTF)) to examine the effect of *Bacopa monnieri* (L.) Wettst., a known adaptogen herb, on stress reactivity and mood [23]. This study found a significant effect post-treatment in two of four cognitive measures (improvement in Stroop test and Letter search, but no difference in mental arithmetic or visual tracking). Another placebo-controlled trial investigating two separate acute doses of *Bacopa monnieri* (L.) Wettst. used a CDB consisting of two serial subtraction tasks and the Bakan Rapid Visual Information Processing task along with a "stress and mental fatigue" visual analogue scale (VAS) and blood pressure monitoring [36]. This study found a significant improvement in cognitive performance at both doses; however, it did not find the treatments to attenuate stress or fatigue induced by the CDB.

A prospective, controlled, three-arm parallel group study compared *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (ES) (a well-known adaptogen herb) to Stress Management Training (SMT) in subjects with symptoms of fatigue and chronic exposure to stress using limited CDR battery testing in conjunction with a number of self-reporting instruments and questionnaires [30]. The cognitive factors included memory, attention, verbal, and visual. This study found that test parameters improved in all three treatment groups (ES, SMT, and a combination of the two).

Four studies examined the effect of *Rhodiola rosea* L. in participants under circumstances involving stress and fatigue, using other cognitive testing [31,33-35]. Only one of these studies used concomitant mood measures [31], and three out of four tested physical fitness parameters conjunctively [31,34,35]. One randomized, double-blind, placebo-controlled trial used psycho-motoric function testing and a Mental Work Capacity (cor-

Table 1. Outcome measures used across studies.

		Auddy et al. 2008 (*Withania somnifera* (L.) Dunal)	Benson et al. 2014 (*Bacopa monnieri* (L.) Wettst.)	Cardinal & Engels, 2001 (*Panax ginseng* C.A.Mey.)	Cropley et al. 2002 (*Piper methysticum* G.Forst. & *Valeriana officinalis* L.)	D'Angelo et al. 1986 (*Panax ginseng* C.A.Mey.)	Darbinyan et al. 2000 (*Rhodiola rosea* L.)	De Bock et al. 2004 (*Rhodiola rosea* L.)	Downey et al. 2013 (*Bacopa monnieri* (L.) Wettst.)
Cognitive Measures									
Mood Measures	BL-VAS or VAS		×			×	×	×	×
	SAM test								
	MFI-20								
	HRQOL SF-36								
	STAI		×						×
	PANAS + POMS			×					
	Other validated forms	×							
Biological Measures	BP + HR	×			×				×
	Cortisol testing	×	×						

		Edwards et al. 2012 (*Rhodiola rosea* L.)	Ellis & Reddy 2002 (*Panax ginseng* C.A.Mey.)	Facchinetti et al. 2002 (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.)	Jezova et al. 2002 (*Ginkgo biloba* L.)	Kennedy et al. 2004 (*Panax ginseng* C.A.Mey. & *Paullinia cupana* Kunth)	Kennedy et al. 2001 (*Panax ginseng* C.A.Mey.)	Kennedy et al. 2002 (*Ginkgo biloba* L. & *Panax ginseng* C.A.Mey.)	Olsson et al. 2009 (*Rhodiola rosea* L.)
Cognitive Measures									
Mood Measures	BL-VAS or VAS					×	×	×	
	SAM test								
	MFI-20	×							
	HRQOL SF-36		×						
	STAI					×	×	×	

		Panossian et al. 1999 (*Schisandra chinensis* (Turcz.) Baill. & *Bryonia alba* L.)	Reay et al. 2010 (*Panax ginseng* C.A.Mey.)	Schaffler et al. 2013 (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.)	Scholey et al. 2010 (*Panax quinquefolius* L.)	Scholey & Kennedy 2002 (*Ginkgo biloba* L. & *Panax ginseng* C.A.Mey.)	Shevtsov et al. 2003 (*Rhodiola rosea* L.)	Spasov et al. 2000 (*Rhodiola rosea* L.)	Sunram-Lea et al. 2005 (*Panax ginseng* C.A.Mey.)
	PANAS + POMS								
	Other validated forms	x							x
Biological Measures	BP + HR			x	x				
	Salivary cortisol				x				x
Cognitive Measures									
Mood Measures	BL-VAS or VAS	x	x	x	x	x	x	x	x
	SAM test							x	
	MFI-20			x					
	HRQOL SF-36								
	STAI				x				
	PANAS + POMS								
	Other validated forms			x	x				
Biological Measures	BP + HR			x			x		
	Cortisol testing	x		x					

Abbreviations: BL–VAS: Bond-Lader Visual Analogue Scale; VAS: Visual Analogue Scale; SAM: Self-Assessment Manikin; MFI: Multi-dimensional Fatigue Inventory; HRQOL SF: Health-related Quality of Life Short Form; STAI: State-Trait Anxiety Inventory; PANAS: Positive Affect-Negative Affect Scale; POMS: Profile of Mood States inventory; BP: Blood Pressure; HR: Heart Rate. NB: x indicates which measures were utilized in each study.

Table 2. Tests available in the CDR system.

Attention	Simple reaction time
	Choice reaction time
	Digit vigilance
Executive Function and Working Memory	Rapid visual information processing
	Semantic reasoning
	Logical reasoning
	Articulatory working memory
	Spatial working memory
Episodic Secondary Memory	Word recall
	Word recognition
	Picture recognition
	Face recognition
Motor Control	Joystick tracking task
	Tapping task
	Postural stability task
Psychophysical Thresholds	Critical flicker fusion (with and without pupil size control)

Note. Adapted from "The Value of Assessing Cognitive Function in Drug Development" by K.A. Wesnes, 2000, *Dialogues in Clinical Neuroscience, 2*(3), p.185. Copyright © 2000 LLS.

rection of text) in conjunction with a physical fitness (veloergonomic) test, a self-evaluation test of mental fatigue and a General Wellbeing test (SAM test) [31]. This study found minimal difference in cognitive function (p<0.05 in one of three cognitive tests, the Maze test), and no significant difference in physical fitness, but significant improvement in the self-evaluation of mental fatigue test and SAM test.

Another study examining *Rhodiola rosea* L. used cognitive measures including reaction time and ability to sustain attention in conjunction with exercise endurance capacity, muscle strength and speed of limb movement [34]. The study found no significant difference in parameters with the exception of an increased time to exhaustion (physical parameter) of p = <0.05. The remaining two randomized, placebo-controlled studies examining *Rhodiola rosea* L. against a background of fatigue and stress used a range of cognitive measures derived from a known cognitive test battery and employed a Fatigue Index Score to assess the effect [33,35]. Both of these studies found the Total Fatigue Index (TFI) score on cognitive parameters significantly improved post-treatment. One of these studies [35] used additional biological measures (blood pressure and pulse rate) to indicate physiological stress and fatigue, finding a subsequent beneficial effect on these parameters.

A placebo-controlled trial examining *Ginkgo biloba* L. used cognitive testing including a combined stimulus consisting of mental load (memory test) and static exercise (physical parameter) [37]. Salivary cortisol testing, blood pressure, and heart rate were measured just prior to treatment, and just after mental load and exercise testing. The study found that single administration of *Ginkgo biloba* L. failed to modify memory performance, however it did prevent a stress-induced rise in salivary cortisol in male subjects. No effect of treatment on salivary cortisol was observed in women. Single administration of *Ginkgo biloba* L. resulted in a significant inhibition of blood pressure responses to exercise testing, with heart rate responses unchanged.

Mood Measures

Fourteen studies used mood measures which included questionnaires, self-rated instruments, and subjective rating scales. The BL-VAS was the predominantly used mood measure, with seven studies implementing this tool conjunctively with the CDR Battery [23-29]. One study used an alternative VAS [36]. The BL-VAS is a series of 16 analogue scales (composed of 16 pairs of antonyms) designed to assess the mood effects of anxiolytic substances [47]. From the 16 scales, measures are derived from how the participants mark their subjective state. The resultant measures include three factors: "alertness," "calmness," and "contentedness" [47].

The BL-VAS was used in five out of the six studies examining *Panax ginseng* C.A.Mey. with the CDR battery [24-27,29]. No significant main effects were seen across these studies with the exception of one placebo-controlled, randomized trial which found a significant main effect in "calm" rating (but no effect in "alert" or

"content" ratings) [27]. Another trial found a significant reduction in "alert" factor post-ginseng treatment, but no significant effect on "calm" or "content" factors [26].

The BL-VAS mood measure was used in one *Bacopa monnieri* (L.) Wettst. study [23] and found there was a significant main effect post-treatment in absence of induced mental stress (MTF) only. Biological measures (salivary cortisol) used in this study again found a significant main effect of treatment in absence of MTF only. The second *Bacopa monnieri* (L.) Wettst. study which used VAS found the treatment to have no significant effect on indicators of stress and fatigue [36].

Two placebo-controlled trials used a Health Related Quality of Life (HRQOL) Short-form survey (SF-36) alone [43,45], to assess the effects of *Panax ginseng* C.A.Mey. [43] after 4 weeks and 8 weeks of treatment and *Rhodiola rosea* L. [45] on mental and social functioning in healthy individuals. The HRQOL questionnaire is a validated self-reporting measure comprised of a set of questions regarding how one perceives their mental and physical health at that time [48]. The *Panax ginseng* C.A.Mey. study found significantly higher social functioning in the treatment group at 4 weeks as well as a significantly higher mental component summary score [43]. These changes did not persist to the 8-week evaluation. The *Rhodiola rosea* L. trial used the SF-36 in conjunction with two other mood measures: The Pines Burnout Scale used to assess fatigue, and the Montgomery-Asberg Depression Rating Scale (MADRS) used to assess symptoms of depression as well as cognitive measures; and biological measures [45]. This study found significantly improved fatigue scores on the Pines Burnout Scale and a tendency towards improved physical health (p = 0.056) on the SF-36, with mental health not significantly changed on this scale.

The general wellbeing (SAM test) was used in another *Rhodiola rosea* L. study [31] along with a self-evaluation of mental fatigue (and physical and cognitive parameters). The SAM test consists of a 5-point scale assessing general state, degree of activity, mood and motivation to work [31]. The self-evaluation of mental fatigue was a specific Russian designed psychometric test in questionnaire form, where students were asked to evaluate and score signs of fatigue [31]. This study found significant improvements in both the self-evaluation of mental fatigue and the general wellbeing test (though minimal improvements in cognitive testing as outlined previously).

One double-blind, placebo-controlled trial examining *Panax ginseng* C.A. Mey. used differing mood measures again, measuring three psychological variables: positive effect, negative effect, and total mood disturbance [41]. Positive and negative effect were determined from the 20-item Positive Affect-Negative Affect Scale (PANAS)

and total mood disturbance was determined with the 65-item Profile of Mood States Inventory (POMS). In this study no significant effects were found from chronic (60 days*) Panax ginseng* C.A.Mey. supplementation.

An open-label study investigating *Rhodiola rosea* L. treatment in life-stress symptoms [42] used Numerical Analogue Scales (NAS) along with five different subjective questionnaires (including MFI-20 and MDMQ also used in the *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. study) [30]. All outcome variables used showed consistent and steady improvement with significant improvement at the 4-week time point.

A trial investigating the effects of *Withania somnifera* (L.) Dunal in chronically stressed humans used a version of a modified Hamilton anxiety (mHAM-A) scale for stress, along with biological measures [44]. It found significant improvement in wellbeing at both time points (30 and 60 days).

Biological Measures

In total, 10 studies used biological measures including blood pressure, heart rate, and/or salivary or serum cortisol testing. Four of the studies utilizing the CDR battery also measured blood pressure and heart rate [30,35-37]. In three studies biological parameters were improved by treatment [30,35,37], however in one of those studies there was an equal beneficial effect observed in the stress management training group who were not administered an herbal medicine [30]. The type of extract was not specified in this study and it is unknown whether a standardized extract was used. In the fourth study no effect of treatment was observed in blood pressure measurements [36].

Three studies used biological measures as a stand-alone assessment of the effect [38-40]. One randomized, controlled trial assessed the effect of *Piper methysticum* G.Forst. (kava) and *Valeriana officinalis* L. (valerian) on physiological and psychological responses to mental stress [38]. The measures used were BP and HR while the subjects were under induced mental stress with a color-word interference task which has been shown to increase blood pressure and heart rate [38]. In the *Piper methysticum* G.Forst. group a significant beneficial effect was seen on blood pressure (reduction) post-treatment, and in the *Valeriana officinalis* L. group a significant reduction in BP and HR was also observed.

Another placebo-controlled trial examining *Schisandra chinensis* (Turcz.) Baill. and *Bryonia alba* L. utilized salivary cortisol testing against a background of heavy physical exercise [40]. This study found that both *Schisandra chinensis* (Turcz.) Baill. and *Bryonia alba* L. significantly decreased plasma and salivary cortisol in well-trained athletes. However, this effect was not observed in beginner athletes.

The *Withania somnifera* (L.) Dunal trial [44] examined serum cortisol, blood pressure and heart rate along with a mood measure and found all parameters (biological and mood) to be significantly improved after both 30 and 60 days treatment.

DISCUSSION

A network meta-analysis was initially intended for this review to identify domains that have been used to measure the effect and outcome of adaptogenic herbal medicines in human studies. However, due to the significant heterogeneity in clinical studies of adaptogens this was not possible. As such, a critical review was conducted to ascertain the major domains used in clinical research on adaptogens. A critical review methodology was chosen to go beyond mere description and to include a degree of analysis identifying the most important aspects of the field [49].

The review identified relevant consistencies in outcome measures used, finding three broad categories of measurement including cognitive measures, mood measures, and biological measures. Despite these broader consistencies, significant heterogeneity in choice of measurement tools was identified in each of these areas. Individual studies had used modified and varying selections of tests included in those measurement tools, in particular varying and minimized selections of tests from the CDR battery to measure cognitive function. Even when similar measurement tools had been employed, they were used and analyzed in differing ways, often resulting in contradictory results between those studies. For example, studies examining *Rhodiola rosea* L. where CDR battery derived testing had been used in each study (although a differing selection of tests from the battery between studies). Two studies utilized a Total Anti-fatigue Index (TAFI) as their method of analysis and found significant benefits of treatment [33,35]; whereas other *Rhodiola rosea* L. studies [31,34] using tailored cognitive testing had used either Students t-test or repeated measures ANOVA as methods of analysis finding little or no benefit of treatment on cognitive function, in stark contrast.

The cognitive tests selected varied between studies, producing an additional type of heterogeneity, and there was a vast diversity between dosing regime and timing amongst studies, with differing (and in some cases contradictory) results between doses, and in one study differing results between sexes [37]. Many of the studies examining adaptogens had utilized only a narrow selection of cognitive tests, with the average number of cognitive tests used per study being five (out of a possible 16 tests across five categories (described in Table 2) in a complete CDR battery test panel [46]).

Furthermore, significant diversity in results was identified within categories of outcome measures. Mood measures had particular diversity, where the most commonly used mood measure (BL-VAS) reported little or no effect in studies, and yet alternative validated mood measures used in other studies reported significant effects. Such heterogeneity suggests there has not been sufficient consistency in domains used to measure adaptogenic activity to capture the potential clinical outcomes, and that the domains used may have been too narrowly focused. Within the collective heterogeneity of the data, the individual studies appear to have used measures more narrowly focused than could be expected to capture a multi-system action such as adaptogenic activity. For example, a proportion of the studies tested the effect of adaptogens on cognitive function only, and although the overall findings were significant, to test this effect alone is drastically insufficient to provide insight into a class of herb which has a non-specific stress-protective effect across multiple body systems [2].

The biological parameters tested in the human studies (salivary cortisol, blood pressure, and heart rate) were narrow in comparison to the wide range of hormones and key mediators of stress and homeostasis identified in laboratory work [2]. The body of laboratory literature on adaptogens investigates their mode of action [50], molecular mechanisms, proteins, and key signaling pathways associated with stress-protective effects of adaptogens [6,10], biological activity [7] and implications in stress resistance [16,51]. Yet this laboratory-based knowledge is not well-reflected in domains used to measure adaptogenic activity in the clinical studies reviewed.

One factor which may have contributed to the diversity of measures used and subsequent heterogeneous results is the diversity of views around the concept and definition of adaptogen. Many adaptogen herbs were traditionally documented as tonics prior to the adaptogenic concept being formally codified by Lazarev in 1947. These include *Panax ginseng* C.A.Mey. and *Schisandra chinensis* (Turcz.) Baill., which are listed as tonics in the State Pharmacopoeia of the USSR [4]. The first known literature to define the action of plant adaptogens also refers to these plants as "tonic plants" [5]. Modern phytotherapy texts now differentiate the two phytotherapeutic actions and highlight key differences, such as tonics considered to be "revitalizing" herbs and adaptogens considered to "improve response to stress" [52]. Wagner, Nörr [9] discuss the conundrum of differentiating between tonics and adaptogens where both concepts have overlapping features (such as improving performance) yet distinct differences (where tonics ameliorate a lack of tonus in an organism or organ), yet neither concept has been clearly defined. Such common misunderstanding, general confusion and competing – often vague – definitions of adaptogen may be contributing factors to the diverse array of

methods which have been used to measure adaptogenic activity in clinical research.

Interestingly, of the 24 papers reviewed nearly 70% of papers predated 2006. While laboratory and theoretical data on adaptogens has increased in the last 10 years, it appears clinical trials have plateaued. Reasons for this are unknown, however it could be that as laboratory research evolves so too does the understanding of the complexity of the inter-systems activity of adaptogens, highlighting the need for more diverse methods of measurement which have not yet been identified. Identifying appropriate methods to capture adaptogenic activity may assist in remedying the lack of up-to-date research on adaptogens.

Although cognitive testing holds promise as a useful measurement tool in conjunction with other tools, in order to gain a thorough indication of cognitive effects a more comprehensive and standardized set of cognitive tests may need to be implemented. Moreover, cognitive enhancement is only one potential facet of adaptogenic activity which appears to exhibit activity across multiple body systems [2]. Therefore, tests measuring the effects on individual body systems may only be relevant to adaptogens when used alongside additional tools to measure other parameters in line with the current understandings of the action incorporating pharmacological, traditional, and expert clinician perspectives. In short, the heterogeneity of the collective data makes it difficult to draw conclusions on the effect and efficacy of adaptogens based on current research, or even how these effects may be best measured. Nevertheless, the significant heterogeneity uncovered highlights the need for more research studies on adaptogens, and more consistency in those studies.

This review has some limitations, including the overall quality and reporting of the studies as assessed with the Jadad Scale (and the required use of the simple Jadad scale itself, given the heterogeneity of studies) and the deficit in current data with nearly 70% of studies predating 2006. The clinical data have a number of shortcomings including study design and methods of analysis (described earlier within the results). Further, the review included human studies only, meaning there is a substantial body of animal studies missing from this picture. However, the purpose of the paper is to determine domains used to measure adaptogenic activity in humans, in order to open pathways for the translation of theory into practical applications. Recently, attempts have been made to develop and evaluate combination products that are specifically marketed as adaptogenic, though have not been included in our study because – although often marketed as adaptogenic – they have not been formally assessed or verified in accordance with traditional texts or official pharmacopeia. However, domains used to evaluate these appear to follow similar domains to the individual herbal medicines assessed in our study (*i.e.* stress or fatigue scores, cortisol-focused biological studies) [53].

In summary, three broad areas of outcome measures have been used to measure the outcome and effect of adaptogens, which include cognitive measures, mood measures, and biological measures. Significant heterogeneity amongst studies was identified, making it difficult to compare the outcome measures and effects and derive definitive conclusions on the action of adaptogens or the most appropriate way to measure them capturing the holistic activity in humans. Individually, these studies give some level of information regarding the action and efficacy of certain herbal medicines in stress related conditions; however, collectively, the level of heterogeneity could be seen to render each individual study redundant based on the differing results found depending on the methods, outcome measures and methods of analysis used. Comprehensive cognitive testing holds promise as a measurement tool when used with additional measures relevant to the scope of adaptogenic activity as it is understood to date. Those additional measures need clarification. A key area of focus for future research on adaptogens is on the development of a standardized battery of tests designed for capturing the broad-spectrum multi-system activity of adaptogens. Standardization in measures as well as in methods of analysis of studies is crucial for the interpretation, reliability and clinical relevance of adaptogen research. This data provides evidence of the need for further research to develop appropriate measures and methods of analysis suitable to adaptogenic herbal medicines, in order to bridge the gap between traditional understanding and use, and modern evidence.

REFERENCES

1. Panossian A. Adaptogens in mental and behavioral disorders. Psychiat Clin N Am. 2013;36(1):49-64.
2. Panossian A. Understanding adaptogenic activity: Specificity of the pharmacological action of adaptogens and other phytochemicals. Ann NY Acad Sci. 2017;1401(1):49-64.
3. European Medicines Agency. Reflection paper on the adaptogenic concept. In: Agency EM, editor. London: European Medicines Agency; 2008.
4. Shikov A, Pozharitskaya O, Makarov V, Wagner H, Verpoorte R, Heinrich M. Medicinal plants of the Russian Pharmacopoeia; their history and applications. J Ethnopharmacol. 2014;154(3):481-536.
5. Brekhman II, Dardymov IV. New substances of plant origin which increase nonspecific resistance. Annu Rev Pharmacol. 1969;9(1):419-30.
6. Panossian A, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associ-

ated with their stress—protective activity. Pharmaceuticals. 2010;3(1):188-224.

7. Panossian A, Wagner H. Adaptogens. HerbalGram. 2011(90):52-63. PubMed PMID: 61468174.

8. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Curr Clin Pharmacol. 2009;4(3):198-219.

9. Wagner H, Nörr H, Winterhoff H. Plant adaptogens. Phytomedicine. 1994;1(1):63-76.

10. Panossian A, Seo E-J, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. Phytomedicine. 2018;50:257-84.

11. European Scientific Cooperative on Phytotherapy. ESCOP monographs: The scientific foundation for herbal medicinal products. United Kingdom: European Scientific Cooperative on Phytotherapy; 2003.

12. World Health Organization. WHO monographs on selected medicinal plants. Geneva: World health Organization; 1999.

13. Shikov A, Pozharitskaya O, Makarov V, Yang W-Z, Guo D-A. *Oplopanax elatus* (Nakai) Nakai: chemistry, traditional use and pharmacology. Chin J Nat Medicines. 2014;12(10):721-9.

14. Shikov A, Pozharitskaya O, Makarov V. *Aralia elata* var. *mandshurica* (Rupr. & Maxim.) J.Wen: An overview of pharmacological studies. Phytomedicine. 2016;23(12):1409-21.

15. Food and Drug Administration. Regulations on statements made for dietary supplements concerning the effect of the product on the structure or function of the body. In: Services DoHaH, editor. USA: Federal Register; 1998.

16. Panossian A. Adaptogens: Tonic herbs for fatigue and stress. Altern Complement Ther. 2003;9(6):327-31.

17. Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytother Res. 2005;19(10):819-38.

18. Clarivate Analytics. EndNote. X8.2 ed. Boston2018.

19. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A Product From the ESRC Methods Programme Version 1. 2006:b92.

20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

21. Moher D, Sampson M, Campbell K, Beckner W, Lepage L, Gaboury I, et al. Assessing the quality of reports of randomized trials in pediatric complementary and alternative medicine. BMC Pediatr. 2002;2:2.

22. Pellow J, Nienhuis C. Medicinal plants for primary dysmenorrhoea: A systematic review. Complement Ther Med. 2018;37:13-26.

23. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of *Bacopa monnieri* (CDRI 08) on multitasking stress reactivity and mood. Phytother Res. 2014;28(4):551-9.

24. Kennedy DO, Haskell CF, Wesnes KA, Scholey AB. Improved cognitive performance in human volunteers following administration of guarana (*Paullinia cupana*) extract: Comparison and interaction with *Panax ginseng*. Pharmacol Biochem Be. 2004;79(3):401-11.

25. Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of *Ginkgo biloba*, ginseng, and a ginkgo/ginseng combination to healthy young adults. Physiol Be. 2002;75(5):739-51.

26. Kennedy DO, Scholey AB, Wesnes KA. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. Nutr Neurosci. 2001;4(4):295-310.

27. Reay JL, Scholey AB, Kennedy DO. *Panax ginseng* (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults. Hum Psychopharmacol. 2010;25(6):462-71.

28. Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, et al. Effects of American ginseng (*Panax quinquefolius*) on neurocognitive function: An acute, randomized, double-blind, placebo-controlled, crossover study. Psychopharmacology. 2010;212(3):345-56.

29. Sunram-Lea SI, Birchall RJ, Wesnes KA, Petrini O. The effect of acute administration of 400mg of *Panax ginseng* on cognitive performance and mood in healthy young volunteers. Curr Top Nutraceut Res. 2005;3(1):65-74.

30. Schaffler K, Wolf OT, Burkart M. No benefit adding *Eleutherococcus senticosus* to stress management training in stress-related fatigue/weakness, impaired work or concentration, a randomized controlled study. Pharmacopsychiatry. 2013;46(5):181-90.

31. Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine. 2000;7(2):85-9.

32. D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E, Lecchini S, et al. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. J Ethnopharmacol. 1986;16(1):15-22.

33. Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. *Rhodiola rosea* in stress induced fatigue — A double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine. 2000;7(5):365-71.

34. De Bock K, Eijnde BO, Ramaekers M, Hespel P. Acute *Rhodiola rosea* intake can improve endurance exercise performance. Int J Sport Nutr Exe Metabol. 2004;14(3):298-307.

35. Shevtsov VA, Zholus BI, Shervarly VI, Vol'skij VB, Korovin YP, Khristich MP, et al. A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control of capacity for mental work. Phytomedicine. 2003;10(2-3):95-105.

36. Downey LA, Kean J, Nemeh F, Lau A, Poll A, Gregory R, et al. An acute, double-blind, placebo-controlled crossover

study of 320 mg and 640 mg doses of a special extract of *Bacopa monnieri* (CDRI 08) on sustained cognitive performance. Phytother Res. 2013;27(9):1407-13.

37. Jezova D, Duncko R, Lassanova M, Kriska M, Moncek F. Reduction of rise in blood pressure and cortisol release during stress by *Ginkgo biloba* extract (EGb 761) in healthy volunteers. J Physiol Pharmacol. 2002;53(3):337-48.

38. Cropley M, Cave Z, Ellis J, Middleton RW. Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. Phytother Res. 2002;16(1):23-7.

39. Facchinetti F, Neri I, Tarabusi M. *Eleutherococcus senticosus* reduces cardiovascular stress response in healthy subjects: A randomized, placebo-controlled trial. Stress Health. 2002;18(1):11-7.

40. Panossian A, Oganessian A, Ambartsumian M, Gabrielian E, Wagner H, Wikman G. Effects of heavy physical exercise and adaptogens on nitric oxide content in human saliva. Phytomedicine. 1999;6(1):17-26.

41. Cardinal BJ, Engels HJ. Ginseng does not enhance psychological well-being in healthy, young adults: Results of a double-blind, placebo-controlled, randomized clinical trial. J Am Diet Assoc. 2001;101(6):655-60.

42. Edwards D, Heufelder A, Zimmermann A. Therapeutic effects and safety of *Rhodiola rosea* extract WS® 1375 in subjects with life-stress symptoms--results of an open-label study. Phytother Res. 2012;26(8):1220-5.

43. Ellis JM, Reddy P. Effects of *Panax ginseng* on quality of life. Ann Pharmacother. 2002;36(3):375-9.

44. Auddy B, Hazra J, Mitra A, Abedon B, Ghosal S. A standardized *Withania somnifera* extract significantly reduces stress-related parameters in chronically stressed humans: A double blind, randomized, placebo-controlled trial. J Am Nutraceut Assoc. 2008;11(1):50-6.

45. Olsson EMG, Von Scheele B, Panossian A. A randomized, double-blind, placebo-controlled, parallel-group study of the standardized extract SHR-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. Planta Med. 2009;75(2):105-12.

46. Wesnes KA. The value of assessing cognitive function in drug development. Dialog Clin Neurosci. 2000;2(3):183-202.

47. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Brit J Med Psychol. 1974;47(3):211-8.

48. Centers for Disease Control and Prevention. Health-related quality of life (hrqol): U.S. Department of Health and Human Services; 2016 [cited 2018 6/4/18]. Available from: https://www.cdc.gov/hrqol/concept.htm.

49. Grant MJ, Booth A. A typology of reviews: An analysis of 14 review types and associated methodologies. Health Info Libr J. 2009;26(2):91-108.

50. Panossian A, Wikman G, Wagner H. Plant adaptogens III. Earlier and more recent aspects and concepts on their mode of action. Phytomedicine. 1999;6:287-300.

51. Panossian A, Wikman G, Kaur P, Asea A. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. Phytomedicine. 2009;16:617-22.

52. Bone K, Mills S. Principles and practice of phytotherapy, modern herbal medicine. 2nd ed. Sydney, NSW: Elsevier; 2013.

53. Hovhannisyan A, Nylander M, Wikman G, Panossian A. Efficacy of adaptogenic supplements on adapting to stress: A randomized, controlled trial. J Athl Enhancement. 2015;4(4).

Appendix A: Supplementary Data

Table S1
Example of search strategy used across databases

Database	Search Term	Limits Applied
EMBASE	(Rhodiola/ OR Withania/ OR Eleutherococcus/ OR Panax/ OR Ginseng.mp. OR Schisandra/ OR (Astragalus plant/ OR Astragalus membranaceus/)) OR (Adaptogen.mp.) OR ((Adaptation, Physiological/ OR Stress, Physiological/) AND (Phytotherapy/ OR Plants, medicinal/ OR Herbal medicine/ OR Plant extracts/))	Humans Clinical trials

Table S2 *Summary of the characteristics of included studies*

Author, Year, Country	Study design and duration	Participants, setting and sample	Research objective	Herb Being Examined	Outcomes Measured\ Domains Used	Summary of Findings	Comments
Auddy et al. (2008), India	Randomised, placebo-controlled study. 60 Days.	Ninety-eight participants, men and women, 18-60 years, identifying as stressed, but otherwise healthy.	To examine the efficacy of *Withania somnifera* in reducing stress-related parameters in chronically stressed humans.	*Withania somnifera* (L.) Dunal Standardised extract	1) mHAM-A questionnaire 2) Serum cortisol 3) BP + HR	Analysis: 1-way ANOVA, pair-wise. 1) Significant improvement in wellbeing in Withania group at day 30 and day 60 p < 0.001. 2) Significant decrease in serum cortisol in Withania group at day 60 p <0.05. 3) Significant decrease in BP + HR p <0.05.	Found that Withania reduces experiential feelings of stress and anxiety at all dosage levels at both day 30 and day 60.
Benson et al. (2014), Australia	Double-blind, placebo controlled, cross-over. Acute dosing.	17 volunteers (4 male and 13 female) 18-44 years.	To examine whether a standard clinical dose of an extract of *Bacopa monnieri* would acutely effect cognition, mood, anxiety, and stress.	*Bacopa monnieri* (L.) Wettst. standardised (CDRI 08)	Four MTF tasks set to 'medium' difficulty with the score being dictated by the accuracy and speed of response: 1) Mental arithmetic 2) Stroop 3) Letter Search 4) Visual tracking Three treatment groups: a) Placebo b) 320mg c) 640mg Testing occurred 1h post-dose and 2h post dose. Mood Measures: Bond-Lader VAS and STAI (STAI-S and STAI-T). Biological measures: Salivary samples of cortisol levels.	Total MTF: no significant effect by any of the three treatments. 1) N.S. by any treatment. 2) Increase from baseline to 1h post-dose in 320mg p=.028; Placebo increase in baseline to 2h post-dose p=.000; Increase from baseline to 1h post-dose in 640mg p=.001 and baseline to 2h post-dose p=.003. 3) Significant main effect of time p=.033. Baseline to 2h post-dose change score greater in 320mg compared to placebo p=.028. 4) N.S. Mood: In absence of MTF significant main effect of condition (by ANOVA) p=.023. Change baseline to 2h greater in 320mg p=.001. State anxiety scores trend for a main effect of condition p=.086. No other statistically significant effects. Cortisol: In absence of MTF main effect of condition p=.012. At 1h greater change in 640mg to 320mg p=.017 and placebo p=.018. At 2h greater change score in 640mg to 320mg p=.002 and placebo p=.022. No significant effects in change scores post-MTF.	N/A

Cardinal & Engels (2001), USA	Prospective, double-blind, placebo-controlled, randomised clinical trial. 60 days.	96 original participants with 83 completing the study. Healthy volunteers.	To determine whether chronic ginseng supplementation enhances affect or mood.	*Panax ginseng* C A Meyer (G115)	Measures administered pre and post-intervention consisting of 3 psychological variables: positive effect, negative effect, and total mood disturbance. Positive and negative affect determined from PANAS. Total mood disturbance determined from POMS.	Positive effect for both pre and post-intervention were normally distributed *K-S d=.08, P>.05* and *K-S d.08, P>.05*, respectively. Total mood disturbance was normally distributed at both time periods *K-S d=.14, P>.05* and *K-S d=.13, P<.05*, respectively. Negative effect data were not normally distributed at either pre- or post-intervention, *K-S d=.15, P<.05* and *K-S d=.20, P<.05*, respectively. All main effects and interaction effects P>.016 .	Does not support favourable claims for chronic ginseng supplementation on mood and effect.
Cropley et al. (2002), UK	Randomised, controlled experiment. 7 days.	Fifty-four volunteer students at the University of Surrey (30 female, 24 male) from 18-30 years.	Effect of Kava and Valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions.	*Piper methysticum* G. Forst. (Kava) and *Valeriana officinalis* L. (Valerian) Standardised	6 min colour/word interference task completed with BP and HR measured at 0.5, 2.5 and 4.5 min. Post task subjects completed rating of pressure with 7-point scale. Final BP and HR measurements taken after 5 min of rest. Identical testing was completed after 7 days of either kava or valerian supplementation. Differences between resting and task BP and HR were calculated at both Time 1 (T1 – pre-intervention) and Time 2 (T2 – post-intervention).	T1: n.s. change in BP between groups. T2: Resting systolic BP P<.05 and diastolic P<0.005, resting HR P<0.01 – significant difference. Valerian group: Reduction at T2 in resting systolic BP P<0.05 and HR P<0.05; reduction in diastolic BP P<.0.06 approaching significance. Kava: Reduction at T2 in resting diastolic BP P<0.05. No significant difference in BP or HR between T1 and T2 in controls.	N/A
D'Angelo et al. (1986), Italy	Double-blind, placebo-controlled clinical trial. 12 weeks.	Thirty-two male university students, 20-24 years.	A study on the effect of a standardised ginseng extract on psychomotor performance in healthy volunteers.	*Panax ginseng* C.A. Mey. (G 115 standardised extract)	1) Tapping test. 2) Simple (visual and auditory) reaction time 3) Choice reaction time 4) Cancellation test 5) Digit symbol substitution test 6) Mental arithmetic 7) Logical deduction	1) Neither treatment significantly affected performance. 2) Neither treatment affected visual reaction time significantly. Auditory reaction time post-treatment P<0.05 or better. 3) Post-treatment P<0.05 or better. 4) Post-treatment G 115 group p<0.05 or better from pre-treatment. 5) N.S. 6) Post-treatment G 115 P<0.05 or better from pre-treatment, and between the two experimental groups. 7) Post-treatment G 115 P<0.05 or better.	G115 superior to placebo in at least four independent and objective parameters.
Darbinyan et al. (2000), Armenia	Randomised, placebo-controlled, double-blind, cross-over study with	Fifty-six young, healthy physicians on night duty (both genders).	A study to investigate the efficacy of a standardised extract	*Rhodiola rosea* L.standardised extract SHR-5 170mg.	1) Speed of determination of words associated by meanings, scored in seconds. 2) Speed of backward spelling of a 6-letter word, scored in seconds.	1) Group A: P-0.013 Group B: P-0.005 2) Group A: P-0.01 Group b: P-0.006 3) Group A: P-0.002 Group B: P; 0.0001	N/A
	wash-out period. 6 weeks.		SHR/5 from *Rhodiola rosea* rhizome in non-specific fatigue.		3) Speed of subtraction of a given digit sequentially as far as possible from a number between 90 and 99 to 0, scored in seconds. 4) The number of correctly recalled words, irrespective of sequence and with no time-limit, ten of which were presented audially to the subject, scored in numbers. 5) Speed of rearranging digits into an order of decreasing magnitude. The digits were randomly distributed in a square, scored in seconds. Each test was given a fatigue index. Group A: treatment Group B: placebo.	4) Group A: P-0.54 Group B: P-0.003 5) Group A: P-0.075 Group B: P-0.712 Total fatigue index significantly improved after two weeks' treatment.	
De Bock et al. (2004), Belgium	Double-blind, placebo-controlled trial with two phases. Acute dosing and four weeks.	Twenty-four healthy and physically active male and female students.	Examining the hypothesis that acute Rhodiola rosea intake can improve endurance exercise performance.	*Rhodiola rosea* L. extract 100mg (standardised)	Phase I: 1h post treatment Phase II: Identical testing post daily treatment for 4 weeks. Testing: Day 1: 1) Speed of limb movement 2) Reaction time 3) Ability to sustain attention Day 2: 4) Muscle strength 5) Endurance exercise capacity	1) N.S. result in phase I or II. 2) N.S. change in visual or aural reaction time in phase I or II. 3) N.S. changes in phase I or II. 4) No change in phase I or II. 5) Phase I: Compared with P, R intake increased time to exhaustion p<.05. Phase II: N.S. difference in parameters.	Articles examining exercise endurance only, were excluded from the review, however this article was included due to mental parameters being included (ability to sustain attention).
Downey et al. (2013), Australia	A double-blind, placebo-controlled, crossover design.	Twenty-four (4 male, 20 female) healthy participants. Acute dosing.	To investigate the effects of a standard clinical dose (320mg) and a 640mg dose of Bacopa on mood, cardiovascular activity and mentally demanding cognitive tasks.	*Bacopa monnieri* (L). Wettst. Standardised CDRI 08.	1. Cognitive Demand Battery (CDB) comprised of a) Serial 3s + serial 7s b) 'stress and mental fatigue' VAS 2) Blood pressure	1.a) Serial 3s significant improved performance after 320mg p = 0.02 and trend towards improvement in 640mg. Serial 7s Improved performance in 640mg p < 0.05. b) VAS neither treatments attenuated the stress or fatigue of CDB. 2) No significant change in blood pressure.	Study found evidence for cognitive facilitation but did not find the treatments to attenuate stress or fatigue induced by a cognitively demanding battery.

Edwards et al. (2012), UK.	Multi-centre, non-randomised, open-label, single-arm study. Four weeks.	Ninety-three participants, 30-60 years, with life-stress symptoms.	To investigate the effects of Rhodiola treatment in subjects with life-stress symptoms.	*Rhodiola rosea* L. . Standardised extract (WS 1375).	1) Numerical Analogue Scales (NAS) of subjective stress symptoms. 2) Perceived Stress Questionnaire (PSQ) 3) MFI-20 4) Numbers Connecting Test (NCT) 5) Multidimensional Mood State Questionnaire (MDMQ) 6) Sheehan Disability Scale 7)Clinical Global Impressions (CGI)	1) Significant reduction in stress symptoms p < 0.0001) 2) Improvements post 4-week treatment p < 0.0001. 3, 4, 5) Significant improvements after 4 weeks' treatment p < 0.05 6) Improvement after 4 weeks' p < 0.0001. 7) All changes statistically significant at any time point.	N/A
Ellis & Reddy (2002), USA	Randomised, double-blind, placebo-controlled trial. 8 weeks.	Thirty healthy subjects 18 years or older recruited through the University of Connecticut.	To assess the effects of Panax ginseng on health-related quality of life (HRQOL).	*Panax ginseng* C.A. Mey. 200mg/day (G115)	HRQOL assessed with the Short Form-36 Health Survey version 2 (SF-36v2) at baseline and at 4 and 8 weeks.	4 weeks: social functioning was significantly higher in *Ginseng* group p=0.014; higher mental health score p=0.075 in *Ginseng* group; mental health component summary score higher in *Ginseng* group p=0.019. No of these differences persisted to the 8-week time point. No other significant differences between groups detected at 4 and 8-week time points.	P. ginseng improves aspects of mental health and social functioning after 4 weeks of therapy although these differences attenuate with continued use.
Facchinetti et al. (2002), Italy	Randomised, placebo-controlled trial. 30 days.	Forty-five healthy volunteers 18-30 years, students.	To examine the hypothesis that *Eleutherococcus senticosus* reduces cardiovascular response to stress in healthy subjects. To verify previously reported evidence that Eleutherococcus increases arousal, stamina and	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (extract type not reported)	Analysis of cardiovascular responses to Stroop Colour-Word test (Stroop CW).	Before treatment subjects reacted to Stroop CW with an increase in both systolic BP and HR and a small increase in diastolic BP. A reduced response of both systolic BP and HR to the Stroop CW was seen in *Eleutherococcus* group in both males and females. Males in *Eleutherococcus* group: systolic and diastolic p=n.s. Females: systolic p=0.01; diastolic p=n.s.; HR p=0.01 significant.	N/A

			stress resistance.				
Jezova et al. (2002), Slovakia	Parallel, randomised, double-blind, placebo-controlled trial. Single dose administration.	Seventy (33 male and 37 female) healthy volunteers 20-30 years, university students.	To evaluate the effects of EGb 761 (standardised *Ginkgo biloba* extract) on salivary cortisol and blood pressure responses during stress in healthy volunteers.	*Ginkgo biloba* L. (EGb 761 standardised extract 120mg).	Stress model: A combined stimulus consisting of mental load (memory test) and static exercise (hand grip) was applied. Salivary cortisol, blood pressure and heart rate were measured just prior to treatment or placebo administration and just after mental load and static exercise testing	Static exercise: BP: EGb 761 had a significant effect on systolic (p<0.05) and diastolic (p<0.05) blood pressure in handgrip test. HR responses were similar in both treatment groups (not significant). Salivary Cortisol: EGb 761 prevented a stress-induced rise in cortisol levels (noted at pre-stress testing) in males. In the same time period of investigation, no effect of stress exposure or of EGb 761 was observed in women. Memory Test: EGb 761 administration failed to modify the memory performance.	Single administration. Reduced BP and cortisol to a combined stress stimulus.
Kennedy et al. (2004), UK	Double-blind, placebo-controlled, counter-balanced experiment. Five study days, seven days apart.	Nineteen female and nine male healthy undergraduate volunteers.	To examine the effects on cognitive performance of Guarana and Panax ginseng in humans.	*Panax ginseng* C.A. Mey. (standardised extract G115 200mg) and *Paullinia cupana* Kunth. (Guarana standardised extract 75mg)	Outcomes from CDR battery: 1)Speed of Attention factor – 1.1 simple reaction time, 1.2 choice reaction time and 1.3 digit vigilance 2)Speed of memory factor 3)Accuracy of attention factor 4)Secondary memory factor 5)working memory factor Other measures: a) Logical reasoning task b) Sentence verification task c) Serial threes' and 'Serial sevens' subtraction tasks Subjective mood measure: d)The Bond-Lader Visual Analogue Scales	1) Effect following guarana at 1h p=0.011, 4h p=0.007, 6h p=0.025 post-dose; ginseng at 4h p=0.003, 6h p=0.04 post-dose. 1.1 ginseng at 6h p=0.005 post-dose 1.2 Guarana at 1h pp=0.029, 4h p=0.031 post-dose; ginseng at 4h p<0.001, 6h p=0.047 1.3 Guarana at 1hr p=0.011, 4h p=0.018, 6h p<0.001 post-dose; ginseng at 6h p=0.005 post-dose. 2) Enhanced performance following ginseng at 1h post dose p=0.03 and 4h p=0.001; guarana n.s. 3)N.S. differences. 4) Enhanced for guarana p=0.002 and ginseng p=0.04 at 2.5h testing post-dose. 5) Not significantly affected by the treatment. Other measures: a) Not significantly affected. b) Significantly speeded for both guarana p=0.003 at 2.5h, p=0.029 at 4h and p=0.038 at 6h and ginseng at 1h p=0.007, 2.5h p=0.001, 4h p=0.002, 6h p=0.005. c) No effect on total number of subtractions in serial threes. Serial sevens: Guarana at increase at 1h p<0.001, 4h p=0.011, 6h p=0.012; ginseng at 1h p=0.001, 6h p=0.024. d)N.S. effect of treatments.	The study also tested the combination of Guarana and Ginseng together, however this review is only including trials on single herbal medicines, so those results have not been recorded. In part c) ginseng led to reduction in errors at 2.5h p=0.03, 4h p=0.049.

Kennedy et al. (2001), UK	A placebo-controlled, double-blind, balanced, cross-over design. Five study days conducted seven days apart.	Fourteen female and six male healthy undergraduate volunteers.	To investigate whether acute and differing doses of *Ginseng* had any consistent effect on mood and cognitive performance.	*Panax ginseng* C.A. Mey. extract (G115 200, 400, or 600mg)	Tailored CDR battery test. 1) Quality of Memory (Incl. percentage accuracy scores from spatial working memory, numeric working memory, word recognition, picture recognition, immediate word recall and delayed word recall) 2) Speed of memory (incl. combined reaction times of numeric working memory, spatial working memory, delayed word recognition and delayed picture recognition) 3) Speed of Attention (incl. combined reaction times of simple reaction time, choice reaction time and digit vigilance) 4) Accuracy of Attention (incl. combined percentage accuracy of choice reaction time and digit vigilance tasks) Secondary cognitive measures: a) Working memory sub-factor. b) Secondary memory sub-factor. Subjective Mood Measure: The Bond-Lader Visual Analogue Scales ('alert', 'calm' or 'contented' factors).	1) Improvement in accuracy of memory task for 400mg *Ginseng* at 1h p=0.0043, 2.5h p=0.026, 4h p=0.035 and 6h post-dose p=0.002. No improvement with 200mg. 2) Decrement in speed for 200mg *Ginseng* at 4h p=0.0045 only significant difference. 3) Speed of performance reduced with 200 (p=0.0001) and 600mg (p=0.0019) respectively at 4h; and 6h p=0.0006 and p=0.0003 respectively. Speed was not however affected for 400mg dose. 4) Enhancement in accuracy of performance restricted to 200mg dose at 6h post-dose p=0.048. Secondary measures: a) No significant difference at any dose or any time point. b) Performance enhanced by 600mg *Ginseng* at 1h p=0.046, 2.5h p=0.0034, 4h p=0.034. 400mg *Ginseng* at 1h p=0.0022, 2.5h p=0.0027, 4h p=0.013 and 6h p=0.0036; restricted to 4h post-dose for 200mg *Ginseng* p=0.039. Subjective measures: 200 and 400mg *Ginseng* significant reduction in scores on 'alert' factor (p<0.001 and p<0.01 respectively). No significant difference in 'calm' or 'contented' factors.	Quality of memory factor enhanced at all time points following 400mg of *Ginseng*.
Kennedy et al. (2002), UK.	A randomised, placebo-controlled, double-blind, balanced, cross-over design. Five study days conducted seven days apart.	Fifteen female and five male healthy university students.	To directly compare the effects of single doses of *Ginkgo biloba* and *Panax ginseng* on two aspects of mood and cognitive performance in healthy volunteers.	*Ginkgo biloba* L. (GK501) 60mg and *Panax ginseng* C.A.Mey. (G115) 100mg.	Cognitive measures: 1) Quality of Memory factor 2) Secondary Memory factor (accuracy of immediate and delayed word recall, picture, and word recognition tasks). 3) Speed of Memory factor (speed of performance of spatial and numeric working memory and picture and word recognition) 4) Speed of Attention factor (speed of performing simple and choice reaction time tasks and digit vigilance task). 5) Quality of Attention factor (accuracy of performing choice reaction time and digit vigilance tasks)	1) Significant improvement in accuracy of memory task for both *G. biloba* (6h post-dose p=.008 and *P. ginseng* 4h p=.015. 2) Performance enhanced in both treatments Ginkgo at 1h p=.032, 6h p=0.011; ginseng improvements at 4h p=.029 and 6h p=.019. Immediate word recall: ginkgo at 6h improvement p=.0005 and 4h p=.09; ginseng improvement at 4h p=.00008 and 6h p=.00002; delayed work recall improvement with ginkgo1h p=.015, 6h p=.024; ginseng improvement 2.5h=.033, 6h p=.001. 3) Spatial memory ginseng at 2.5h p=.014 and word recognition p=.022 the latter at 4h p=.001. 4) N.S. differences. 5) Ginseng at 2.5h p=.004. Ginkgo reduced false alarms at 2.5h p=.036.	Modest improvement in quality of memory factor. Study also looked at ginkgo/ginseng combination however this data isn't included in the review due to combination treatment not fitting the inclusion criteria.
					6) Serial Threes 7) Serial Sevens 8) Bond-Lader visual analogue mood scales ('alert', 'content' and 'calm' factors)	6) both ginkgo and ginseng improved performance at same time point p=.064 and p=.064 respectively. 7) Ginkgo at 6h p=.0012. 8) Alert factor: Ginkgo more alert at each time point 1h p=.025, 2.5h p=.024, 4h p=.005, 6h p=.001. Content factor: more content following ginkgo at 1h p=.005, 4h p=.0006, 6h p=.0007. Calm factor: no significant differences.	
Olsson et al. (2009), Sweden	Randomised, placebo-controlled study with parallel groups. Twenty-eight days.	Sixty volunteers 20-55 years, presenting with stress-related fatigue (a diagnosis of "fatigue syndrome") with no co-morbidities (healthy subjects)	To assess the efficacy of the standardised extract SHR-5 of *Rhodiola rosea* L. in the treatment of stress related fatigue in humans.	*Rhodiola rosea* L. extract SHR-5	1) Primary endpoint: reduction in fatigue symptoms assessed according to Pines' burnout scale. 2) Reduction in depressive symptoms estimated with Montgomery-Asberg depression rating scale (MADRS). 3) Quality of life (QOL) measured with SF-36 questionnaire. 4) Cortisol response to awakening measured from saliva samples. 5) Attention assessed with CCPT II (incl. five indices: omissions, commissions, response reaction time (Hit RT), standard error of the reaction time (Hit RT SE) and variability of the response).	1) Pines' burnout scale p=0.047. 2) MADRS p=0.64 3) Physical health SF-36 p=0.056; mental health SF-36 p=0.33 4) Significant reduction in cortisol and cortisol response to awakening stress post-treatment: Treatment vs placebo p=0.08; pre-treatment vs post-treatment p=0.30; response x treatment vs placebo p=0.67. 5) Tendency towards positive effect in treatment group: Omissions p=0.02; Commissions p=0.35; Hit RT p=0.06; Hit RT SE p=0.001; Variability p=0.005.	At least one of the saliva samples was lost for eight subjects in the treatment group (8/29) and for five in the placebo group (5/30).
Panossian, et al. (1999), Armenia	Three trials on three groups of athletes: Study 1) Double-blind, randomised, placebo-controlled trial for 10 days (*Bryonia & placebo)* Study 2) Double-blind, randomised study (*Schisandra & Bryonia*) for Study 3) Double-blind,	Study 1) Forty-four 15-16 year-old athletes (jumpers, sprinters, wrestlers and sprinters). Study 2) Thirty-two 15-16 year-old athletes (jumpers). Study 3) One hundred and nine athletes (boxers, wrestlers and weightlifters).	To evaluate the effects of *Schisandra chinensis* and *Bryonia alba* on concentration of NO and cortisol in blood plasma, and determine whether NO test can be used for evaluation of stress protective	*Schisandra chinensis* (Turcz.) Baill. and *Bryonia alba* L. Both standardised	During the three trials athletes followed the same training course and feeding regimes. Tested before and after treatment and before and after exercise for: 1) Salivary NO 2) Plasma and salivary cortisol 3) Working capacity (maximal oxygen consumption/physical working criteria, PWC$_{170}$ test) 4) Endurance (number of jumps per minute for boxers, throw of wrestling dolly for wrestlers, maximal weight jerk lifted in 12 approaches for weightlifters, etc.).	1) After treatment with adaptogens (both *Schisandra* and *Bryonia*) heavy physical exercise does not increase salivary NO in athletes p<0.05. In placebo control group heavy physical exercise increased salivary NO. 2) Both *Bryonia* and *Schisandra* decreased plasma and saliva cortisol in well-trained athletes.	Blood cell counts were also performed; these are not reported in this review due to not being relevant to the topic. *Bryonia* and *Schisandra* have the same effect as heavy physical exercise in beginner athletes: elevation of both NO and cortisol

	randomised, placebo-controlled trial (*Schisandra* & *Bryonia* & placebo) for 8 days.		effect of an adaptogen.				in plasma and saliva. In well-trained athletes, both adaptogens decreased salivary cortisol and increased salivary NO. Physical exercise did not increase both NO and cortisol levels in saliva after treatment with adaptogens.
Reay et al. (2010),	Placebo-controlled, double-blind, randomised, cross-over trial. 8 days.	Thirty healthy adult volunteers.	To investigate *Panax ginseng's* effects upon working memory processes following single and repeated ingestion.	*Panax ginseng* C.A.Mey. (G115)	Groups: Placebo 200mg 400mg 1) Subjective mood: Bond-Lader visual analogue scales (16 items combined to form three mood factors: 'alert', 'calm' and 'contented'. Cognitive battery: 2) Working memory: Computerised Corsi block tapping task. 3) N-back task: Three-back sensitivity index (SI) and reaction time (RT) recorded. 4) Random number generation task.	Sub-chronic effects (7 days treatment). No significant treatment related effects for any outcome measure. Acute effects (day 1) 1) Significant main effect of treatment 'calmness' ratings (p=0.014) at 2.5h p=0.012 and 4h p=<0.0001. Significantly improved ratings of 'calmness' on day 8 post-treatment (at the same dose) at 1h p=0.029 and 4h p=0.015. 2) Not significantly modulated. 3) RT: significant main effect of treatment on average reaction times p=0.006. SI: Significant main effect (average of treatment doses) of treatment p=0.003. 4) N.S.	Findings confirm that acute dose can modulate cognitive function and mood, however no effects following 7-day dosing.
Schaffler et al. (2013), Germany	A multi-centre, prospective, exploratory, open, controlled, randomised 3-arm parallel group comparison study. Two and eight weeks.	One hundred and forty-four participants, male and female, 30-50 years with symptoms of fatigue and chronic exposure to occupational and/or social stress.	To explore efficacy of *Eleterococcus senticosus* (ES) compared to stress management training (SMT) and combination of ES and SMT (COM)	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. Extract not sufficiently described.	1. Cognitive performance (memory, attention, verbal, visual); 2. Sheehan Disability Scale (SDS); 3. Fatigue, exhaustion MFI-20; 4. Multi-dimensional mood state questionnaire (MDMQ); 5. ASS-SYM; Beck depression inventory (BDI-II); 6. Well-being index (WHO-5); 7. Leeds Sleep Evaluation Questionnaire (LSEQ); 8. Heart rate (HR); electrodermal activity; 9. Salivary cortisol.	Test parameters improved from visit to visit in all 3 treatment groups with the exception of WHO-5 and the BDi-II score reporting values within the reference range for normal population. Indicates ES was not significantly different to SMT, and COM may be more effective the ES alone.	N/A

			for stress-related symptoms.				
Scholey et al. (2010), Australia	A randomised, double-blind, placebo-controlled crossover trial. 4 study days, 7 days apart.	Thirty-two (16 male and 16 female) healthy participants 18-40 years.	To evaluate the effects of a highly standardised extract of *P. quinquefolius* for its effects on cognitive function, mood and blood glucose in humans.	*Panax quinquefolius* L.commercial extract Cereboost.	Four doses: 0mg, 100, 200 and 400mg. Cognitive measures: Computerised Mental Performance Assessment System (COMPASS) battery incl.: 1)Word presentation 2)Immediate word recall 3)Picture presentation 4)Face presentation 5)Simple reaction time 6)Choice reaction time 7)Four choice reaction time 8)Stroop colour-word task 9)Numeric working memory 10)Alphabetic working memory 11)Corsi blocks (tapping task) 12)N-back 13)Delayed word recall 14)Delayed word recognition 15)Delayed picture recognition 16)Delayed face recognition 17)Serial sevens subtraction task 18)Serial threes subtraction task 19)Rapid visual information processing or Bakan task Mood measures: Bond-Lader VAS Other: a) Depression anxiety and stress scale (DASS) b) State-trait anxiety inventory (STAI) c)Symptom checklist	2) Significant main effect of Treatment p=0.006 and a Treatment x Time interaction p=0.006 improvements associated with 200mg dose at all time points (p=0.003, p=0.002, p=0.002 at 1hr, 3h, 6h respectively). 6) Significant main effect of treatment p=0.030. 9) Significant main effect of treatment p=0.007. 10) Significant main effect of treatment p=0.04. 11) Significant main effect of treatment p=0.041. Mood: single effect of treatment, the Treatment x Time interaction on self-rated calmness p=0.034. No significant effects on 1, 3, 4, 5, 7, 8, 12, 13, 14, 15, 16, 17, 18, 19 or on a, b or c.	Blood glucose results not included due to not being relevant to this review.
Scholey & Kennedy, (2002), UK	Two randomised, double-blind, counterbalanced, placebo-controlled trials. Five study days,	Study 1: Eighteen female and two male healthy undergraduate volunteers. Study 2: Fourteen female and six	To examine the dose-dependent cognitive effects of *Ginkgo biloba* and *Panax ginseng* in healthy	*Ginkgo biloba* L. (GK501) and *Panax ginseng* C.A. Mey. (G115).	Cognitive measures: 1)Serial threes 2)Serial sevens Testing took place at 1, 2.5, 4 and 6h following each treatment.	Ginkgo: !) Significant increase in number of subtractions at 4h following 120mg p=<0.05, 240mg p=<0.001, and 360mg p=<0.01. More errors were made at 120mg at 4h p<0.01. 2)No significant reduction for number of subtractions for any dose, though significant improvement in number of errors for all doses at 2.5h p=<0.05 Ginseng:	Ginkgo/Ginseng combination was also tested in a third trial and those results not included in this review due to combinations falling outside

	conducted 7 days apart.	male healthy undergraduate volunteers.	young volunteers, and to examine differential interactions with cognitive demand.			1) N.S. differences from placebo in number of subtractions or number of errors at any dose. 2)Significant decrement in performance for 200mg (fewer subtractions) p=<0.05 at 1h, 2.5h and 6h. Significant improvement in accuracy following 400mg at 4h an d6h p=<0.05.	the inclusion criteria.
Shevtsov et al. (2003), Russia	Randomised, double-blind, placebo-controlled, parallel-group study. Acute dose (1 day).	One hundred and twenty-one healthy male volunteers.	To study the anti-stress and stimulant effects of a single dose of SHR-5 in healthy young males against a background of fatigue and stress.	*Rhodiola rosea* L. (SHR-5) 370mg (2capsules) and 555mg (3 capsules).	1. Capacity for mental work: Total Anti-fatigue Index (TAFI) (assessing visual perception, short-term memory and perception of order). 2. Pulse pressures	1. Rhodiola 2 capsules difference in TAFI p<0.0001 Rhodiola 3 capsules p<0.0001. Highly significant difference in TAFI between the placebo and the Rhodiola groups, specifically the Rhodiola 3 capsules. 2. Significant beneficial effect of treatment p0.007 for Rhodiola 2 capsules and 3 capsules.	N/A
Spasov et al. (2000), Russia	Randomised, double-blind, placebo-controlled trial, Twenty days	Forty male students from India 17-19 years old during an examination period of first year studies at Volgograd Medical Academy.	To study the anti-stress and stimulatory effects of SHR-5 in healthy foreign students during stressful circumstances.	*Rhodiola rosea* L. (SHR-5)	1. Physical fitness - two parameters: a) veloergonomic test PWC-170 measured in kg/min, and b) pulse rate before and after the ergometric test. 2. Psycho-motoric function: a) Maze test b) Tapping test. 3. Mental work capacity: Correction of text test. 4. Tests based on self-evaluation: mental fatigue. 5. General well-being test (SAM test).	Improvement of verum vs placebo: 1. a) p~0.1 (N.S.) b) Improvement of pulse rate p<0.05 2. a) p<0.05 b) N.S. 3. N.S. 4. p<0.01 5.p<0.05	N/A
Sunram-Lea et al. (2005), UK	Double-blind, placebo-controlled, balanced, cross-over design. Two study days with 7 day washout	Thirty (15 male, 15 female) healthy participants, 18-25 years.	To examine the effect of acute administration of 400mg of *Panax ginseng* on cognitive performance	*Panax ginseng* C.A. Mey. (G115)	1. CDR Battery with primary outcome measures: a) Quality of memory factor b) Speed of memory factor c) Speed of Attention factor d) Accuracy of attention Secondary outcome measures: e) Working memory sub-factor f) Secondary memory sub-factor	1. a) N.S. b) N.S. c) p=0.03 d) N.S. e) N.S. f) N.S. g) N.S.	400mg improved speed of attention indicating a beneficial effect on subjects' ability to allocate attentional processes to a
	period between these days.		and mood in healthy young volunteers.		g) CDR factor scores Bond-Lader VAS		particular task. No other effects seen.

Table S3

Critical appraisal results across studies using the Jadad tool

Literature	Auddy et al. (2008)	Benson et al. (2014)	Cardinal et al. (2001)	Cropley et al. (2002)	D'Angelo et al. (1986)	Darbinyan et al. (2000)	De Bock et al. (2004)	Downey et al. (2013)	Edwards et al. (2012)	Ellis & Reddy (2002)	Facchinetti et al. (2002)	Jezova et al. (2002)
Described as randomised[a]	1	0	1	1	1	1	1	1	0	1	1	1
Described as double-blind[a]	1	1	1	0	1	1	1	1	0	1	1	1
Description of withdrawals[a]	1	0	1	0	0	1	1	0	1	1	0	0
Randomisation method described and appropriate[b]	1	1	0	0	0	0	0	1	0	1	0	0
Double-blinding method described and appropriate[b]	0	0	0	0	0	1	0	0	0	1	0	0
Score	4	2	3	1	2	4	3	2	1	5	2	2

Literature	Kennedy et al. (2004)	Kennedy et al. (2001)	Kennedy et al. (2002)	Olsson et al. (2009)	Panossian et al. (1999)	Reay et al. (2010)	Schaffler et al. (2013)	Scholey et al. (2010)	Scholey & Kennedy, (2002)	Shevtsov et al. (2003)	Spasov et al, 2000	Sunram-Lea et al. (2005)
Described as randomised[a]	1	0	1	1	1	1	1	1	1	1	1	0
Described as double-blind[a]	1	1	1	1	1	1	0	1	1	1	1	1
Description of withdrawals[a]	0	0	0	1	0	1	1	0	0	0	0	0
Randomisation method described and appropriate[b]	1	1	1	1	0	1	1	1	1	1	1	1
Double-blinding method described and appropriate[b]	1	0	0	1	0	1	1	1	0	0	1	1
Score	4	2	3	5	2	5	4	4	3	3	4	4

a) A study receives a score of 1 for "yes" and 0 for "no"

b) A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, and -1 if the method is described but inappropriate