A Pharmacological and Clinical Monograph of *Rhodiola rosea* and *Rhodiola crenulata*: Phytochemical, Mechanistic, and Autonomic Differentiation

1.0 Introduction: The *Rhodiola* Genus as a Pharmacological Adaptogen

1.1 Defining the Adaptogen Concept

In pharmacology, an adaptogen is a therapeutic agent that enhances the body's nonspecific resistance to stress, aiming to restore homeostatic balance across physiological systems.[1] Adaptogenic action is primarily characterized by the modulation of the body's key stress-response systems: the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS).[1–3] Specifically, adaptogens modulate the dynamic balance between the sympatho-adrenal system (SAS) and the parasympathetic nervous system (PNS).[1] A true adaptogen must normalize physiology, regardless of the direction of the stress-induced pathology; for example, it should attenuate an overactive sympatho-adrenal system while simultaneously supporting a depleted one.[5] This report analyzes the *Rhodiola* genus within this rigorous pharmacological framework.

1.2 The *Rhodiola* Genus (Crassulaceae): A Tale of Two Species

The genus *Rhodiola* (family Crassulaceae) comprises more than 90 distinct species,[4] many of which are used in traditional medicine.[6] However, two species have risen to prominence in traditional and clinical pharmacology: *Rhodiola rosea* L. and *Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba.[6]

- ***Rhodiola rosea* L.** Known colloquially as "Golden Root" or "Arctic Root," *R. rosea* has a long and well-documented history of use in Russian and Scandinavian traditional medicine to treat anxiety, fatigue, and depression, and to enhance physical endurance and work productivity.[9]
- ***Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba.** Known as "Hong Jing Tian," *R. crenulata* is a cornerstone of Traditional Chinese Medicine (TCM) and Himalayan herbalism, where it is used primarily to prevent and treat high-altitude sickness.[12]

1.3 The Central Thesis: Phytochemical Divergence and Pharmacological Specificity

A prevailing and critical issue in the global commodity market for *Rhodiola* is the widespread, and often undisclosed, substitution or adulteration of *R. rosea* with other species, most notably *R. crenulata*.[7] This is frequently dismissed as a simple quality control failure. This report argues that this is a *fundamental pharmacological substitution* that invalidates the expected clinical outcomes.

The two species are phytochemically distinct. The characteristic compounds of *R. rosea*—the rosavins—are notably absent in *R. crenulata*.[7] This report will analyze how this phytochemical divergence dictates two different, non-interchangeable pharmacological profiles. The evidence supports a model wherein *R. rosea* functions as a *stimulating* adaptogen (providing sympatho-adrenal support) due to its unique rosavin content, while *R. crenulata* functions as a *neuroprotective* adaptogen (providing parasympathetic-sparing and HPA-axis buffering effects) via its high concentration of salidroside.ù

2.0 Comparative Phytochemistry and Standardization

2.1 *Rhodiola rosea*: The Rosavin-Signature Profile

The root of *R. rosea* is a complex matrix, containing more than 140 identified chemical constituents.[10] Its pharmacological activity is attributed to two primary classes of compounds:

1. **Phenylpropanoids (Rosavins):** This class of cinnamyl alcohol glycosides is the unique, defining chemotaxonomic marker for *R. rosea*.[7] The term "rosavins" collectively refers to **rosavin**, **rosin**, and **rosarin**.
2. **Phenylethanoids:** This class includes **salidroside** (also known as rhodioloside) and its aglycone, **p-tyrosol**.[9]

The gold standard for *R. rosea* extracts used in human clinical trials, such as the proprietary extracts SHR-5 and WS 1375, is a standardization to a minimum of **3.0% total rosavins** and **0.8% to 1.0% salidroside**.[5] This specific 3:1 ratio of rosavins to salidroside is not an arbitrary formulation; it was designed to mimic the naturally occurring ratio of these compounds found in the raw plant material.[15] This strongly suggests that the clinically validated adaptogenic effect of *R. rosea* is a synergistic or additive effect derived from this specific phytochemical fingerprint, rather than the action of a single isolated compound.

2.2 *Rhodiola crenulata*: The Salidroside-Dominant Profile

Rhodiola crenulata is phytochemically distinct from *R. rosea* in one critical aspect: it **lacks the rosavins**.[7] Its pharmacological profile is instead dominated by its high content of phenylethanoids, primarily **salidroside** and **p-tyrosol**.[21]

Metabolomic analyses comparing the two species have confirmed that *R. crenulata* possesses higher total phenolic content and demonstrates greater *in vitro* antioxidant activity than *R. rosea*, effects that are attributed to its high concentration of salidroside.[12] Consequently, commercial *R. crenulata* extracts are

standardized *only* to their salidroside content, which typically ranges from 2.0% to 4.0%.[14]

This phytochemical divergence provides a clear framework for analysis. *R. crenulata* can be viewed as a "high-salidroside, zero-rosavin" intervention, while the standardized *R. rosea* extract functions as a "high-rosavin, moderate-salidroside" combination therapy.

3.0 Pharmacology of Salidroside (The Shared Neuroprotective Agent)

Salidroside is the primary bioactive compound common to both species and many others in the genus.[7] Its pharmacology establishes the baseline neuroprotective and HPA-axis-buffering effects of *Rhodiola* extracts.

3.1 Pharmacokinetics (PK) of Salidroside

- **Absorption:** Preclinical studies in rats indicate that the intestinal absorption of salidroside is not simple diffusion but a saturable process. Evidence suggests it is actively transported via the **sodium-dependent glucose transporter (SGLT)**.[25] This transport mechanism implies a direct competition for absorption with glucose. This finding has significant posological implications, suggesting that the bioavailability of salidroside-dominant extracts (*R. crenulata*) may be inhibited if administered concurrently with a high-carbohydrate meal.
- **Distribution:** Following intravenous administration in rats, salidroside distributes widely, with notable concentrations found in skeletal muscle, ovary, and testis. Plasma levels generally remain higher than tissue levels.[25]
- **Metabolism:** Salidroside is a glycoside of tyrosol and is metabolized to its active aglycone, **p-tyrosol**.[27] Emerging research underscores the critical role of the **gut microbiota** in this metabolic conversion and in mediating the downstream biological effects of salidroside, particularly its anti-inflammatory and anti-atherosclerotic properties.[28] This reliance on the host microbiome suggests a high potential for inter-individual variability in clinical efficacy.
- **Excretion:** Excretion appears limited. In preclinical models, only a very small percentage of the administered dose (2.86% after intravenous injection, 0.02% after gavage) is recovered in the bile.[27]

3.2 Pharmacodynamics (PD) and Mechanisms of Salidroside

Salidroside is a multi-target compound [29] that primarily functions as a homeostatic buffer and neuroprotective agent.

- **3.2.1 Molecular and *In Silico* Targets:** Salidroside's actions are broad, affecting key signaling pathways related to stress, inflammation, and cellular survival.
    - ***In silico* Analysis:** Molecular docking simulations have identified high binding affinities for several key stress-regulating proteins. These include **FKBP51**, a co-chaperone that decreases the sensitivity of the glucocorticoid receptor (GR), suggesting salidroside may restore GR function.[30] Other targets include **Galectin-3** and **Galectin-9**, which are implicated in neuro-

angiogenesis and inflammation.[31]
    - **Anti-inflammatory and Antioxidant Action:** *In vitro* studies have repeatedly demonstrated that salidroside exerts potent antioxidant effects by scavenging reactive oxygen species (ROS).[21] It provides significant anti-inflammatory effects by inhibiting the phosphorylation and activation of the **MAPK**, **NF-κB**, and **STAT3** signaling pathways.[28]
    - **Anti-Hypoxia:** Salidroside has demonstrated protective effects against hypoxia-induced cellular damage *in vitro* [25], a mechanism that provides a clear biological basis for the traditional use of *R. crenulata* in high-altitude conditions.
- **3.2.2 Neuroendocrine (HPA Axis) Modulation:** This is the primary adaptogenic mechanism of salidroside. It functions as a classic HPA-axis reset.
    - In animal models of chronic stress, salidroside directly modulates the HPA axis by attenuating the expression of **corticotropin-releasing hormone (CRH)** in the hypothalamus.[34]
    - This upstream action leads to a normalization of elevated serum **corticosterone** (the rodent equivalent of cortisol).[34]
    - Most importantly, salidroside has been shown to increase **glucocorticoid receptor (GR)** levels in the hippocampus.[34] This action is critical, as it enhances the sensitivity of the HPA axis's negative feedback loop, allowing the brain to more efficiently terminate the stress response and preventing the pathogenic cascade of chronic cortisol exposure.
- **3.2.3 Neurotransmitter Homeostasis:** Salidroside does not appear to be a primary stimulant but rather a homeostatic regulator of neurotransmitter systems depleted by stress.
    - It modulates monoamine neurotransmission by affecting their release, degradation, and reuptake.[34] *In vivo* studies in stressed rats show that salidroside administration can increase levels of **serotonin (5-HT)**, **norepinephrine (NE)**, and **dopamine (DA)** in the brainstem and prefrontal cortex.[34]
    - It also provides a neuroprotective effect against stress-induced excitotoxicity by modulating the balance between the excitatory neurotransmitter glutamate (which is elevated in stress) and the primary inhibitory neurotransmitter, GABA.[36]

In summary, the pharmacodynamic profile of salidroside is that of a *neuroprotective buffer*. It does not block the stress response but rather prevents it from becoming pathogenic by enhancing HPA-axis negative feedback, protecting against oxidative stress, and preventing the depletion of key monoamine neurotransmitters. This positions it as an ideal agent for managing chronic stress and enhancing resilience.

4.0 Pharmacology of Rosavins (The *R. rosea* Stimulating Agent)

The rosavins (rosavin, rosin, and rosarin) are unique to *R. rosea* and are responsible for the distinct, stimulating pharmacology of its extracts.[7]

4.1 Pharmacokinetics (PK) of Rosavins

The pharmacokinetics of rosavins present a significant pharmacological paradox.

- **Absorption and Bioavailability:** Preclinical data for rosavin, the primary glycoside in this class, indicates a **very low oral bioavailability of only 4.7%**.[37]
- **Metabolism:** This poor absorption is attributed to the hydrolysis of the cinnamyl-glycosidic bond in the acidic environment of the gastrointestinal tract, as well as significant first-pass metabolism.[37]

This presents a critical question: If the primary biomarker compounds (rosavins) for *R. rosea* are so poorly absorbed, how do the 3% rosavin extracts demonstrate such robust clinical efficacy?[38] This paradox suggests several possibilities: 1) The small fraction of rosavin that is absorbed is exceptionally potent; 2) The rosavins are prodrugs, and their metabolites (eg, the aglycone, rosin) are the true active compounds; or 3) Most plausibly, the rosavins are not intended to act in isolation but function *synergistically* with salidroside, perhaps altering its absorption, distribution, or action at the receptor level to produce the total effect of the 3:1 extract.

4.2 Pharmacodynamics (PD) and Mechanisms of Rosavins

While the PK is poorly understood, the PD effects of rosavin-containing extracts are clearly defined as stimulating and anti-fatigue.

- **4.2.1 Central Nervous System (CNS) Effects:** Preclinical models using the 3% rosavin/1% salidroside *R. rosea* extract demonstrate significant **CNS-stimulating**, antidepressant-like, and anxiolytic-like effects *after a single dose*.[5] This manifests as increased locomotor activity in mice [40] and reduced immobility time in the forced-swim test [5], a classic indicator of antidepressant and stimulating activity.
- **4.2.2 Enzymatic Inhibition (Monoamine Modulation):** This is the most widely hypothesized mechanism for the stimulating and antidepressant effects of *R. rosea*.
    - *In vitro* and *in vivo* studies suggest that *R. rosea* extracts (and by extension, the rosavins) function as inhibitors of **monoamine oxidase A (MAO-A)** and **MAO-B**.[5]
    - Inhibition of MAO-A and MAO-B prevents the enzymatic degradation of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin), thereby increasing their synaptic concentration and duration of action.
    - Some evidence also points to the inhibition of a second enzyme, **Catechol-O-methyltransferase (COMT)** [43], which is also involved in the degradation of catecholamines.
- **4.2.3 Receptor Modulation (Hypothesized):** Grey literature and preclinical reviews suggest that rosavin-containing extracts may also directly modulate neurotransmitter systems by binding to **GABA receptors** [5] and modulating **5-HT1A receptors**.[5]

The rosavin component of *R. rosea* provides a direct, *activating* mechanism (monoamine oxidase inhibition) that is absent in *R. crenulata*. This action directly increases levels of dopamine and norepinephrine, providing a clear pharmacological basis for the "stimulating" and "anti-fatigue" effects observed in human trials.[5]

5.0 The Critical Ratio: Synthesizing Sympathetic and Parasympathetic Effects

The pharmacological data reveals that *R. rosea* (3:1 extract) is a combination therapy (Salidroside + Rosavins), while *R. crenulata* is a mono-therapy (Salidroside only). The differentiation of their effects on the autonomic nervous system (ANS) is best demonstrated by preclinical studies that directly compare the two.

5.1 The Keystone Preclinical Study: Abidov et al (2003)

This preclinical study is the most critical piece of evidence for differentiating the two species, as it directly compares their effects in a *sympathetic-loaded* model: exhaustive physical exercise.[42]

- **Performance Finding:** Rats administered an *R. rosea* extract (50 mg/kg) demonstrated a **24.6% increase** in exhaustive swimming time compared with controls. Rats administered the *exact same dose* (50 mg/kg) of *R. crenulata* extract showed **no significant improvement** over the control group.[45]
- **Mechanistic Finding:** The study further demonstrated that the *R. rosea* extract *activated the synthesis or resynthesis of adenosine triphosphate (ATP) in mitochondria* and stimulated reparative energy processes following the exercise. *R. crenulata* did not possess this mechanism.[45]

This study demonstrates unequivocally that the rosavin-containing fraction of *R. rosea* is responsible for the profound *in vivo* effects on mitochondrial energy production and physical anti-fatigue performance. The salidroside-only *R. crenulata* extract lacks this mechanism entirely.

5.2 Modulation of the Autonomic Nervous System (ANS)

The data from Abidov et al (2003) and other studies allows for a synthesis of the two species' differential effects on the ANS.[1]

- **Sympathetic Support (*R. rosea* Profile):** The "stimulating" effects of *R. rosea* are a clear *sympathetic-supporting* action. The rosavins provide the two key components needed to meet an acute stressor:
  1. **Metabolic Fuel:** Increased mitochondrial ATP synthesis.[45]
  2. Neurochemical Drive: Increased dopamine and norepinephrine via MAO inhibition.41
     This profile is designed to enhance performance during acute, high-demand, "fight-or-flight" events.49
- **Parasympathetic-Sparing (*R. crenulata*/Salidroside Profile):** The effect of salidroside is more subtle, focusing on buffering and resilience. A human study on a *Rhodiola*/Cordyceps supplement during high-altitude training provides the key insight.[50]
  - **HRV Data:** Heart Rate Variability (HRV), specifically the high-frequency (HF) component, is a direct, noninvasive measure of parasympathetic (vagal) tone.[50]
  - **Finding:** Chronic stress (like altitude training) causes a "withdrawal" of the parasympathetic system, seen as a significant decline in HF-HRV. In this study, the placebo group showed this expected decline. However, the *Rhodiola*-supplemented group showed a **significantly smaller**

decline in HF, indicating that the extract *attenuated the decline of parasympathetic activity*.[50]

This is the central answer to the query. Salidroside (the key driver of the *R. crenulata* profile) acts as a **parasympathetic-sparing** agent. It does not sedate; it *prevents the parasympathetic system from collapsing* under chronic stress. This is the physiological basis for anxiolysis and enhanced resilience.

5.3 Synthesis: The 3:1 Ratio as the Complete Adaptogen

The 3:1 *R. rosea* extract is the complete adaptogen because it combines both actions:

1. The **Rosavins** provide the **Sympathetic-Supporting** action: energy (ATP) and neurochemical drive (monoamines) to *perform* during an acute stressor.[41]
2. The **Salidroside** provides the **Parasympathetic-Sparing** action: HPA-axis buffering (via GR upregulation) and protection of vagal tone (HF-HRV) to *endure* chronic stress.[34]

This synergy allows for a "calm, focused, and energetic" state under pressure, as opposed to the "panicked, depleted" state of an unbuffered stress response. *R. crenulata*, lacking rosavins, provides *only* the buffering component.

6.0 Clinical Efficacy in Human Trials: Selecting the Right Extract

The preclinical differentiation is clearly reflected in the human clinical trial data.

6.1 *Rhodiola rosea* (High-Rosavin Extract): For Fatigue, Cognition, and Burnout

The human evidence for *R. rosea* (standardized 3:1 extract) is robust for conditions of *asthenia* (fatigue), burnout, and cognitive decline *under acute sympathetic-loaded events*.[9]

- **Acute Stress and Mental Fatigue:**
  - **Shevtsov et al (2003):** This landmark randomized controlled trial (RCT) evaluated 161 healthy military cadets during sleep deprivation. A *single dose* of SHR-5 (370 mg or 555 mg) resulted in a pronounced anti-fatigue effect, significantly improving cognitive function and capacity for mental work.[42]
  - **Darbinyan et al (2000):** A double-blind, placebo-controlled, crossover study in 56 healthy physicians on night duty found that a repeated low-dose regimen of SHR-5 (170 mg/day) significantly improved total mental performance and reduced fatigue.[39]
- **Chronic Fatigue, Burnout, and Mood:**
  - **Olsson et al (2009):** An RCT involving 60 individuals with stress-related fatigue found that 576 mg/day of SHR-5 for 28 days significantly reduced fatigue and burnout symptoms, improved attention [38], and, critically, showed a *normalizing effect on the cortisol awakening response*, confirming HPA-axis modulation.[38]

    - **Kasper et al (2017):** An open-label trial in 118 outpatients with burnout symptoms found that 400 mg/day of *R. rosea* extract (WS 1375) provided clear improvements in stress and depression scores, with effects beginning in the first week.[9]
- **Anxiety and Stress Perception:**
    - **Cropley et al (2015):** A trial in 81 mildly anxious students demonstrated that 400 mg/day (200 mg twice daily) significantly reduced self-reported anxiety, stress, anger, and confusion, and improved total mood.[7]
    - **Bystritsky et al (2008):** An open-label study in 10 patients with Generalized Anxiety Disorder (GAD) found that 340 mg/day for 10 weeks significantly reduced Hamilton Anxiety Rating Scale (HARS) scores.[9]

6.2 *Rhodiola crenulata* (High-Salidroside Extract): The Clinical Disconnect

The strong preclinical promise of *R. crenulata* and salidroside [21] has *not* translated into robust human clinical efficacy.

- **Chiu et al (2013):** This is the most significant human trial on *R. crenulata*, as it was a high-quality (randomized, double-blind, placebo-controlled, crossover) study in 125 adults for its primary traditional indication: Acute Mountain Sickness (AMS).[14]
- **Intervention:** 800 mg/day of *R. crenulata* extract (standardized to 2.38% salidroside).[14]
- **Result:** The extract **failed to demonstrate efficacy**. There was *no significant difference* in the incidence or severity of AMS between the *R. crenulata* group and the placebo group.[14]

This clinical failure, combined with the preclinical failure in the Abidov et al (2003) anti-fatigue model [45], indicates that *R. crenulata* extracts are not a viable substitute for *R. rosea* and are not supported by current human evidence even for their own traditional indications.

6.3 *Rhodiola* and Decision-Making Under Stress

No studies were identified that tested *Rhodiola* in isolation for decision-making tasks. However, proxy data from human experimental studies using *Rhodiola* in combination with magnesium, B vitamins, and green tea provides insight into the neurological effects under stress.[67]

- **EEG Findings:** This combination, when administered to healthy individuals under induced social stress, **significantly increased frontal midline theta wave activity** during attentional tasks.[68]
- **Subjective Findings:** The combination also attenuated subjective stress, anxiety, and mood disturbance.[67]

Increased frontal theta activity is a neurological signature of a "relaxed, alert state" [67] and is directly associated with executive function and sustained attention. This suggests that the *Rhodiola*-containing intervention helps the brain maintain attentional capacity and *resist* the shift to a purely reactive, stressed state, thereby preserving the cognitive foundation required for effective decision-making under pressure.

7.0 Summary of Evidence, Posology, and Standardization

The evidence strongly indicates that *R. rosea* and *R. crenulata* are pharmacologically distinct and should be used for different, specific purposes.

7.1 Recommendation: *Rhodiola rosea* Extract

- **Standardization:** To ensure clinical efficacy, the extract **must be standardized to *both* rosavins and salidroside**. The only clinically-validated standard is **~3% total rosavins and ~1% salidroside**.[5] An extract standardized only to salidroside is not pharmacologically equivalent, is likely *R. crenulata* [7], and will lack the anti-fatigue mechanisms.
- **Primary Application:** Conditions requiring **sympathetic support and cognitive activation**. This includes stress-related fatigue, asthenia, burnout, mental fog, and enhancing physical and mental performance under acute, high-demand scenarios (eg, examinations, night-shift work, athletic competition).[38]
- **Posology (Based on Clinical Trials):**
  - **For acute anti-fatigue/cognitive enhancement:** 370 mg to 555 mg as a single dose.[42]
  - **For chronic stress-related fatigue/burnout:** 400 mg to 600 mg per day, often in divided doses (eg, 200 mg twice daily, or 576 mg as a single morning dose).[9]
  - **For mild anxiety/mood:** 340 mg to 400 mg per day.[9]

7.2 Recommendation: *Rhodiola crenulata* Extract

- **Standardization:** Standardized to **salidroside only**, typically **2.0% to 4.0%**.[14]
- **Primary Application:** *Hypothetical* applications based on preclinical data. The strong neuroprotective [21], anti-inflammatory [33], and parasympathetic-sparing [50] mechanisms of salidroside suggest a *potential* use for chronic anxiety or as a neuroprotective agent.
- **Posology:** 800 mg/day (of a 2.38% extract) was used in the human AMS trial.[14]
- **Evidence Caveat:** The strong preclinical promise of *R. crenulata* is **not yet supported by human clinical data**. The Abidov et al (2003) preclinical study [45] strongly suggests it is *inferior* to *R. rosea* for anti-fatigue effects, and the Chiu et al (2013) human trial [14] found it *ineffective* for its primary traditional indication.

8.0 Table 1: Comparative Analysis of *Rhodiola rosea* and *Rhodiola crenulata* Extracts

Table 1 provides a summary of the core differentiators between the two primary commercial *Rhodiola* extracts.

Characteristic	**Rhodiola rosea L. (Golden Root)**	**Rhodiola crenulata (Hook.f. & Thomson) H.Ohba (Hong Jing Tian)**
Key bioactive markers	**Rosavins** (rosavin, rosin, rosarin)(a) AND Salidroside [7]	**Salidroside** AND *p*-Tyrosol [21]
Presence of rosavins	**Yes** (defining chemotaxonomic markers) [7]	**No** (or trace amounts); primary adulterant of *R. rosea* products [7]
Typical commercial standardization	**3% total rosavins** AND **1% salidroside** (Ratio ~3:1) [9]	**2.0%-4.0% salidroside** (Rosavins not specified) [14]
Primary mechanistic hypotheses	• Stimulates mitochondrial **ATP synthesis** [45] • Inhibits **MAO-A and MAO-B** [41] • Modulates HPA axis [34]	• Modulates HPA axis [34] • Inhibits **NF-κB** and **MAPK** [28] • Binds **FKBP51** [30] • Anti-hypoxia effects [25]
ANS modulation profile	**Sympathetic-supporting:** (Energy/ATP; ↑DA/NE) [45] **Parasympathetic-buffering:** (HPA modulation) [2]	**Parasympathetic-sparing:** (Attenuates HF-HRV decline) [50] **HPA-axis buffering** [34]

Hypothesized clinical effect	Stimulating adaptogen; anti-fatigue; cognitive activator [5]	Protective adaptogen; neuroprotective; anxiolytic; acclimatization [21]
Primary human trial applications	• Stress-related fatigue [38] • Burnout [9] • Mental performance under stress [58] • Mild anxiety and depression [9]	• Acute mountain sickness (AMS)(b) [14] • (Primarily preclinical data for neuroprotection) [21]
Typical clinical dosages	200 mg-600 mg daily (of 3% rosavin / 1% salidroside extract) [9]	800 mg daily (of 2.38% salidroside extract) [14]

a. Rosavins are a class of cinnamyl alcohol glycosides unique to *R. rosea*, including rosavin, rosin, and rosarin.[7]

b. The primary human RCT for *R. crenulata* in Acute Mountain Sickness *failed to show efficacy* versus placebo.[14]

9.0 Table 2: Summary of Selected Clinical and Preclinical Literature

Table 2 provides the evidential basis for this report's conclusions, focusing on key studies that differentiate the species or establish mechanisms and clinical efficacy.

Study (Reference No.)	Species & Extract (Standardization)	Model / Study Type	Dosage / Posology	Key Outcomes and Findings
Abidov et al, 2003[10]	*R. rosea* vs *R. crenulata*	Preclinical (Rat, exhaustive swim test)	50 mg/kg, oral	*R. rosea* significantly (+24.6%) prolonged swim time; *R. crenulata* had no effect. *R. rosea* activated mitochondrial ATP synthesis.[45]
Shevtsov et al, 2003[11]	*R. rosea* (SHR-5)	Human RCT (N=161 military cadets, sleep deprived)	370 mg or 555 mg (single dose)	Pronounced anti-fatigue effect; significantly improved capacity for mental work (TAFI index) vs placebo.[42]
Darbinyan et al, 2000[12]	*R. rosea* (SHR-5)	Human RCT Crossover (N=56 physicians, night duty)	170 mg/day (2 weeks)	Significant improvement in total mental performance and reduced fatigue levels vs placebo group on night duty.[39]
Olsson et al,	*R. rosea* (SHR-	Human RCT (N=60, stress-	576 mg/day (28	Significantly reduced fatigue

2009[13]	5)	related fatigue)	days)	(Pines' burnout scale) and improved attention (CPT II). Normalized the cortisol awakening response.[38]
Cropley et al, 2015[14]	*R. rosea* (Vitano) (3% rosavins, 1% salidroside)	Human Trial (N=81, mild anxiety)	200 mg twice daily (14 days)	Significantly reduced self-reported anxiety, stress, anger, and confusion; improved total mood.[60]
Chiu et al, 2013[15]	*R. crenulata* (2.38% salidroside)	Human RCT Crossover (N=125, AMS)	800 mg/day (9 days)	**No significant effect.** *R. crenulata* did not prevent Acute Mountain Sickness (AMS) vs placebo.[14]
Chen et al, 2014[16]	*Rhodiola* / Cordyceps	Human Trial (N=18, altitude training)	Not specified	Supplementation *attenuated the decline in parasympathetic activity* (HF-HRV) caused by altitude training.[50]
Panossian et al, 2021[17]	Salidroside (isolated)	Preclinical Review	N/A	Salidroside modulates the HPA axis by decreasing CRH/cortisol and increasing glucocorticoid receptors (GR).[34]

You et al, 2000[18]	*R. crenulata* (compound)	Preclinical (Mice)	Not specified	Improved learning and memory; demonstrated anti-hypoxia effects in mice.[63]

Abbreviations: *AMS, acute mountain sickness; ANS, autonomic nervous system; ATP, adenosine triphosphate; CPT II, Conners' Computerised Continuous Performance Test II; CRH, corticotropin-releasing hormone; DA, dopamine; GAD, generalized anxiety disorder; HARS, Hamilton Anxiety Rating Scale; HF-HRV, high-frequency heart rate variability; HPA, hypothalamic-pituitary-adrenal; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; NE, norepinephrine; NF-κB, nuclear factor-kappa B; RCT, randomized clinical trial; TAFI, Total Antifatigue Index.*

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