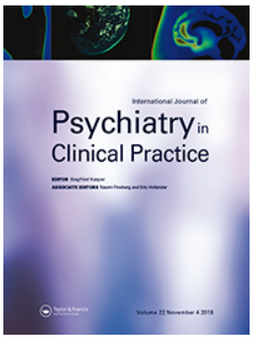

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REVIEW ARTICLE

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Stress management and the role of *Rhodiola rosea*: a review

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ABSTRACT

Objective: Stress describes the physiological reaction to threat or pressure, which manifests as physical symptoms of exhaustion or energy loss and psychological symptoms, including irritability or tension. If untreated, chronic stress or burnout may develop, both are areas of unmet medical need. Evidence-based treatment and prevention measures are needed.

Methods: Prevention strategies and existing treatment options for stress-related symptoms were evaluated to establish criteria for an adequate pharmacological approach to stress. The authors reviewed the literature to reach a clinically meaningful strategy for prevention and treatment of persistent stress symptoms and their consequences, including burnout and secondary diseases.

Results: Current medication reveals a treatment gap. Most drugs target only psychological or physical stress symptoms. Furthermore, psychotropic medications sometimes prescribed for stress often have unacceptable side effects and bear a risk of overtreatment. Ideally pharmacological therapy should afford comprehensive treatment of all stress symptoms with a favourable safety profile.

Conclusions: *Rhodiola rosea* extract (RRE) fulfils important requirements. It is the main adaptogen approved by the HMPC/EMA for the indication 'stress' and influences the release of stress hormones while boosting energy metabolism as revealed in animal literature. RRE offers comprehensive treatment of stress symptoms and can prevent chronic stress and stress-related complications.

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Rhodiola rosea; stress; burnout

Introduction

Stress describes the physiological reaction to environmental threats or pressures, which can be self-driven e.g., striving for perfection, high ambition or external such as social pressures, excessive demands or workloads. Although the body may initially adapt to perform under stress, it soon becomes dysfunctional if stress persists and has a too high intensity. Stress manifests itself in a wide variety of both physical and psychological symptoms, has a negative impact on performance and leads to absence from work. Work-related stress occurs across all groups of society and affects 22% of the European workforce. It is a crucial factor in 50–60% of all lost working days (Milczarek, Schneider, & González, 2009) with a rising trend. In 2016, a survey of a large German health insurance company revealed that over 60% of survey participants are now more stressed than in 2013 (Techniker Krankenkasse, 2016). The World Health Organization (WHO) has called stress 'the health epidemic of the 21st century'.

If stress persists and is left untreated, it can result in serious health problems including burnout and secondary conditions, e.g., depression, anxiety, cardiovascular, gastrointestinal, neurological or musculoskeletal disease or diabetes – consequently with higher costs to the community and a higher impact on individuals' lives. The main implications for individuals related to health impairment are lower income and reduced quality of life. However, stress has not only individual, but also social and economic consequences. Organisations are affected by rising costs related to sick leave, reduced productivity and higher staff turnover (European Agency for Safety and Health at Work [EU-OSHA], 2014).

Methods

The authors reviewed the current literature to identify and assess prevention strategies and treatment options for stress-related symptoms and thus established criteria for an adequate and holistic pharmacological approach to stress. The aim of this process was to propose a consensus for prevention and treatment of symptoms of persistent stress as well as for prevention of health consequences of stress such as burnout and secondary diseases. In this review article we have outlined current understanding of the pathophysiology of stress and identified the areas of greatest clinical need for intervention, which occurs at two stages: as a preventive treatment for a patient with stress to avoid the development of chronic stress and for those already suffering from persistent stress, an appropriate therapy to avoid burnout and secondary diseases. Assessment of prevention and treatment strategies identified some non-pharmacological approaches and some pharmacological approaches which have shown limited efficacy targeting the symptoms of stress and these are outlined below. The literature review process identified a significant amount of data on the clinical effects of *Rhodiola rosea* extract (RRE) on stress and stress-related disorders and mechanistic studies allude to the ability of RRE to normalise stress and boost energy levels. Thus, in the latter part of this review article we have focused our attention on RRE as a specific pharmacological approach to stress management.

Stress, allostatic state and allostatic (over)load

In 1936 Hans Selye postulated the so-called general adaptation syndrome which describes the stereotyped response of an

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organism in reaction to a stressor. This syndrome consists of three stages. The first stage is the alarm reaction ('fight or flight' response) in which resources are mobilised to maintain homeostasis. This has subsequently been termed as allostasis, which describes the biological response to stressors to promote stability through change (McEwen, 2000). Primary mediators of allostasis include, but are not confined to, hormones of the hypothalamic-pituitary-adrenal (HPA) axis, catecholamines and cytokines.

Restoration of allostasis leads to the second stage of resistance, in which defence and adaptation are sustained and optimal. However, many current stressors are persistent and can lead an organism into stage three where the body's capacity to withstand them is surpassed by the consequences of exhaustion and depleted reserves. Extreme psychological stress impacts on the complex regulation of emotion by the brain and on human psychological resilience and vulnerability to psychopathology (Charney, 2004).

The concepts of allostasis and allostatic load link the protective and survival values of the acute response to stress to the adverse consequences that result if the acute response persists and becomes chronic (McEwen & Wingfield, 2003). An allostatic state may result from an imbalance of the primary mediators, reflecting excessive production of some and inadequate production of others (McEwen, 2005). In some cases, the stress mediators themselves can turn on the body and cause problems. If recovery from the acute event is not accompanied by an adequate homeostatic response to terminate the acute adaptive response of stress mediators, the deleterious effects on psychological and physiological function termed allostatic load occur. The allostatic load is the burden borne by a brain and body adapting to challenges, both physiological and psychological. A sustained allostatic state may ensue, termed allostatic overload. The tipping point for allostatic overload will vary among individuals. It manifests as disease e.g., chronic hypertension and the generation of atherosclerotic plaques, elevated glucocorticoids leading to insulin resistance and increased risk for cardiovascular disease, immunosuppression or elevation of inflammatory cytokines (see below).

Pathomechanism, symptoms and health consequences of chronic stress

The symptoms of stress can be multiple and affect many organ systems. The physiological stress response involves stimulation of the autonomic nervous system (ANS) and the hormonal system, with potentially negative impact on the cardiovascular system, the musculoskeletal system, the immunological system and others (Figure 1).

Fatigue and exhaustion manifest as key physical stress symptoms. Others can be gastrointestinal symptoms, headache, backache or sexual dysfunction. Psychological and emotional symptoms of stress include e.g., tension, irritability, anxious or depressive mood, bad temper and the feeling of losing control. Concomitantly, changes in cognition, including forgetfulness and inability to concentrate may occur. Behavioural symptoms of stress include social withdrawal, alcohol and cigarette abuse, eating disorders, proneness to mistakes and work absence (Edwards, Heufelder, & Zimmermann, 2012; Milczarek et al., 2009).

These symptoms result from several postulated pathomechanisms. The HPA axis is one of the main stress response pathways. Stress induces the release of corticotropin releasing hormone (CRH) in the hypothalamus. This activates the pituitary gland to release adrenocorticotropic hormone (ACTH). The latter stimulates the release of adrenaline, noradrenaline and cortisol in the adrenal gland. The actions of this hormone system are tightly regulated normally to ensure that the organism can respond quickly and adequately to stress, via negative feedback mechanisms, levels of hormones e.g., cortisol return to normal values.

Chronic stress, however, results in persistently elevated levels e.g., of cortisol, as demonstrated in animal and cell models. Studies of rabbits under immobilisation stress revealed an

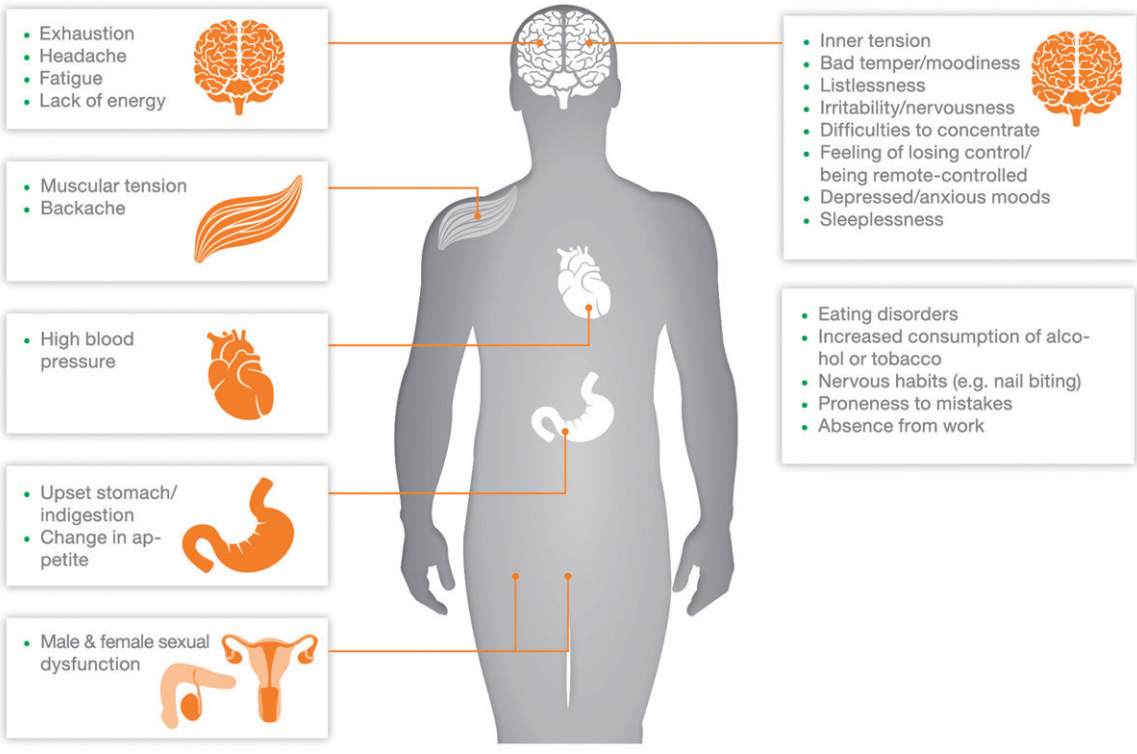

Figure 1. Multi-faceted symptoms of stress.

activation of e.g., stress-activated protein kinase/Jun N-terminal protein kinase (SAPK/JNK) (Panossian, Hambardzumyan, Hovhanissyan, & Wikman, 2007). Previous studies, e.g., with mouse hippocampal (HT22) cells, indicate that JNK leads to an inhibition of glucocorticoid receptor function. This again results in a blockade of the negative feedback mechanism of cortisol release (see Figure 2(A); Panossian, 2013; Panossian et al., 2007; Wang et al., 2005). Consequently, cortisol levels in the blood remain high which may lead to fatigue, depression, impaired cognitive performance, hyperglycaemia, high blood pressure and other health problems as a long-term consequence.

At the intracellular level, high cortisol levels impact on the balance between trophic and atrophic factors within neurones, thus affecting neurogenesis and brain plasticity in the hippocampus and frontal cortex, which results in neurodegenerative changes involved in mood regulation (Gould & Tanapat, 1999).

Investigations with rat cells showed that the release of SAPK leads to an increase in nitric oxide (NO) release (Guan, Buckman, Springer, & Morrison, 1999). The latter impairs both glycolysis and mitochondrial function which results in a decrease in adenosine triphosphate (ATP) synthesis (see Figure 2(B); Brown, 2001; Giulivi, 1998). Low ATP levels are associated with symptoms such as loss of energy, fatigue and exhaustion (Panossian, 2013; Panossian & Wikman, 2009).

A role of inflammatory mechanisms involving cytokines has also been hypothesised in chronic stress-related mental diseases, such as depression, anxiety or dementia (Bagyinszky et al., 2017; Kim et al., 2017).

An association between type 2 diabetes and depression has recently been explained, to some extent, by unspecific pathophysiological mechanisms involved in the stress response (Berge & Riise, 2015). Chronic stress is also associated with an increased risk of cardiovascular disease (CVD) (Bot & Kuiper, 2017; Nabi et al., 2013). Long-term work stress accounts for an estimated 16% of male and 22% of female CVD in the EU (Houtman, 2005). Recent studies report that the activity of the amygdala, a key component of the brain involved in emotion and stress, is of predictive value for the incidence of acute cardiovascular events during a median follow up period of 3.7 years among nearly 300 individuals with no prior history of CVD (Tawakol et al., 2017).

Burnout

Burnout is a stress disorder of unspecific risk stage which is characterised by symptoms of mental exhaustion and physical fatigue,

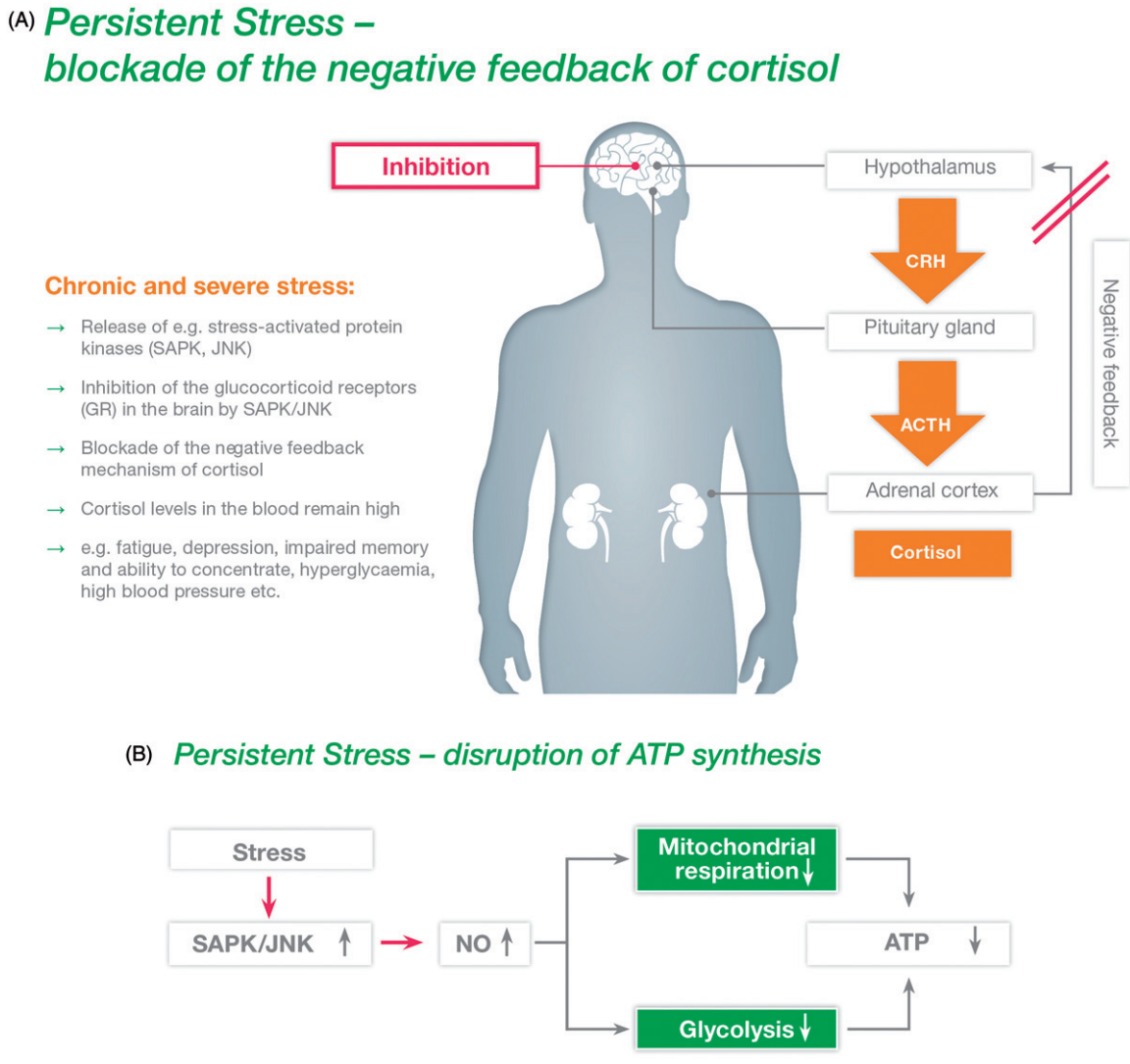

Figure 2 (A) Postulated pathomechanisms of stress: persistent stress leads to a blockade of the negative feedback of cortisol. (Adapted from Panossian, 2013; Panossian et al., 2007). (B) Postulated pathomechanisms of stress: persistent stress leads to a disruption of ATP synthesis. (Adapted from Panossian & Wikman, 2009).

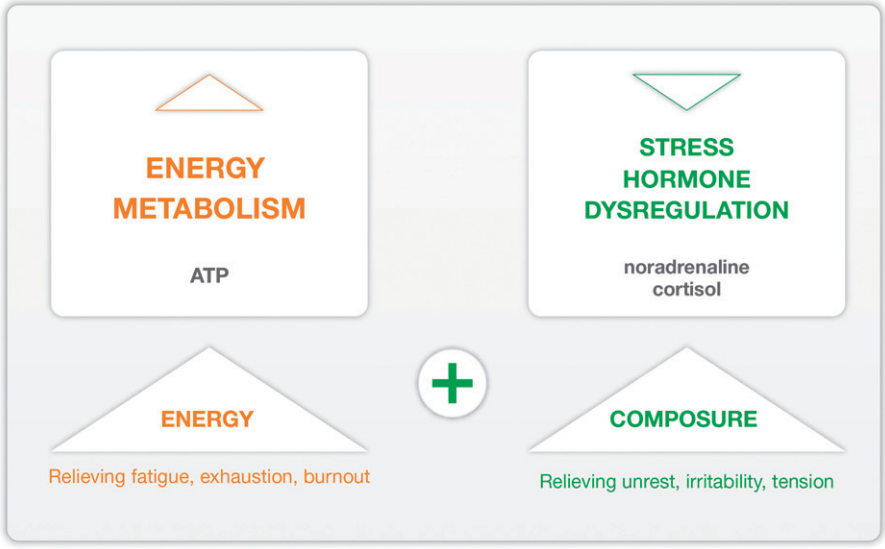

Figure 3. Proposed model for the mode of action of *Rhodiola rosea* extract (RRE): normalisation of stress hormone release and activation of ATP synthesis.

cynicism or depersonalisation and reduced personal accomplishment (Hochstrasser et al., 2016). It represents a risk factor not only for psychiatric diseases such as depression and anxiety, but also for cardiovascular, metabolic and other somatic diseases. Work-related burnout has been associated with an increased 10-year mortality risk (Ahola, Väänänen, Koskinen, Kouvonen, & Shirom, 2010). Thus, the prevention of burnout deserves special attention.

The usual non-pharmacological treatment is cognitive behavioural therapy or psychotherapy and there is currently no specific pharmacological treatment for burnout. Several biomarkers have been tested for association with burnout, but the results are contradictory and there are currently no established biochemical markers which can be considered as reliable indicators for burnout (Danhof-Pont, van Veen, & Zitman, 2011).

Stress-vulnerability and resilience, respectively, play an important role in the predisposition for, or resistance against, burnout and are an area of focus in stress research. The stress-vulnerability model was first hypothesised by Zubin and Spring (1977) to identify and treat relapses of mental illness. It suggests that people inherit a genetic predisposition to mental illness. This vulnerability in itself is not sufficient to manifest the disorder and requires interaction with bio-pyscho-social stressors (Goh & Agius, 2010). Increased vulnerability is potentially influenced by genetic factors and/or individual stress experience and may lead to decreased resilience to stress. Conversely, stress overload and burnout may be prevented by enhancing resilience. Hence, the prevention of burnout and exhaustion by enhancement of resilience on the one hand and by the adequate treatment of stress symptoms on the other is very important and appears to be an area of a considerable unmet medical need.

Stress management strategies

Popular coping strategies, such as distraction, physical activities, relaxation, socialising and healthy food, may be employed in order to get out of the stressful situation with the aim of regaining inner calm and strength. The usual form of care for work-related chronic stress is coaching, using a cognitive-behavioural approach whose primary aim is to reduce symptoms and improve functioning (Schoutens, Frings-Dresen, & Sluiter, 2016). As an alternative non-pharmacological approach, mindfulness-based stress reduction is a clinically standardized meditation technique that has demonstrated an effect on stress reduction in healthy people, with benefit similar to that of standard relaxation training (Chiesa & Serretti, 2009).

However, many modern stressors are persistent and the body's capacity to withstand them is surpassed by the consequences of exhaustion and depleted reserves, leading to burnout (German Association for Psychiatry, Psychotherapy and Psychosomatics [DGPPN], 2012). Thus, as mentioned above, the areas of unmet clinical need for intervention may be identified in two stages: as a preventive treatment in a patient with stress or a lack of vitality to avoid the development of chronic stress or exhaustion, and secondly, as a first-line treatment when persistent stress and exhaustion are present, to avoid burnout and secondary diseases. It should not be the goal of a treatment strategy to make one keep going while neglecting the signs and symptoms of exhaustion, but rather to assist in coping with temporary unusual demands, allowing for rapid readaption to normal states once the stressful situation has subsided.

Pharmacological interventions

If stress symptoms persist, together with continuously demanding life circumstances that cannot easily be avoided, pharmacological intervention may become necessary to prevent serious mental and social sequelae. However, current pharmacotherapy reveals a treatment gap. Many herbals, vitamin combinations or prescription medicines tend to focus only on single symptoms, rather than comprehensively on all aspects of stress or burnout. Besides, psychiatric prescription drugs like antidepressants, anxiolytics or β-blockers are mostly indicated for more severe diseases, such as depression or anxiety and there is a risk of overtreatment including severe side effects and/or risk of dependency.

Herbal treatment options or other drugs available over-the-counter (OTC) tend to focus either on increasing/preserving energy reserves (treatment of physical symptoms) or on promoting relaxation (treatment of psychological symptoms). For example: those acting as energisers, including vitamins/minerals and tonics; and those acting on mood, relaxation and sleep, such as St. John's wort, valerian, passion flower, lavender and antihistamines. An ideal pharmacological therapy should offer a comprehensive treatment of all relevant stress symptoms combined with a favourable safety profile.

Table 1. Clinical studies with *Rhodiola rosea* extract (RRE) in subjects with stress symptoms.

Reference	Study design	Patient population	Treatment	Duration	Outcome measures	Results
Heldmann et al. (2016)	Single centre, open-label pilot study	50 healthy male and female computer workers (30–50 years)	RRE (WS® 1375; Rosalin®) 200 mg BID	12 weeks	Effects on attention and task performance (reaction time and error rate). Event-related brain potentials were measured.	Treatment led to an increase of attention resources under a strong attention burden (simulated multitasking). Treatment also led to an increase in both working speed and working quality.
Cropley et al. (2015)	Open-label, randomised (vs. control), repeated measures	$n = 80$ mildly anxious participants (18–35 years), with score >30 on Spielberger State-Trait Anxiety Inventory (STAI)	RRE (WS® 1375, Rosalin®) 200 mg BID	2 weeks	STAI; Perceived Stress Scale; Profile of Mood States Inventory; Milford Epworth Sleepiness Scale; Leeds Sleep Evaluation Questionnaire (LSEQ); Cognitive function tests.	Significant reduction in self-reported anxiety, stress, anger, confusion and depression; significant improvement in total mood; no impairment in cognitive performance versus control.
Edwards et al. (2012)	Open, multicentre, single-arm	$n = 101$: male ($n = 33$) and female ($n = 68$) outpatients (44.5 ± 7.5 years), with distinct stress symptoms treated in general practice	RRE (WS® 1375, Rosalin®) 200 mg BID	4 weeks	Seven Numerical Analogue Scales (NAS) of subjective stress symptoms measures; Perceived Stress Questionnaire (PSQ); Multidimensional Fatigue Inventory 20 (MFI-20); Numbers Connecting Test (NCT); Sheehan Disability Scale (SDS); Multidimensional Mood State Questionnaire (MDMQ); Clinical Global Impression.	All outcome variables showed clinically relevant improvement in stress symptoms, fatigue, quality of life, mood, concentration, disability, functional impairment and overall therapeutic effect. Significant improvements were observed after three days of treatment and continued for four weeks.
Darbinyan et al. (2000)	Randomised, placebo-controlled, double-blind, cross-over	$n = 56$ healthy physicians (24–35 years)	Standardised SHR-5 RRE (4.5 mg salidroside) 170 mg OD	3×2 weeks	Anti-fatigue effect during night duty using five different tests.	Less fatigue in medical doctors on night duty with treatment versus placebo after two weeks of treatment.

Adaptogens

The term 'adaptogen' is used to describe medicinal plants that have the capacity to normalise body functions and strengthen systems compromised by stress and are able to enhance the 'state of non-specific resistance' of an organism to stress described above as allostasis. The Committee on Herbal Medicinal Products (HMPC) which is the European Medicines Agency's (EMA) committee responsible for compiling and assessing scientific data on herbal substances, preparations and combinations developed the reflection paper on the adaptogenic concept (EMA, 2008).

In this paper, adaptogens are defined as virtually non-toxic to the recipient. They are non-specific in pharmacological properties and act by increasing the resistance of an organism to a broad spectrum of adverse biological, chemical and physical factors. Adaptogens act as regulators with a normalising effect on the various organ systems and their effect is the more pronounced the deeper the pathologic changes in the organism are.

As such, adaptogens should be differentiated from traditional herbal medicinal products of related action, such as tonics and stimulants. The EMA has established HMPC monographs on many herbals including some adaptogens, i.e., preparations deriving from *Eleutherococcus senticosus, Panax ginseng* and *Rhodiola rosea*. These monographs cover their therapeutic use and safety as registered drugs.

Rhodiola rosea extract (RRE)

Extract from the roots and rhizomes of *Rhodiola rosea* (RRE) is an adaptogen that acts to increase the body's resistance to stress, exhaustion and fatigue. It is the main adaptogen given the indication 'stress' by the HMPC (European Medicines Agency's [EMA], 2011, 2012). A wide variety of preclinical *in vivo* and *ex vivo* studies conducted in cell lines and animal models have elucidated the presence of several biochemical and pharmacological stress-reducing actions of RRE. It possesses a unique mechanism of action: it normalises the release of stress hormones while simultaneously boosting energy metabolism via activation of ATP synthesis in mitochondria (Figure 3; Abidov, Crendal, Grachev, Seifulla, & Ziegenfuss, 2003; Olsson, von Schéele, & Panossian, 2009; Panossian et al., 2007). Blood levels of several stress mediators (e.g., p-SAPK/p-JNK, NO, cortisol) were assessed in rabbits under immobilisation stress; in the animals under stress that received placebo the levels of the above-mentioned markers were significantly elevated while in animals which received RRE (1 mg/kg for seven days) the stress mediators remained virtually unchanged (Panossian et al., 2007). In other studies, rats treated with RRE (50 mg/kg) exhibited a significantly prolonged duration of exhaustive swimming in comparison with untreated rats. Furthermore, RRE induced the (re)synthesis of ATP in rat mitochondria from skeletal muscles and stimulated recovery after exercise (Abidov et al., 2003).

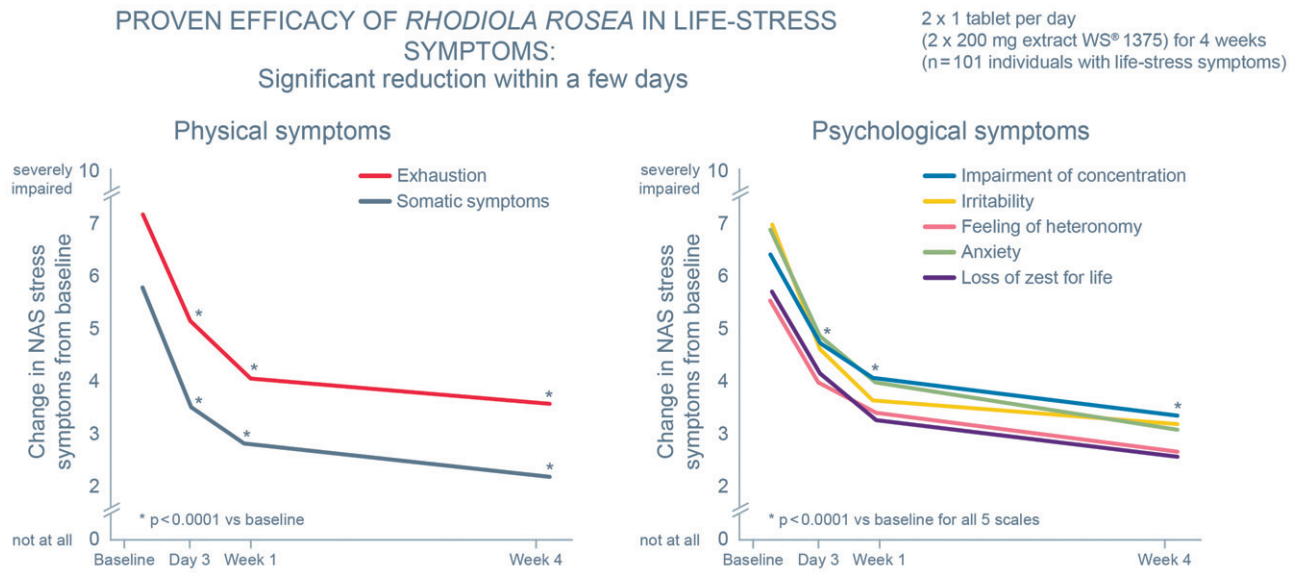

Figure 4. Efficacy of *Rhodiola rosea* extract (RRE) in management of life stress symptoms. NAS: Numerical Analogue Scales-rating of symptoms from 0 (not at all) to 10 (severely impaired). (Adapted from Edwards et al., 2012).

RRE acts to normalise cortisol synthesis potentially through inhibition of the SAPK pathway involved in the pathogenesis of glucocorticoid resistance, which is also found in certain chronic immune/inflammatory diseases and in some patients with depression (Panossian, 2013; Panossian et al., 2007). At the same time, through inhibition of the SAPK/JNK pathway, RRE potentially prevents the formation of NO and the associated decline in ATP synthesis (Guan et al., 1999; Panossian & Wikman 2009).

Stress leads to a damage of the mitochondrial function and the excessive production of reactive oxidative species (ROS) in mitochondria, which may cause damage e.g., to proteins, nucleic acids, and membranes, which in turn can lead to activation of cell death processes such as apoptosis (Zhang, Wu, Lu, Guo, & Ma, 2006). RRE may also offer potential protection against heart and brain diseases (e.g., heart attack, stroke, depression and Alzheimer's disease) through anti-oxidative/anti-inflammatory mechanisms (Lee et al., 2013; Olpe & Seifritz, 2014; Zhang et al., 2016).

RRE products with medicinal drug status must fulfil high pharmaceutical requirements with regard to their quality and safety, e.g., products containing RRE WS® 1375 (Rosalin®). It should also be noted that there are many dietary supplements available which contain *Rhodiola rosea* drug or extracts that do not comply with the high standards set by the HMPC and pharmaceutical quality requirements for registered medicinal drugs.

Clinical studies with RRE

In several clinical studies of stress, burnout and chronic fatigue, RRE was found to be effective, safe and well tolerated.

Stress symptoms

In clinical studies, mental work capacity, attention, task performance and overall mood improved during the course of treatment with RRE and stress and self-reported mild anxiety were reduced (Table 1; e.g., Cropley, Banks, & Boyle, 2015; Darbinyan et al., 2000; Edwards et al., 2012; Heldmann, Roth, Dienel, & Münte, 2016).

Among people suffering from life-stress symptoms, clinically relevant improvement in stress symptoms, stress-related disabilities in work, social and family life, functional impairment and overall therapeutic effect were observed with RRE treatment over four weeks (Figure 4; Edwards et al., 2012). In this single-arm study, adult subjects with life-stress symptoms ($n = 101$) treated in general practice received open-label RRE (200 mg, twice-daily). Seven widely recognised questionnaires to cover various aspects of stress symptoms and psychological well-being were employed to assess the outcome of treatment. Invariably, all outcome variables showed significant, consistent and steady improvement in stress symptoms, fatigue, quality of life, mood, concentration, disability, functional impairment and overall therapeutic effect. The improvements were observed as early as after three days of treatment and continued throughout the whole study duration of 28 days.

RRE has also demonstrated positive effects in the treatment of symptoms of mild anxiety associated with stress. Among students with self-reported anxiety and stress ($n = 81$) who were randomised to receive either RRE or a control (no treatment), the RRE group reported a significant reduction in self-reported anxiety, anger, confusion, stress and vigour at 14 days and a significant improvement in total mood as compared with the no treatment group (Cropley et al., 2015).

The effect of RRE on neuropsychological and neurophysiological measures of attention and mental resource allocation has recently been studied (Heldmann et al., 2016). The results of this trial of 50 healthy volunteers (aged 30–50 years) at risk for stress symptomatology showed increased performance under multi-tasking conditions over the course of RRE administration for 12 weeks. Overall, RRE had a positive influence on attention and mental resource allocation and thus on speed and quality of performance under conditions of high cognitive demand.

In an earlier study, the effect of RRE on healthy physicians on night duty ($n = 56$) was evaluated using a combination of tests that measured overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, calculation and ability of concentration and speed of audio-visual perception. A significant improvement in these test results was observed in the RRE group during

Table 2. Clinical studies with *Rhodiola rosea* extract (RRE) in subjects with chronic fatigue.

Reference	Study design	Patient population	Treatment	Duration	Outcome measures	Results
Lekomtseva et al. (2013)	Open, multicentre, single-arm	One hundred male and female outpatients (18–60 years) with chronic fatigue symptoms	RRE (WS® 1375, Rosalin® 200 mg BID	8 weeks	Multidimensional Fatigue Inventory 20 (MFI-20) measures; three Numerical Analogue Scales (NAS) of chronic fatigue symptoms; Sheehan Disability Scale (SDS); Number Connecting Test (NCT); Pittsburgh Sleep Quality Index (PSQI); Recent Perceived Stress Questionnaire (PSQ-R); Beck's Depression Inventory (BDI-II); Clinical Global Impression (CGI).	Statistically significant improvement in all dimensions of chronic fatigue symptoms (MFI-20 and NAS) from week 1–8 ($p < .001$) and concomitant conditions related to CF comorbidity and general well-being (PSQI, PSQ-R, BDI-II, SDS and NCT).
Olsson et al. (2009)	Randomised, placebo-controlled, double-blind, parallel-group	Sixty adult (20–55 years) burnout patients experiencing difficulties equivalent to the criteria of fatigue syndrome	Proprietary SHR-5 RRE 288 mg BID	4 weeks	Quality of life (SF-36 questionnaire); symptoms of fatigue (Pines burnout scale); depression (Montgomery - Asberg depression rating scale - MADRS); attention (Conners computerised continuous performance test II - CCPT II) and saliva cortisol response to awakening were assessed on day 1 and after 28 days of medication.	Anti-fatigue effect that increased mental performance, particularly the ability to concentrate, and decreased cortisol response to awakening stress. Significant effects of SHR-5 RRE in comparison with placebo were observed in Pines burnout scale and the CCPT II indices omissions, Hit RT SE, and variability.

the two-week treatment period, suggesting that RRE can reduce general fatigue under certain stressful conditions (Darbinyan et al., 2000).

Chronic fatigue symptoms and exhaustion

Unexplained chronic fatigue is a widespread healthcare problem that significantly affects the working population (Jackson & Macleod, 2017) and which is often associated with stress. First-line treatments are cognitive behavioural or graded exercise therapy (Daniels & Loades, 2017). However, these treatments yield only moderate effect sizes. RRE is shown to improve mental performance in people with stress-related fatigue and further to improve all dimensions of chronic fatigue symptoms (Table 2; Lekomtseva, Zhukova, & Tartakovsky, 2013; Olsson et al., 2009).

In a double-blind study, participants ($n = 60$) selected according to diagnostic criteria for fatigue syndrome were randomised to receive RRE (576 mg extract/day) or placebo for four weeks. Significant effects of RRE in comparison with placebo were observed for symptoms of fatigue (Pines burnout scale) and in tests of attention (Connors computerised continuous performance test II [CCPT II]). Pre- versus post-treatment cortisol responses to awakening were significantly different in the treatment group compared with the control group. Thus, RRE is found to exert an anti-fatigue effect that increases mental performance, particularly the ability to concentrate and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome (Olsson et al., 2009).

Significant improvements in specific chronic fatigue outcomes (e.g., multi-dimensional fatigue inventory 20 [MFI-20], recent perceived stress questionnaire [PSQ-R], Sheehan disability scale [SDS]) have been demonstrated with RRE treatment among 101 patients with chronic fatigue treated in an open-label, single-arm study for up to eight weeks ($p < .001$). Furthermore, the results of the trial supported the therapeutic effect on concomitant conditions related to chronic fatigue such as mood, concentration, quality of life and general well-being which was demonstrated with RRE treatment (200 mg, twice-daily; Lekomtseva et al., 2013).

Burnout symptoms

The aim of the treatment of stress and burnout with an adaptogen is to increase stress resistance, thus addressing the source rather than the symptoms of the syndrome and preventing subsequent diseases associated with a history of burnout. The core indicators of burnout are subjective perceptions of chronic demand-related stress with subsequent emotional exhaustion and decreased performance in work-related or self-set tasks. Reported symptoms of burnout comprise not only psychiatric or mood disorders such as fatigue, cynicism, impaired sexual life, lack of concentration or a generally negative attitude toward work, but also somatic symptoms such as headaches, hypertension or irritable stomach. Treatment with RRE for eight and 12 weeks, respectively, was accompanied by a clear improvement in burnout symptoms (Table 3; Goyvaerts & Bruhn, 2012; Kasper & Dienel, 2017).

Investigating the effects of RRE on burnout-related symptoms, a German non-interventional study was conducted in 128 primary care practices and included 330 patients with two or more burnout indicator symptoms (exhaustion, depression, insomnia, fatigue or drop in performance). A considerable alleviation of these symptoms after the administration of RRE for eight weeks was reported based on the results of the self-rating questionnaires used in this trial (Goyvaerts & Bruhn, 2012).

An exploratory single-arm, multi-centre study investigated the clinical outcomes in burnout patients ($n = 118$) treated with RRE

Table 3. Clinical studies with *Rhodiola rosea* extract (RRE) in subjects with burnout symptoms.

Reference	Study design	Patient population	Treatment	Duration	Outcome measures	Results
Kasper and Dienel (2017)	Open, multicentre, single-arm	$n = 118$ male ($n = 49$) and female ($n = 68$) outpatients (44 ± 8 years) with burnout symptoms	RRE (WS® 1375, Rosalin®) 200 mg BID	12 weeks	Seven Numerical Analogue Scales (NAS) of subjective stress symptoms; Burnout-Screening-Scales BOSS I and BOSS II; Maslach-Burnout-Inventory (MBI); Perceived Stress Questionnaire (PSQ); Numbers Connecting Test (NCT); Sheehan Disability Scale (SDS); Clinical Global Impression (CGI); Multidimensional Mood State Questionnaire (MDMQ); Patient questionnaire for sexual function (PSFQ); Numerical Analogue Scales of Subjective Stress Symptoms (NAS).	Treatment caused a significant and clinically relevant improvement in burnout symptoms from week 1 to week 12 (NAS, BOSS I and II, NCT, CGland MDMQ).
Goyvaerts and Bruhn (2012)	Open, multicentreand single-arm	330 patients (> 18 years) with at least two of the following symptoms: exhaustion, depression, insomnia, fatigue and drop in performance	Proprietary SHR-5 RRE 288 mg BID	8 weeks	Burnout total score.	Significant improvement in burnout symptoms total score after 4–8 weeks.

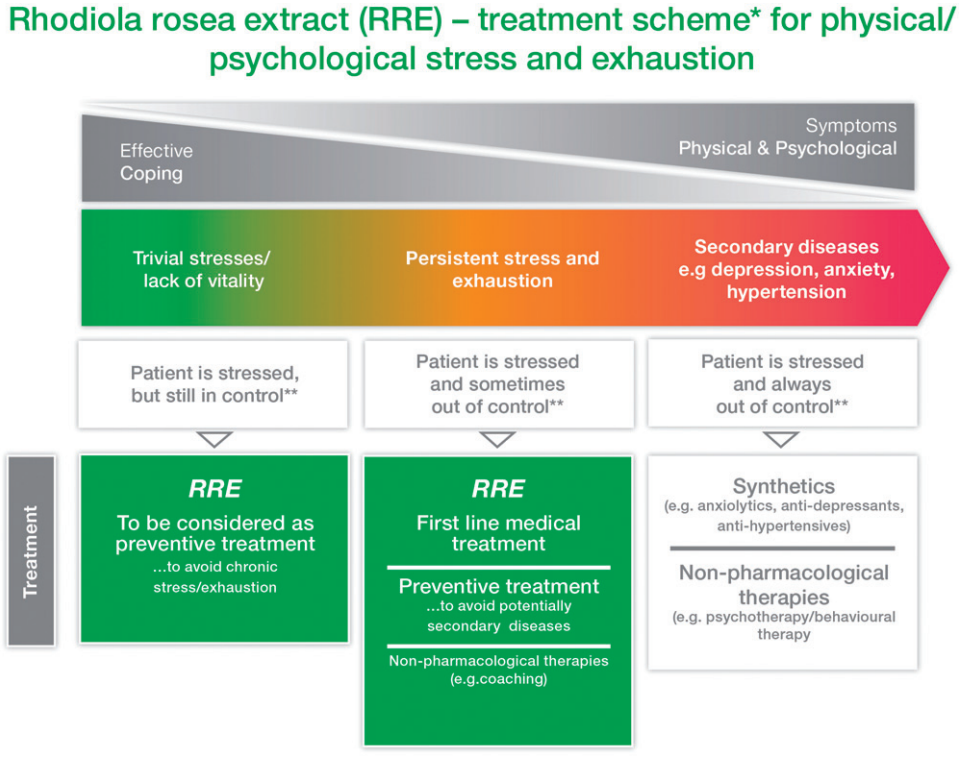

Figure 5. Intervention stages for treatment of physical/psychological stress and exhaustion. Patients with medical conditions that may result in symptoms of stress and exhaustion such as anaemia, migraine, IBS (irritable bowel syndrome), cancer and hormonal disturbances, may also receive RRE after assessment and management of the medical condition. **'Control' in this context means: normal functioning in daily life.

(200 mg, twice-daily) over 12 weeks. The aim of the treatment with RRE was to increase stress resistance and thus to aim at the source rather than at the symptoms of the syndrome and to further prevent subsequent diseases associated with a history of burnout. A broad spectrum of rating scales was employed to evaluate the therapeutic effect of RRE in the treatment of burnout symptoms, such as fatigue, cynicism, difficulties to concentrate, impaired sexual life and also somatic symptoms. A wide range of the evaluated outcome measures improved considerably over the course of treatment. Some of these changes were already

significant after the first week of RRE administration (Kasper & Dienel, 2017).

The trials to date, although limited in participant numbers and often exploratory in design, nonetheless provide promising results and an encouraging basis for future randomised controlled trials further investigating the clinical outcomes of RRE in patients with high symptom load of chronic stress, chronic fatigue and burnout. Clinical experience of sexual problems in individuals that were predominately due to stress have been helped by RRE and recent studies involving male and female stressed rats have confirmed this finding (Edwards, Eltbogen, & Nöldner, 2017; Edwards, Kumar, & Nöldner, 2016). RRE has also shown encouraging data in exploratory studies of diseases that can occur as a consequence of stress, including depression (Darbinyan et al., 2007) and anxiety (Bystritsky, Kerwin, & Feusner, 2008).

Safety and tolerability of RRE

RRE presents a very favourable safety profile. In clinical studies, no serious side effects that could be attributed to RRE were reported (e.g., Cropley et al., 2015; Edwards et al., 2012; Kasper & Dienel, 2017; Lekomtseva, Zhukova, & Wacker, 2017).

The HMPC monograph on *Rhodiola rosea* roots and rhizomes states that there are no known side effects (EMA, 2012). In addition, to date no drug-drug interactions have been reported for RRE (EMA, 2012).

Treatment recommendation

RRE has the potential to close the treatment gap for clinically relevant stress symptoms, which is due to its dual mode of action providing both physical and psychological symptom relief, normalising stress hormone levels and increasing energy and its excellent safety profile. RRE potentially addresses multiple aspects in the management of stress and burnout:

- Prevention of stress symptoms from becoming chronic.
- Treatment of stress symptoms.
- Prevention of stress-related complications (burnout) and secondary diseases.

Figure 5 summarises the authors' treatment recommendations for the use of RRE in various stages of stress.

Limitations

There is still much to learn about the pathophysiology of stress, resilience and stress vulnerability, including cellular and cerebral network mechanisms which are the focus of current research interests. In parallel to increasing knowledge of these phenomena, additional investigations are needed to further elucidate the impact of RRE on mechanisms that play a significant role in stress in the human body. Clinical evidence for the effect of RRE on stress and stress-related symptoms to date may be limited to studies of exploratory design; appropriate study populations are sometimes difficult to define. However, the studies so far provide promising results, especially in frequently difficult to treat populations. Further randomised controlled trials are needed to confirm the promising results of the existing studies with RRE in patients with symptoms of chronic stress, chronic fatigue and burnout.

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