A Comprehensive Guide to Modern and Alternative Approaches to High Altitude Training

♦ How to acquire biological adaptations to high altitude up to 7 times faster without any altitude exposure
♦ Secrets to increasing endurance, aerobic capacity, v02 max, training volume, and recovery time
♦ Ways to pre-acclimatize the body and endure the extreme altitude of Mt. Everest
The 1968 Olympics in Mexico City catalyzed one of the most innovative athletic training trends in history that persists to this day. Since then, clinical studies, scientific theorization, and the expertise of athletic coaches have formed a foundational body of knowledge on both athletic performance at high altitude and high altitude training. This body of work has led to a number of insights about the physiological adaptations to high altitude and their effect on both high altitude and sea level athletic performance.

As altitude training has been studied, it has evolved into four distinct training techniques. These four types of high altitude training include live high train high (LHTH), live high train low (LHTL), intermittent hypoxic exposure (IHE), and intermittent hypoxic training (IHT). LHTH involves both living and training at a sufficient altitude to induce performance adaptations. LHTL involves living at high altitude while training in low altitude conditions via traveling in between locations, the use of altitude simulation devices, or the use of supplemental oxygen. IHE involves brief periods of frequent exposure to significantly high altitudes at rest (>16,400ft) generally using altitude simulation equipment. IHT entails bouts of hypoxic exercise at varying intensities at simulated altitudes typically above 10,000 ft. The effectiveness of each of these techniques is a function of its ability to provide the beneficial performance adaptations of high altitude exposure while minimizing limitations and performance inhibiting factors of high altitude training.

Beneficial Physiological Adaptations of Altitude Training:

Altitude training has been shown by many clinical studies to result in biological adaptations that improve the body's oxygen efficiency. These biological adaptations also improve athletic performance at high altitude and sea level. Altitude training adaptations and their associated performance benefits are described and listed below.

1) Improved Oxygen Carrying Capacity of Blood
Increased red blood cell and hemoglobin production enhances the blood's ability to transport oxygen and has been shown to increase both maximal oxygen consumption (VO2 max) and endurance (Ekblom and Berglund 1991).

2) The Hypoxic Ventilatory Response (HVR)
The HVR is an increase in lung ventilation that enhances oxygen uptake and performance at exhaustive phases of exercise (Asano et al. 1997).
3) Increased Oxidative Enzyme Generation
2,3 DPG Synthesis” and replace the associated sentence with “The enzyme 2,3 diphosphoglycerate (2,3 DPG) improves hemoglobin’s ability to deliver oxygen to muscles during exercise and is strongly correlated with an athlete’s VO2 max (Sutton et al. 1988).

4) Improved Muscle Buffering Capacity
Improved muscle buffering capacity increases muscular endurance by reducing hydrogen ion build up that contributes to muscular fatigue and inhibits aerobic energy production (McComas 1996).

Other Possible Beneficial Physiological Adaptations:
Some altitude training studies indicate that cellular exposure to hypoxia causes localized adaptations to muscle tissue itself that may contribute to athletic performance. These adaptations include increased mitochondria density and capacity, increased muscular capillarity, and increased myoglobin concentrations. We have addressed the clinical research pertaining to each of these proposed cellular adaptations to altitude training below.

Muscle Tissue Capillarity
Theoretically, a denser network of blood vessels enhances oxygen delivery to skeletal muscle. Scientists have proposed that altitude training may enhance this process, called angiogenesis, because hypoxia increases the production of vascular endothelial growth factor (VEGF), the key protein involved in this process. Studies on humans have mixed results regarding altitude training’s ability to provide this benefit. Several studies have failed to demonstrate any changes in muscle capillarity (Saltin et al. 1995; Terrados et al. 1988).

Some studies on intermittent hypoxic training have demonstrated a higher capillary density in athletes (Geiser et al. 2001; Vogt et al. 2001; Hoppeler et al. 2003). However, three clinical studies attributed reported increases in skeletal muscle capillarity to losses in overall muscle mass as opposed to the proliferation of blood vessels (Boutellier et al 1983; Hoppeler et al. 1990; Green et al. 1989).

Overall, the majority of evidence suggests that new blood vessel proliferation is not a performance benefit of altitude training protocols. Furthermore, the upregulation of angiogenic proteins has also been linked to the development of acute mountain sickness and high altitude pulmonary and cerebral edema (Maloney et al. 2000; Sagi et al. 2014; Patir et al. 2012). Due to the fact that many athletes will use Mountain Might for high altitude applications, it would also be detrimental to include ingredients that enhance or induce angiogenesis.

Muscle Tissue Myoglobin
Myoglobin is an iron containing protein located almost exclusively in muscle tissue. Its affinity for oxygen assists in oxygen diffusion from hemoglobin to muscle tissue and may potentially provide a short term oxygen store. An increased synthesis of this pigment would theoretically improve aerobic performance by enhancing oxygen delivery. Very few clinical studies have examined the effect of altitude training on myoglobin concentrations. Two studies have concluded no significant improvement as a result of altitude training (Saltin et al. 1995; Terrados et al. 1988). One study on non-athletes did report a significant increase in skeletal muscle myoglobin concentrations (Terrados et al. 1990). Authors of another altitude training study have also concluded that myoglobin does not play a role in enhancing performance as a result of altitude training (Masuda et al. 2001). Interestingly, recent evidence has demonstrated that myoglobin synthesis is down regulated during acclimatization to altitude. The study authors also reported markers of iron exportation from muscle tissue and suggested that iron was preferentially utilized for hemoglobin synthesis. (Robach et al. 2007)

Myoglobin’s importance for aerobic performance is also controversial. Myoglobin concentrations have been shown to be the same in both trained and untrained muscle fibers and to have no correlation with aerobic capacity (Sylven et al. 1984). However, another study provided evidence for myoglobin stores role in athletic performance by demonstrating that the muscle fibers of endurance athletes had higher concentrations, which enabled better phosphocreatine replenishment (Thomas et al. 1984). The majority of scientific evidence suggests that altitude training induced increases in myoglobin confer negligible or insignificant gains in athletic performance.
Production of Mitochondria and Mitochondrial Enzymes

Increased synthesis of mitochondria and mitochondrial enzymes would theoretically increase the aerobic capacity of muscle tissue. However, the prevailing scientific consensus asserts that acclimatization to altitude either has no effect or down-regulates mitochondrial capacity (Schumacher, 2013). Numerous altitude-training studies have shown significant declines in mitochondrial enzymes in both elite athletes and high altitude residents (Mizuno et al. 1990; Boutellier et al. 1982; Green et al. 1989). Numerous mechanisms have been suggested to reduce mitochondrial capacity in skeletal muscle at altitude including HIF-1α mediated mitochondrial autophagy, HIF-1α mediated suppression of mitochondrial biogenesis, and oxidative stressed induced mitochondrial damage (Murray, 2009). In addition to down regulation associated with acclimatization, these decrements may also be due to altitude’s limiting effect on training load.

Some studies on intermittent hypoxic training (IHT) have shown increases in mitochondrial growth (Geiser et al. 2001; Vogt et al. 2001). Despite evidence of this biological change, the majority of studies on IHT have failed to demonstrate any athletic performance improvement. Leading altitude physiologist Dr. Benjamin Levine has explained this phenomenon by pointing out that humans, unlike most mammals, have a cellular aerobic metabolism that exceeds the ability of our cardiovascular system to supply oxygen (Levine, 2002). In other words, the delivery of oxygen to cells is the bottleneck operation, not the cells utilization of oxygen. Though intermittent hypoxic training may enhance mitochondrial capacity, the theoretical and empirical evidence suggest this benefit may be less important than those that enhance oxygen transport.

Limitations of Altitude Training:

The performance benefits mentioned above are subject to a variety of limitations that make altitude training inconvenient and impractical for many athletes. These restraints apply differently to each altitude training technique.

1) Geographical Restraints:
Clinical data on altitude training suggests that there is a limited altitude range at which athletes can live and train to achieve the beneficial physiological adaptations. Training in altitudes below 6,890 ft (2,100 m) may not bring about beneficial hematological changes (Ri-Li et al. 2002). Conversely, elevations exceeding 8,200 ft (2,500 m) may drastically stunt training volume and intensity and prolong recovery time (Witkowski et al. 2001). This narrow window of elevation limits the number of locations at which altitude LHTH and traditional LHTL can be properly performed. In many cases, accessing this level of altitude exposure requires traveling hundreds of miles, which is not a viable option for most athletes.

2) Financial Restraints:
LHTL training using high altitude simulation devices eliminates the geographical restraints of altitude training. However, these devices range in price from $2,500 to over $25,000. These devices also require significant daily exposure time, and may result in sleep disturbances and partner annoyances related to sleep requirements. For these reasons their use tends to be limited to professional and Olympic level athletes.

3) Time Restraints:
There are a variety of time restraints associated with acquiring and maintaining the performance benefits of high altitude training. These time restraints associated with each physiological benefit are provided in the table below.

<table>
<thead>
<tr>
<th>Physiological Benefit</th>
<th>Altitude Acquisition Time</th>
<th>Post Sea-Level Lasting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>4 weeks</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Hypoxic Ventilatory Response</td>
<td>2-3 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Elevated 2,3 Diphosphoglycerate</td>
<td>2-7 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>Muscle Buffering Capacity</td>
<td>4 weeks</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Increased Cardiac Output</td>
<td>Unknown (LHTL Specific)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table data summarized from (Gore et al. 2001; Stray-Gundersen et al. 2001; Asano et al. 1997; Sato et al. 1992, 1994; White et al. 1987).

It takes an average of 4 weeks of high altitude exposure to acquire all the physiological benefits of altitude training (Gore et al. 2001; Stray-Gundersen et al. 2001). General performance improvements, which are subject to individual variability, are estimated to last 2-3 weeks post sea-level return (Levine and Stray-Gundersen 1997). Increased lung ventilation, however, has been shown to subside in athletes 2-3 days post sea-level return (Sato et al. 1992, 1994; White et al. 1987).
Performance Inhibiting Factors of Traditional Altitude Training:

In addition to the logistical and financial limitations, athletes may experience performance inhibiting decrements as a result of high altitude training. These decrements include anaerobic deconditioning and decreases in cardiac output. It is of note that these performance inhibiting factors are only associated with LHTH training techniques.

1. Detraining Effects

One major performance-inhibiting factor of high altitude training is the “detraining effect.” Maximal training capacity is impeded by the lack of oxygen flux, which can hamper the subsequent exercise adaptation. According to altitude training expert Dr. Joe Vigil, it is necessary to decrease training intensity because of the reduced levels of performance that can be achieved at altitude as well as the increased risk of overtraining (Wilber, Randall 143, 2004). Dr. Benjamin Levine also asserts that this reduction in oxygen flux particularly hampers performance adaptations to intense aerobic interval training, which is a crucial component of an endurance athlete’s regimen (Levine 2002). Knowledge of this phenomenon has become the primary reason for the proliferation of the LHTL model, where maximal training intensity and oxygen flux can be attained.

2) Cardiovascular Response to High Altitude:

Cardiac output is a measure of the total blood pumped by the heart per minute. It is an important component of an athlete’s VO2 max and declines are associated with decreased aerobic performance (Wilber, Randall, 4, 2004). Cardiac output during exercise is widely accepted to decline during altitude training (Alexander et al. 1967; Wolfel et al. 1994). Several factors govern this decline, including, reductions in blood volume, peripheral vasoconstriction, catecholamine production, and reduced heart metabolism and contractility (CITE). Some clinical studies have suggested that this decrement to an athlete’s maximal oxygen consumption may last several days and even weeks after sea-level return (Hartley et al. 1967; Ferretti et al. 1990). A decline in cardiac output may thus be a lasting performance inhibiting effect of high altitude training that compromises improvements in aerobic power, VO2 max, and endurance. Interestingly, recent studies examining elevated catecholamine levels during altitude acclimatization demonstrated that despite full recovery of sea-level oxygen saturation, there was no improvement in muscle oxygen delivery due to catecholamine mediated reductions in blood flow (Wolfel et al. 1991).

Though this cardiovascular response clearly results in reduced athletic performance, scientists currently disagree as whether it may confer resistance to the negative symptoms of high altitude. Similarly to the mammalian diving reflex, the cardiovascular response to altitude may be designed to centrally conserve oxygen and protect vital organs. Additionally, losses in plasma volume may help reduce the excessive fluid retention that characterizes acute mountain sickness and other forms of high altitude edema (Hacket et al. 1981). However, increased catecholamine production and its resulting effects on peripheral vasoconstriction and blood pressure are correlated with higher incidence of acute mountain sickness (Kamimori et al. 2009). Overall, the reduction in maximal cardiac output at altitude is mediated by central and peripheral factors and results in reduced aerobic capacity, while potentially serving as an oxygen conservation mechanism.

Which Technique Most Effectively Improves Performance?

As mentioned earlier, LHTH, IHE, and LHTL improve athletic performance to the degree that they can provide beneficial physiological adaptations, while eliminating the discussed limitations of these benefits and altitude related performance decrements. Though each technique may suit the circumstances of an athlete’s life differently, the cumulative data suggest that LHTL appears to be the most effective in improving overall athletic performance.

1) LHTH

The LHTH technique has been shown in various studies to produce all four beneficial performance adaptations (Adams et al. 1975; McArdle et al. 1996; Mizuno et al. 1990; Sato et al. 1992). As discussed earlier these benefits are subject to geographical restraints given the narrow window of altitude appropriate for training. Benefit acquisition time for LHTH is 28 days and the lasting time is approximately 2–3 weeks. Conversely, and most notably, LHTH training has been shown to result in both reduced cardiac output and anaerobic deconditioning (Hartley et al. 1967; Ferretti et al. 1990; Green et al. 2000). Most likely due to these anaerobic decrements, the scientific consensus regarding LHTH is that it improves athletic performance at high altitude but may not improve sea-level performance (Wilber, Randall 88, 2004).
2) IHE
The clinical evidence regarding IHE’s effectiveness in providing the four altitude training induced performance adaptations is inconclusive. Studies have focused almost exclusively on hematological and general performance metrics. Among these studies there are several that demonstrated significant hematological and performance improvements and several that showed none at all (Hellemans 1999; Casas et al. 2000; Glyde-Julian et al. 2003; Hahn et al. 1992; Frey et al. 2000). Access to IHE is limited by the high cost of purchasing these systems and the shortage of training centers that offer it as a service. In regards to the time limitations of IHE, analysis of clinical studies done by world renown altitude expert, Dr. Randall Wilber suggests that exposure at above 16,400ft for 3 hours per day for a period of 2-4 weeks may be the minimal effective load (Wilber, Randall 209, 2004).

3) LHTL
LHTL is the most promising technique and has the most conclusive clinical data regarding its ability to improve both sea-level and high altitude performance. (Stray-Gundersen et al. 2001; Levine and Stray-Gundersen 1997; Chapmen et al. 1998; Beidleman et al. 1997; Benoit et al 1992; Geiser et al. 2001). This author theorizes that this is because LHTL is the only technique that consistently provides the performance adaptations of high altitude training without any performance decrements. However, time and financial limitations restrict LHTL use to Olympic and professional athletes. In order to acquire these benefits, experts recommend 8 to 10 hours of daily hypoxic exposure for a period of 4 weeks (Wilber, Randall, 225, 2004). These can be theoretically sustained via continuous LHTL use. This technique requires the largest financial investment of roughly $2,500 to $25,000 for altitude simulation devices.

4) IHT
IHT has been extensively studied over the last 20 years with minimal positive outcomes. Dr. Benjamin Levine systematically reviewed much of this data in his work, *Intermittent Training: Fact and Fancy*, in which he concludes that IHT is unlikely to deliver any substantial performance benefit to athletes (Levine 2002). However, IHT may be the only effective technique for delivering molecular and cellular performance adaptations. As discussed previously, the importance of these adaptations is equivocal regarding enhancement of athletic performance at both sea-level and altitude.
What is Mountain Might?

Mountain Might is a performance supplement that activates the major performance benefits of high altitude training without requiring any form of high altitude exposure. Our research department, Alpine Performance Laboratories, formulated Mountain Might to induce these performance benefits without any of the significant geographical, financial, and time limitations or performance decrements typically attached to altitude training. The product concept offers athletes 1) the ability to reap the major benefits of the world’s most elite training technique, 2) rapid pre-acclimatization enabling athletes to arrive for high altitude competitions ready to perform, and 3) enhanced well-being and performance for high altitude travel and trekking. The ingredients in Mountain Might have been clinically demonstrated to collectively induce the five major altitude training performance adaptations in 4–8 days. All ingredients are legal, natural, and safe. These ingredients are not banned by any doping agency, including the World Anti-Doping Agency (WADA), or on any banned substance list and have been approved by the Banned Substance Control Group. The subsequent reading will divulge and analyze the clinical data regarding the Mountain Might formula. This analysis includes quantitative comparisons between modern altitude training protocols and ingredients regarding both physiological and performance markers. These comparisons are the basis of the specific ingredient dosages and suggested use of the Mountain Might formula.

How Does Mountain Might Work?

N-Acetyl cysteine: Ventilation and RBC Production

A basic notion in high altitude physiology was that hypoxia-induced erythropoietin (EPO) secretion is brought about directly by reductions in kidney oxygenation, the organ that produces EPO (Porter and Goldberg et al. 1994; Richalet et al. 1994). However, it is increasingly being shown that numerous biological pathways regulate both the hematological and ventilatory response to altitude. One such pathway involves the production of molecules called nitrosothiols that occurs as a result of red blood cell oxygen desaturation. After forming from red blood cell nitric oxide donor reactions, nitrosothiols then act as key signaling molecules to increase the ventilatory drive and blood oxygen carrying capacity. (Wulf Hildenbrandt et al. 2002).

In accordance with this discovery, clinical studies have demonstrated that supplementation with the amino acid and antioxidant, N-Acetyl cysteine (NAC), induces these two physiological adaptations of altitude training and acclimatization. NAC is a nitrosothiol precursor and induces altitude acclimatization by naturally increasing nitrosothiol levels in the bloodstream. Increased ventilatory drive and red blood cell production, have been demonstrated by numerous clinical studies to be both induced in normal oxygen conditions and enhanced during hypoxia by daily NAC supplementation (Wulf Hildenbrandt et al. 2002, Kelly MK et al. 2009; Zembron-Lacny et al. 2008). Furthermore, both physiological adaptations have been demonstrated to occur far more quickly than they can be achieved by way of modern altitude training techniques (Kelly MK et al. 2009; Zembron-Lacny et al. 2008; Gore et al. 2001; Stray-Gundersen et al. 2001). Additionally, NAC has been shown to produce these benefits in both untrained subjects and trained athletes (Kelly MK et al. 2009; Wulf Hildenbrandt et al. 2002; Zebron-Lacny et al. 2008; Momeni, M et al. 2011). The Mountain Might formula contains a dosage of NAC within the clinically effective range for inducing both significant gains in red blood cell production and heightened respiratory drive.
Sodium Phosphate: 2,3 DPG, Cardiac Output, Buffering Capacity

The other three major performance adaptations of altitude training have also been successfully achieved by way of supplementation with natural compounds. Sodium phosphate has been shown in multiple clinical trials to significantly increase levels of 2,3 DPG, increase cardiac output, and improve the buffering capacity of skeletal muscles (Bremmer K. et al. 2002; Farber et al.1984; Stewart I. et al. 1990; Cade R. et al. 1984; Krieder et al. 1992; Bredle et al. 1988). Increasing dietary phosphate intake at significant levels supplies the heart and skeletal muscle with extra high-energy phosphate substrate as well as enhances red blood cell 2,3 DPG production and overall function. As will be discussed in the subsequent pages a dosage of sodium phosphate capable of increasing in 2,3 DPG, cardiac output, and skeletal muscle buffering capacity comparably to modern altitude training protocols was approximated for the Mountain Might formula.

Hawthorn Berry Extract: Cardiac Output and Vascular Function

Hawthorn berry extract has also been shown in multiple clinical studies to increase cardiac output and positively affect other aspects of heart function (Schmidt et al. 1994; O’Connolly et al. 1986; O’Connolly et al. 1987; Leuchtgens, 1993). Interesting this natural cardiac adaptogen and inotropic may also mimic the beneficial cardiac adaptation to high altitude as well as increase the hearts resistance to hypoxia mediated oxidative stress. Unlike sodium phosphate, which enhances cardiac output by increasing high-energy phosphate availability in heart cells, hawthorne berry exerts its effects via multiple pathways including coronary vasodilation, antioxidant activity, and cardiac enzyme function. The clinical research demonstrating these beneficial effects will also be analyzed in detail in the subsequent reading.

Mountain Might Versus Altitude Training: A Deeper Look

1. Hematological Adaptations
An increase in the oxygen carrying capacity of the blood is the principal biological adaptation that athletes seek from altitude training. This adaptation is also activated by carotid bodies as part of the HRS. In response to low blood oxygen, carotid bodies signal the kidneys to produce erythropoietin (EPO), which stimulates the formation of new red blood cells and hemoglobin. (Wilber, Randall, 11, 2004) Higher levels of red blood cells and hemoglobin increase the amount of oxygen the blood is capable of transporting to muscles and tissues.

In addition to initiating the HVR, NAC supplementation has also been shown to significantly increase EPO, red blood cell, and hemoglobin production by activating the hypoxic response system (Wulf Hildenbrandt et al. 2002; Zebron-Lacny et al. 2008; Momeni, M et al. 2011). Supplementation of this natural amino acid has also been shown to induce all of these hematological improvements in four days (Zembron-Lacny et al. 2008). LHTL techniques take an average of 4 weeks to reach comparable hematological adaptations (Gore et al. 2001; Stray-Gundersen et al. 2001).

2. The Hypoxic Ventilatory Response
The hypoxic ventilatory response (HVR) is an increase in lung ventilation that occurs shortly after initial exposure to high altitude. This increase in both lung volume and breathing rate is signaled through neural pathways by blood oxygen sensing chemoreceptors as part of the hypoxic response system (HRS) (Dempsey, Forster 1982). With prolonged exposure to high altitude, the HVR is sustained due to an increased sensitivity of ventilation signaling chemoreceptors called carotid bodies (Katayama et al. 1999, 2001). The HVR improves athletic performance by increasing oxygen uptake in the lungs during exercise. This adaptation, however, only lasts a few days after return to sea level (Sato et al. 1992, 1994; White et al. 1987).

<table>
<thead>
<tr>
<th>Adaptations</th>
<th>NAC</th>
<th>LHTL</th>
</tr>
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<tbody>
<tr>
<td>EPO</td>
<td>26.0%</td>
<td>92.0%</td>
</tr>
<tr>
<td>RBC</td>
<td>9.0%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.0%</td>
<td>8.5%</td>
</tr>
<tr>
<td>V02 Max</td>
<td>7.0%</td>
<td>4.0%</td>
</tr>
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</table>

In addition to providing the hematological adaptations roughly seven times faster, NAC supplementation has also been shown to improve performance more significantly than LHTL training. The table below summarizes the evidence for this assertion. Altitude training data are calculated averages from findings in two LHTL altitude training studies (Levine, Stray-Gunderson, 1997; Stray-Gunderson et al., 2001). NAC supplementation data are taken from studies previously cited (Zebron-Lacny et al.; Leelarungrayub D. et al.).

The results of this comparison reveal that though LHTL altitude training increased EPO levels more significantly, NAC supplementation produced more positive results for hemoglobin levels, RBC concentration, and v02 max. This analysis suggests that NAC supplementation alone may improve blood oxygen carrying capacity and athletic performance more effectively than LHTL training.
N-Acetylcysteine initiates the HVR by enhancing the sensitivity of carotid bodies. N-Acetylcysteine has been shown in multiple clinical studies to both enhance the HVR in subjects during hypoxic conditions as well as activate the HVR in subjects exposed to normal oxygen conditions (Wulf Hildenbrandt et al. 2002, Kelly MK et al. 2009). A placebo-controlled, double-blind study recently conducted on healthy males showed that NAC supplementation significantly increased the HVR in simulated hypoxic conditions as compared to placebo (Wulf Hildenbrandt et al. 2002). This study suggests that NAC supplementation should improve performance at high altitudes by enhancing pulmonary acclimatization. Another placebo-controlled study of NAC supplementation on trained athletes in normoxia found a significant, 14% higher respiratory inhalation pressure among the trained athletes who consumed NAC than the control group. (Kelly MK et al. 2009) This study reveals that NAC supplementation not only enhances the HVR during hypoxia, but also improves sea level performance by strengthening lung ventilation in normal oxygen conditions.

3. Production of Enzyme 2,3 DPG
Several clinical studies indicate that altitude training results in higher levels of the enzyme 2,3 diphosphoglycerate (2,3 DPG) in blood and muscle tissue (McArdle et al. 1996, Rusko 1996). Scientists purport that 2,3 DPG synthesis is accelerated as a result of both increased production of red blood cells and as a byproduct of altered blood PH that results from increased ventilation (McArdle et al. 1996). This enzyme improves oxygen delivery to muscle tissues by decreasing the affinity of hemoglobin for oxygen. In addition to being an important component of altitude acclimatization increased 2,3 DPG synthesis is also a long-term adaptation to endurance training (Remes et al. 1979). Furthermore, direct evidence suggests that elevated 2,3 DPG contributes to improved oxygen transport and aerobic performance in elite athletes as a result of altitude training (Son et al. 2012).

Similarly to high altitude training, phosphate supplementation has also been demonstrated to improve both athletic performance and altitude tolerance by increasing 2,3 DPG levels in the blood. One clinical study on sodium phosphate supplementation at altitude demonstrated that 500 mg of sodium phosphate per day for four days significantly increased 2,3 DPG concentrations, oxygen delivery, cognitive performance, and psychological well-being at altitude (Jain et al. 1987). In addition, several clinical studies have demonstrated that athletes can use phosphate supplementation to increase athletic performance by elevating 2,3 DPG concentrations at sea-level. (Bremmer K. et al. 2002, Farber et al. 1984, Stewart I. et al. 1990; Cade R. et al. 1984).

Quantitative Comparison of Sodium Phosphate and Altitude on 2,3 DPG
The Pikes Peak Climax study reported average increases of 15-20% after exposure to roughly 14,000 ft (Moore and Brewer, 1980). For comparison, one study performed at the University of Sidney showed that sodium phosphate supplementation increased 2,3 DPG levels more significantly than short term acclimatization to Pikes Peak. Subjects who ingested 4 grams of sodium phosphate for a 7-day loading period had red blood cell 2,3 DPG levels and blood serum 2,3 DPG levels that were 25% and 30% higher, respectively, than control group levels. (Bremmer K. et al. 2002) Furthermore, a significantly lower dosage of 500 mg/d for four days in conjunction with altitude exposure boosted enzyme levels by an additional 18.2% compared to placebo (Jain et al. 1987). Details regarding our consideration of this data for the sodium phosphate dosage in the Mountain Might formula are available in the Dosage Rational section.
4. Muscle Buffering Capacity

Numerous clinical studies on altitude training have demonstrated its ability to improve the buffering capacity of working muscles (Mizuno et al. 1990, Gore et al. 2001). Accumulation of hydrogen ions in the blood and muscles is a major contributor to muscle fatigue during exercise. Increasing the body’s ability to buffer the accumulation of these ions is thus thought to have a positive effect on muscular endurance. Scientists believe that altitude-mediated improvements in muscle buffering capacity occur as a result of changes in protein, phosphate, or carnosine concentrations in muscle fibers (Mizuno et al. 1990, Saltin et al. 1995). These adaptations have been purported to occur as a result of a higher contribution of the anaerobic metabolism for a given exercise intensity at altitude compared to sea-level (Mizuno et al. 1990). As a result of this need for “anaerobic compensation” alterations in metabolic substrate availability, acidic ion buffers, and other physiological factors may also occur that assist in buffering hydrogen ion build up during exercise. Scientists have also suggested that these skeletal muscle adaptations to altitude may occur to favor more anaerobic metabolic pathways in order to reduce the oxidative burden of muscle work (Edwards et al. 2010).

Role of Intramuscular Phosphate in Altitude-Mediated Buffering Enhancement

A recent study conducted on climbers and trekkers in the Himalayans examined the skeletal muscle adaptation to high altitude using modern phosphorus magnetic resonance spectroscopy (P-MRS) technology capable of examining both phosphate synthesis and mitochondrial metabolism. Higher extracellular and, especially, intracellular phosphate concentrations are associated with improved muscle performance due to their roles in both buffering hydrogen ion build up and regenerating ATP. Data analysis prior to altitude exposure revealed that climbers with extensive experience at altitude had significantly higher phosphate concentrations in skeletal muscle than trekkers. Furthermore, analysis of post altitude exposure data demonstrated that both groups experienced a significant increase in skeletal muscle phosphate of approximately 15%. Both groups also scored similarly to pre-altitude values on a muscular performance test after altitude exposure despite significant reductions in muscle mass and mitochondrial capacity. (Edwards et al. 2010)

Though far from conclusive, this study provides evidence that altitude-mediated improvements in muscle buffering capacity may be caused by an increase in intramuscular phosphate. The mechanisms by which altitude training or prolonged altitude exposure can cause intramuscular phosphate to increase have not been clearly established in humans. Researchers from the Yokohama City University School of Medicine reported reductions in serum phosphate in rats exposed to severe hypoxia, which they attributed to increase intracellular phosphate uptake. The authors postulated that increased cellular phosphate uptake can both provide an oxygen-efficient substrate for ATP production as well as further enhance cellular metabolism by stimulating glycolytic enzymes. (Yoshino et al. 1986) This hypothesis is supported by earlier research demonstrating increased cellular phosphate uptake as a means of maintaining cellular metabolism in the face of oxidative metabolic disturbances caused by high altitude (Ramaiah 1974).

Sodium Phosphate’s Impact on Phosphate Levels and Muscle Buffering Capacity

Clinical studies have also examined sodium phosphate’s ability to improve muscle buffering capacity and anaerobic capacity by increasing serum and muscle phosphate concentrations. These studies have focused on time to anaerobic threshold and exercise intensity at anaerobic threshold as markers of performance. One study conducted at the Galen Medical Institute in Poland demonstrated a 7% increase in exercise intensity at anaerobic threshold along with a significant increase in serum phosphate during a graded exercise test (Czuba et al. 2009). Athletes in the sodium phosphate experienced a 37.5% increase in serum phosphate throughout the exercise test as compared to a 1% increase in the placebo group. The findings are also supported by another study demonstrating a 12% increase in anaerobic threshold in athletes during a 5 mile run test (Kreider et al. 1990). Jain et al. also reported a significant increase in serum phosphate of approximately 15% using a low dose of 500 mg per day at 3,500 m (Jain et al. 1987).

Overlapping Pathways of Anaerobic Performance Improvement

The nature of altitude-induced adaptations to skeletal muscle is currently a controversial topic among physiologists. Initially research hypotheses focused on improvements in oxidative metabolism, however, more evidence is mounting that the response involves a downregulation of oxidative energy production and a shift towards glycolytic and anaerobic metabolism (Murray 2009). These alterations in substrate uptake kinetics and enzyme production may optimize muscle performance at altitude by favoring less oxygen consuming metabolic pathways. They may also be responsible for improvements in anaerobic performance at sea level as a result of altitude training. As previously discussed, there is an emerging body of evidence suggesting that cellular phosphate uptake is enhanced at altitude in both animals and humans. In addition to being a high ATP yield substrate in hypoxic conditions, cellular phosphate influx can also stimulate glycolysis. Interestingly, phosphofructokinase, a key glycolytic enzyme, is stimulated by both high altitude and cellular phosphate availability (Ptashne et al. 1983; Lichtman et al. 1971; Brazy et al. 1984). Sodium phosphate supplementation may also enhance glucose phosphorylation and stimulate other metabolic enzymes such as lactate dehydrogenase (Buck et al. 2013). Obviously,
sodium phosphate supplementation induced increases in cellular phosphate availability do not completely mimic the cellular metabolic response to hypoxia. However, it provides similar functional benefits by enhancing glycolysis, buffering capacity, and the oxygen cost of ATP production. Additionally, unlike high altitude, it does not downregulate mitochondrial oxidative capacity.

**Quantitative Comparison of Sodium Phosphate and Altitude on Buffering Capacity**

It is difficult to quantifiably relate data between the effects of sodium phosphate and altitude training on muscle buffering capacity because different markers of anaerobic performance have been used. Furthermore, no study on sodium phosphate supplementation has measured actual increases in intramuscular phosphate as was done in the Extreme Everest Study. Additional analysis regarding sodium phosphate dosing is provided in the Dosage Rationale section below.

5. Cardiac Output

The initial cardiac response to high altitude contributes to decreased oxygen utilization during exercise and a reduction in athletic performance (Klausen 1966; Vogel et al. 1967). Several underlying pathways contribute to this deficit in VO2 max including reductions in heart metabolism, peripheral vasoconstriction, and losses in plasma volume (CITE). This adverse response may last weeks after return to sea-level and can be a large barrier to a successful LHTL program (Hartley et al. 1967; Ferretti et al. 1990). There is also evidence that prolonged endurance exercise at high altitude may result in cardiac damage (Shave et al. 2002).

Recent studies, however, show that LHTL training may have a beneficial effect on cardiac output and heart function (O’Riordan, Michael. 2011; Liu et al. 1998). Athletes using this modern training approach experienced 11% increases in both stroke volume and cardiac output compared to control subjects. Study authors theorized that improvements in cardiac performance may have been mediated via increases in cardiac sympathetic sensitivity, enhancement of cardiac metabolic function, or coronary vessel dilation. (Liu et al. 1998) Interestingly, two ergogenic supplements, sodium phosphate and hawthorn berry extract have clinical support regarding their ability to enhance cardiac output via similar pathways.

**Sodium Phosphate Increases Cardiac Output Via Altitude Pathways**

High altitude induced enhancement of cardiac metabolism has been shown to be partially mediated via increased availability of high-energy phosphates in heart cells (Opie et al. 1978). Sodium phosphate supplementation has also been shown to greatly increase cardiac output by increasing high-energy phosphate availability in the muscle cells of the heart (Kreider et al. 1992; Czuba et al. 2009). These effects mirror the skeletal muscle response to sodium phosphate supplementation whereby increased cellular phosphate uptake enhances anaerobic metabolism and buffering capacity. According to these studies, increasing high-energy phosphate concentrations seems to also enable the heart to utilize more energy during contraction.

**Quantitative Comparison with Altitude Training**

In the double blind placebo controlled study lead by Kreider, athletes who consumed four grams of sodium phosphate for three days experienced 26% and 36% improvements in stroke volume and cardiac output during exercise (Kreider et al. 1992). A comparison of the results of the live high, train low approach versus sodium phosphate supplementation depicted below suggests that sodium phosphate produces considerably larger improvements in cardiac output. The difference in resting vs. exercising conditions does detract from the quality of comparison that can be made between the two stimuli’s effect on cardiac output.

**Hawthorn Berry Increases Cardiac Output Via Altitude Pathways**

Hawthorn berry extract supplementation has been shown to induce improvements in cardiac output via similar pathways to the modern live high, train low model. For example, in addition to improvements in cardiac metabolism the LHTL model has been suggested to enhance cardiac output via coronary vessel dilation and, in an in vitro study, improvements in β-adrenergic receptor density (Heistad et al. 1980; Richelet et al. 1988). Animal studies on hawthorn berry supplementation have similarly shown improvements in cardiac output, coronary vessel dilation, and B-adrenergic sensitivity (Petkov, 1979; Taskov, 1977; Ju et al. 2005). Additionally, clinical data support its ability to enhance cardiac output by increasing the force production of heart muscle contractions (Schwinger et al. 2000). These studies suggest that hawthorn berry supplementation can enhance cardiac output via pathways that characterize the beneficial cardiac adaptations to hypoxia.

**Adaptogenic Properties Enhance Tolerance to Hypoxic Stress**

Hawthorn berry extract is classified as both an inotropic and cardiac adaptogen. As such its ability to enhance cardiac function is amplified in times of stress. In addition to the abovementioned improvements, it has clinical support regarding its ability to improve heart function, blood pressure, exercise tolerance, oxidative stress, and outcomes of various heart conditions (Schmidt et al., 1994; O’Connell et al., 1986; O’Connell et al., 1987; Leuchtgens, 1993). Hawthorn berry and its constituents have also been shown to be protective against the negative effects of severe hypoxia in experimental models on animals (Yu et al. 2008; Peng Li et al. 2009). One of hawthorn berry’s active constituents, oligomeric procyanidins has specifically been demonstrated
to reduce oxidative damage during hypoxic conditions (Roddewig et al. 1977; Taskov et al. 1977). Interestingly, the flavanoids in hawthorn berry are likely responsible for the dilation of vessels that direct blood through the heart by activating endothelium derived relaxing factor and inhibiting phosphodiesterase (Miller, AL. 1998). Clinical trials regarding hawthorn berry’s adaptogenic properties on cardiac hypoxic conditions suggest that it may protect the heart from the damaging effects of extreme altitude or prolonged endurance exercise at high altitude.

Efficacy in Trained Athletes
The majority of hawthorn berry studies have been conducted on the elderly and heart patients. The major limitation to current data supporting its ability to improve performance and cardiac output is that there are no clinical trials on trained athletes. However, in addition to cardiac parameters numerous studies in elderly populations demonstrated significant improvements in exercise performance (Leuchtgens, 1993; Reuter, 1994). Improved cardiac output and function tended to be even more significant in healthier patients whose physiology more closely resembles that of athletes (Schwinger et al. 2000). Moreover hawthorn berry extract is frequently used by elite endurance athletes and alpine climbers as a stand-alone performance supplement. It is a common recommendation by naturopathic doctors, including the physicians at the Denver Naturopathic Clinic, for improving performance and tolerance of high altitude.

Dosage Rationale for Active Ingredients

The dosing rationale for the Mountain Might formula was determined according to three criteria: 1) dosages must be within clinically effective range, 2) dosages must minimize adverse side effects, and 3) and dosing must maximize ingredient absorption. All of the ingredients’ dosages the in Mountain Might formula are within the clinically effective range for producing a desirable physiological effect. In other words clinical studies performed on humans have shown that each ingredient improved performance when given at either an identical or lower dosage than is included in Mountain Might. Meeting that criteria is crucial for formula efficacy. Several challenges arose during the formulation and athlete testing process that may limit the scope of beneficial altitude training adaptations provided by Mountain Might. Firstly, mimicking altitude-training adaptations with natural supplements is not an exact science. Furthermore, there was not sufficient data to establish accurate quantifiable comparisons between the dose response relationships of both altitude training and Mountain Might ingredients and their resulting physiological benefits. Finally, including maximal dosages of sodium phosphate resulted in frequent gastrointestinal complaints from our athlete testers. Reducing sodium phosphate dosages may have compromised the formula’s effects on enhancing buffering capacity and cardiac output. A detailed review of the dosing rationale for each active ingredient is provided below.

N-acetylcysteine Dosage Rationale

The Mountain Might formula contains a clinically effective dosage of NAC for both enhancing red blood cell production and the ventilatory drive. We determined this dosage of 1000 mg by assessing quantified ventilatory and hematological parameters between altitude training and NAC supplementation studies. The dosage of NAC demonstrated in numerous studies to markedly increase red blood cell parameters is 1200 mg per day (Zebron-Lacny et al. 2009; Zebron-Lacny et al. 2009). This marked 9% increase in hematocrit and hemoglobin mass achieved within 8 days of supplementation is significantly higher than the average hematological increase reported in multi-week altitude training studies.

The data table in the hematological adaptation section represents the two most successful live high, train low studies as measured by improvements in hematological responses. If we pool the data from those studies with that of the third and fourth most successful LHTL studies, the average respective increases in hematocrit and hemoglobin mass are 5.075% and 7.475% (Levine and Stray-Gundersen 1997; Stray-Gundersen et al. 2002; Wehrlin et al. 2005; Wehrlin & Marti 2006). Using basic linear regression from NAC supplementation studies, 1000 mg is estimated to increase hematocrit and hemoglobin mass by 7.5%.

Additionally, we assessed a meta-analysis of studies regarding the impact of altitude training on hematocrit. According to this meta-analysis an approximate 7.5–10% increase in hematocrit requires 42–49 days at 8,202 ft (2500 m), 35–37 days at 9,843 ft (3000 m), or 23–26 days at 11,483 ft (3500 m) (Rasmussen et al. 2013). This data is illuminating as it enables us to estimate the altitude to which 8 days of 1000 mg of NAC may acclimatize. For example, since the lower bound of the hypoxic stimuli corresponds to a 7.5% increase in hematocrit, 8 days of Mountain Might supplementation may correspond to 35 days spent at 9,843 ft.

In light of clinical studies indicating NAC is capable of enhancing the hematological response to hyperoxia and altitude exposure at 600 mg per day efficacy at 1000 mg becomes stronger (Hildebrandt et al. 2002; Momeni et al. 2011). Finally, the Mountain Might formula is even more likely to deliver substantial performance gains related to hematological improvements given the potential red blood cell production and lifespan enhancing effect of prolonged sodium phosphate supplementation (Kreider.
et al. 1989; Kreider et al. 1990). NAC supplementation’s effect on the hypoxic ventilatory response has been established at lower dosages than its hematological effects. For example, the minimal effective dosage for enhancing ventilation in high altitude conditions has been found to be 600 mg per day (Hildebrandt et al. 2002). Since this dosage is significantly less than that provided in the Mountain Might formula, Mountain Might can be expected to significantly boost the ventilatory drive.

Another observation from clinical studies is that NAC dosing is frequently divided into multiple smaller dosages throughout the course of a day. One reason for this appears to be that blood thiol concentrations do not remain consistently elevated and begin to decrease 2-3 hours post supplementation (Hildebrandt et al. 2002). Dividing NAC daily dosages throughout the day likely provides a more constant respiratory and hematological stimulus, which is optimal for enhancing acclimatization and performance. In summary, the Mountain Might formula contains 1000 mg of N-acetylcysteine divided into two daily dosages of 500 mg. Clinical data support this dosage to provide an adequate stimulus to enhance the ventilatory drive and red blood cell production.

**Sodium Phosphate Dosage Rationale**

Our formulation team included sodium phosphate in the Mountain Might formula to deliver three physiological benefits of altitude training: increased 2,3 DPG synthesis, increased cardiac output, and increased muscle buffering capacity. 2,3 DPG synthesis is considered both the principal performance benefit of phosphate supplementation and the most important physiological benefit for altitude tolerance. We therefore focused primarily on this physiological parameter when formulating Mountain Might.

The clinically effective dosage for significantly boosting 2,3 DPG production is 500 mg/d (Jain et al. 1987). However, the traditional sodium phosphate supplementation protocols used in most clinical studies involves 3-7 day loading periods of approximately 3-5 grams per day (Kreider et al. 1990; Czuba et al. 2009). Unfortunately, dosages above 2 gram/d are commonly associated with stomach upset and can be poorly tolerated by many athletes. This proved to be the case in early product testing using 2 grams of sodium phosphate. Mountain Might was reformulated with 1100 mg of sodium phosphate to avoid these effects while still producing considerable improvements in 2,3 DPG production. Specifically, our team used linear regression from sodium phosphate studies and the Pikes Peak altitude study to establish 1100 mg as an ideal dosage for eliciting 2,3 DPG production comparable to acclimatization to moderate altitude of 7,000 to 9,000 ft, the common “altitude window” for optimal training and altitude benefits.

There is no direct clinical evidence that 1100 mg of sodium phosphate can elicit substantial gains in cardiac output and muscle buffering capacity. Improvements in cardiac output comparable to those gained from the live high, train low model are a feasible expectation. For example, the high dose sodium phosphate loading protocol produced a more than 3-fold higher improvement in cardiac output in cardiac output in a 7X shorter period of time than the live high train low model (Liu et al. 1998; Kreider et al. 1992). The daily dosage of sodium phosphate used in this study was 3.6-fold higher than that of the Mountain Might formula. Linear regression analysis suggests that 3 weeks of live high, train low will improve cardiac output only slightly more than 3 days of 1100 mg sodium phosphate.

No clinical study has ever been conducted on low dose sodium phosphate supplementation on muscle buffering capacity. Improvements in muscle buffering capacity and anaerobic performance have only been demonstrated at loading dosages of 3-5 g/d. Interestingly, the study authors also monitored serum phosphate levels as a biomarker for this key buffering agent. In one study, a 3 day 4 gram loading period increased serum phosphate levels by 17% (Kreider et al. 1992). Promisingly, a much lower dose of 500 mg for 3 days was shown to boost serum phosphate by 15% (Jain et al. 1987). This dose response relationship between phosphate supplementation and its absorption and transport into serum suggests that lower dosages may also provide significant improvements in muscle buffering capacity. Benefits may not be as substantial or simply take more time to occur. Furthermore, long-term phosphate supplementation, which is poorly tolerated using higher loading doses, may confer additional benefits that take time to acquire such as enhanced red cell production and life-span (Kreider et al. 1989).

**Hawthorn Berry Extract Dosage Rationale**

There is not sufficient quantitative data on hawthorn berry extract’s effects to base dosing off of comparisons to altitude training data. The dosage range shown to be effective in clinical trials on humans is 160-900 mg (Leuchtgens, 1993; Reuter, 1994). Occasional mild side effects were noted in the higher dosage ranges and were absent below 200 mg (Reuter 1994). The Mountain Might formula contains 200 mg of hawthorn berry extract considering the strong evidence for efficacy and lack of side effects at that dosage.
Synergisms and Additional Benefits of Active Ingredients

The active ingredients in Mountain Might may interact synergistically to increase athletic performance and altitude tolerance substantially. The physiological basis for these synergisms is outlined in the subsequent reading.

**Oxygen Carrying Capacity and Unloading Potential**
The physiological effects of NAC and sodium phosphate likely combine to produce even greater benefits than demonstrated in clinical data on each nutrient in isolation. NAC's red blood cell production stimulating effect increases overall blood oxygen carry capacity, which enables more oxygen to be circulated to working muscles. Sodium phosphate further enhances the aerobic potential of circulating blood by increasing 2,3 DPG synthesis, which allows more oxygen to diffuse from red blood cells to tissues.

**Enhanced RBC Lifespan and Function**
In addition to enhancing 2,3 DPG production, sodium phosphate increases high-energy phosphate availability for red blood cells. Higher levels of serum phosphate have been reported to increase RBC metabolism, enhance RBC stability and pliability, and extend RBC life-span (Brain et al. 1972; Chanutin et al. 1967). For these reasons sodium phosphate has been successfully used to increase RBC volume in anaemic patients (Gibby et al 1978). Furthermore, 6 day of sodium phosphate supplementation significantly increased hemoglobin levels in trained athletes (Kreider et al. 1989).

**Enhanced Nitrosothiol Formation**
A highly theoretical potential synergistic outcome of the Mountain Might formula is that phosphate supplementation may directly potentiate the hematological and ventilatory adaptations induced by NAC. NAC's formation of nitrosothiols, the key signaling molecules in ventilatory and hematological adaptation, is heightened by the deoxygenation of hemoglobin. This occurs as a result of high altitude hypoxia, but also as hemoglobin releases oxygen to cells during normal circulation. Higher levels of 2,3 DPG in the blood enhance this release of oxygen from hemoglobin to tissues, which may also promote increased nitrosothiol formation in the presence of elevated blood thiol concentrations.

**Complete Balanced Inotropic**
Sodium phosphate and hawthorn berry work together to optimize heart function and improve cardiac output. Sodium phosphate's effect on increasing metabolic output of the heart is complemented hawthorn berry extracts ability to increase cardiac blood flow, enzyme activity, and resilience to hypoxic conditions (i.e. intense exercise or altitude). Combining the two strongest natural inotropic compounds that work via different pathways provides a complete and balanced nutritional approach to both enhance heart function in the face of hypoxia and increase cardiac output during sea-level exercise.

**Maximizing Cellular O2 Availability While Reducing Oxygen Cost of ATP Production**
Performance at both altitude and sea-level is largely a function of maximal energy production at a cellular level. Improved oxygen transport and unloading, which are accomplished by NAC and sodium phosphate, directly increase cellular oxygen availability for oxidative energy production. Simultaneously, increasing intracellular phosphate availability enhances the energy production of numerous less oxygen consuming metabolic pathways. The combined effect of enhancing cellular oxygen availability while also reducing the oxygen cost of cellular energy production may both reduce the "hypoxic strain" at a cellular level and enhance exercise economy at sea-level.

**Neuroprotective Properties**
NAC and sodium phosphate have been demonstrated to have neuroprotective properties during hypoxia. NAC's neuroprotective properties originate from numerous mechanisms. These mechanisms include its ability to positively modulate glutamate activity in neurons by increasing the activity of cysteine-glutamate antiporter, protect against oxidative stress by enhancing neuronal glutathione levels, and activating neuroprotective oxygen sensing pathways (Dean et al. 2011; Jayalakshmi et al. 2005; Zhang et al. 2013). Hypoxia is a known activator of glutamate receptors, which contributes to reductions in cognitive function and neural damage at altitude (Hota et al. 2008). NAC's hypoxic neuroprotective properties have been demonstrated in numerous in vitro and in vivo studies (Jayalakshmi et al. 2005; Jayalakshmi et al. 2007; Zhang et al. 2013).

Sodium phosphate has also been shown to directly enhance cognition in humans exposed to both 3,500 m and 4,300 m (Jain et al. 1987; Moore and Brewer, 1981). The authors reported that enhanced 2,3 DPG production enhanced oxygen delivery to the brain. Enhanced ATP availability in circulating blood was also reported in both studies and may have also improved cognition by enhancing cerebral metabolism.
**Antioxidant Properties**

NAC is an amino acid precursor for the production of glutathione, one of the most important chemicals in the human body’s antioxidant defense system. Prolonged exercise has been shown to deplete glutathione reserves and render cells more vulnerable to oxidative stress damage (Chandan et al. 1999). Numerous studies on humans have also shown that glutathione activity is especially vulnerable to altitude exposure (Ilvazhagan et al., 2001; Joanny et al. 2001). Supplying the body with N-acetylcysteine can help replenish glutathione and reduce oxidative stress during both exercise and altitude exposure. One study demonstrated that the combination of n-acetylcysteine and other antioxidants reduced oxidative damage at altitude (Schmidt et al. 2002). NAC supplementation was also shown to reduce the production of peroxynitrite, a damaging free radical formed from the interaction of superoxide and nitric oxide at altitude (Hildedrandt et al. 2002). Hawthorn berry extract has also been demonstrated to have antioxidant activity, which may help reduce oxidative damage and maintain cellular function at altitude (Chai et al. 2013).

**Enhanced Iron Absorption**

Consumption of cysteine, the amino acid component of N-acetylcysteine, has been shown to double the absorption of dietary iron (Torres et al. 1981). The combination of N-acetylcysteine and iron likely enhances iron absorption and reduces the likelihood of inadequate iron stores stunting hematological adaptation.

**Supporting Ingredients**

**Iron**

**Effect of Iron Deficiency of Hematological Improvements**

Due to the high risk and prevalence of iron deficiency in athletes, acclimatization induced iron mobilization, and negative effects of iron deficiency on hematological performance adaptations, a minimal effective dosage of iron is included in the Mountain Might formula.

Numerous supplemental forms of iron are used to support iron stores in athletes. Ferrous biglycinate is a chelated iron source. The process of chelation neutralizes the electric charge of iron molecules, which is purported to both enhance absorption and reduce gastrointestinal symptoms of supplementary iron. One study examining ferrous biglycinate showed that it is equally effective at preventing anemia as supplementation with twice the dosage of commonly used ferrous sulfate. Gastrointestinal complaints were also significantly reduced in the ferrous biglycinate group during this study. (Milman et al. 2014) Anecdotal evidence regarding its ability to reduce iron deficiency at lower dosages and with less stomach upset is also highly prevalent among athletes, physiologists, and coaches.

**Folic Acid**

The third major nutrient deficiency that can stunt red blood cell production is that of folic acid. This is most evident in the condition of megaloblastic anemia. Patients with this condition have a folic acid deficiency that interferes with the proper DNA synthesis necessary for the formation of new red blood cells. As a result a substantial portion of total red blood cell precursors, or progenitor cells, undergo apoptosis before they can develop into functional cells. (Koury and Ponka 2003) The inclusion of folic acid into the Mountain Might formula will help protect red blood cell health and production by reducing the probability of folic acid deficiency.
**Vitamin B-12**

Vitamin B-12 is also included in the Mountain Might formula because sufficient levels are required for hematological improvements. Supplementation of this vitamin has not been studied for its ability to support red blood cell production during altitude training. However, similarly to folic acid, Vitamin B-12 deficiencies have been shown to inhibit red blood cell production by interfering with the genetic processes of early cell development (Koury MJ, Ponka P 2004). Its inclusion will ensure that hematological improvements are not hindered by a Vitamin B-12 deficiency.

**Safety, Ethicality, and Legality Concerns:**

All members of the Mountain Might product development team and employees of Alpine Performance Laboratories LLC firmly and genuinely assert that this product is completely safe, legal, ethical and effective. The above analysis is testament to the effectiveness of Mountain Might in delivering the five performance adaptations of high altitude training. This section addresses any concerns regarding the safety, legality, and ethicality athletes may have with the product.

**Safety Standards**

The ingredients in Mountain Might have been reviewed by independent experts in nutrition science and shown to have favorable safety profiles at dosages used in human studies. Furthermore, the dosage of every ingredient was meticulously selected to maximize both the safety and efficacy of the supplement. Mountain Might was manufactured in compliance with standards set by the Good Manufacturer Practices (GMP) and Food and Drug Administration (FDA) that help ensure product safety. We have provided a brief review of the scientific literature regarding the safety of each ingredient.

**Warnings**

Precautions should be considered regarding the use of all dietary supplements and doctors should always be consulted before their consumption. Comprehensive information regarding potential interactions with pharmaceutical medications or with existing medical conditions is beyond the scope of this review and should be discussed with a physician prior to use the Mountain Might. Women who are pregnant and children below the age of 18 should refrain from taking Mountain Might without physicians consent. Mountain Might is not intended to prevent or treat any disease including those associated with high altitude. Additionally, Mountain Might may potentiate the effects of high altitude medications such as sildenafil and tadalafil or other medications that exert their efficacy via nitric oxide pathways. This potential interaction is summarized in the subsequent reading and should be discussed with a doctor prior to Mountain Might supplementation. The effects of Mountain Might at extreme altitude or during chronic exposure to high altitude are unknown.

**N-acetylcysteine Safety Profile**

Numerous clinical studies that examined the safety of NAC have demonstrated a benign side effect profile mostly limited to occasional stomach upset (Berk et al. 2008; Grandjean et al. 2000; LaRowe et al. 2006). Long-term studies have also demonstrated no evidence of toxicity or significant negative effects at dosages exceeding 1,800 mg daily (Demedts et al. 2005; Grandjean et al. 2000). This suggests no significant safety concerns for acute or continual NAC supplementation when taken orally at proper dosages.

**Sodium Phosphate Safety Profile**

The scientific consensus regarding sodium phosphate supplementation is also that it possesses a minimal, benign side effect profile (Kreider et al. 2010; Fukuda et al. 2010). Long-term supplementation of sodium phosphate using loading doses of approximately 4 grams per day may potentially interrupt the mineral balance of the stomach and cause gastrointestinal upset (Folland et al. 2008). Accordingly, Mountain Might was formulated with a lower dose of 1100 mg. Clinical evaluation suggests that oral supplementation of sodium phosphate within proper dosages presents minor risk of side effects.

**Hawthorn Berry Safety Profile**

Extensive long-term clinical research on hawthorn berry extract has also demonstrated minimal risk for adverse side effects (Schmidt et al., 1994; O’Connolly et al., 1986; O’Connolly et al., 1987; Leuchtgens, 1993; Reuter, 1994). The majority of this existing safety analysis has been conducted on elderly and patients with heart conditions. One study conducted on patients with heart failure demonstrated that approximately one percent of subjects experienced heart palpitations at 900 mg. Lower doses were associated with no significant side effects. (Reuter, 1994) Reports from long-term and short-term clinical studies suggest that hawthorn berry presents minor risk for serious side effects at the dosage provided in Mountain Might.
Iron Safety Profile

The safety of iron supplementation has been studied extensively. A few early clinical studies on dietary iron raised concern regarding the correlation between high iron levels and cardiovascular disease (Sullivan et al. 1981; Salonen 1992). However, subsequent extensive clinical evaluation has contradicted the relationship with high iron stores and cardiovascular disease (Aronow 1993; Baer et al. 1994; Liao et al. 1994; Morrison et al. 1994; Moore et al. 1995; Sempos et al. 1996; Franco et al. 1998). The high prevalence of iron deficiency has warranted a recommendation of 100 mg per day in athletes with normal iron levels to prevent deficiency (Nielsen et al. 1998). However, gastrointestinal stress is a common finding in iron supplementation studies using dosages of 60 to 300 mg of ferrous sulfate. The Mountain Might formula contains a form of iron with improved bioavailability and reduced gastrointestinal issues than the commonly used ferrous sulfate. In addition, the significantly lower dose of this more tolerable and absorbable form of iron is within the FDA established recommended daily value of iron. Accidental iron overdose can be lethally toxic in children and is associated with acute ingestion of over 900 mg of iron in supplemental form (Food and Drug Administration 1995). Mountain Might is enclosed with a child resistant cap for this reason. However, Mountain should still be kept out of reach of children for maximum safety.

Vitamin B-12 and Folic Acid Safety Profile

Vitamin B-12 and folic acid are considered to have minimal safety issues. No vitamin B-12 toxicity of any kind has been reported in either animal or human studies at any dosage (Miller & Hayes 1982; IOM 1998). Folic acid safety concerns surround its potential to mask B-12 deficiency, potentially disrupt zinc function, and to interact with antifolate medications (Hathcock 2004). However, these concerns relate to the use of excessive supplemental folic acid. Given that the Mountain Might formula contains an amount of folate within FDA daily allowance of 400 mcg, the risk of these negative effects is very low.

Safety Considerations for Extreme Altitude and Chronic Exposure to Very High Altitude

None of the ingredients in the Mountain Might formula, excluding iron, have been clinically tested during exposure to extreme altitude for any duration of time. Prolonged and acute exposures to extreme altitude introduce numerous physiological and pathophysiological occurrences. Theoretically, any variable with the potential to either interfere with physiological tolerance to extreme altitude or exacerbate the pathophysiology of the negative effects of extreme altitude would be considered detrimental to health in these conditions. Accordingly, an assessment of the biological effects of Mountain Might ingredients has been made as they pertain to extreme altitude’s impact on the human body.

1. Oxyhemoglobin Left-Shift Interference

There are numerous effectors of hemoglobin affinity for oxygen including 2,3 DPG, ATP, PH, and temperature. Alterations in oxyhemoglobin affinity have more pronounced effects on the delivery of oxygen to tissue than to oxygen binding to hemoglobin in the lung. For this reason, reducing oxyhemoglobin affinity is considered an adaptive response to high altitude, enabling more oxygen to be unloaded to tissues and utilized by cells. However, there is evidence to suggest that at extreme altitude oxyhemoglobin affinity increases.

A study conducted during an expedition to Mt. Everest demonstrated that the net affinity of hemoglobin for oxygen begins to increase at the extreme altitude of approximately 20,669 ft (6,300 m). The study authors reported that this progressive leftward shift in the oxygen hemoglobin disassociation curve occurs as blood alkalinity begins to increase at a greater rate than 2,3 DPG production. The authors also purported that this effect seemed to be beneficial because it could protect oxygen saturation at extreme altitude. However, this study did not correlate oxygen saturation or any measure of altitude tolerance with the degree to which hemoglobin was “left-shifted.”

Despite these methodological shortcomings, the study does raise concerns regarding phosphate salt ingestion at extreme altitude. Theoretically, stimulating red blood cell metabolism and the production of 2,3 DPG could interfere with the progressive increase in blood oxygen affinity that reportedly begins to occur at approximately 20,000 ft. The highest altitude at which phosphate supplementation has been tested is 14,114 ft (4300 m) at the top of Pike’s Peak. Though oxygen saturation was not measured, supplementation did improve cognitive, psychological, and visual function compared to placebo clearly indicating a beneficial role at this altitude. (Moore and Brewer 1981)

2. Induction of Excessive Erythrocytosis

Altitude-induced production of red blood cells, called erythropoiesis, is the major physiological rationale for altitude training as well as an important component of acclimatization. A higher concentration of red blood cells directly increases blood oxygen carrying capacity. However, exceedingly high hematocrit contributes to increased blood viscosity, which can compromise oxygen transport. Furthermore one rare but dangerous condition, chronic mountain sickness, is characterized by excessive hematocrit at high altitude. Additionally, high hematocrit has been proposed as a risk factor for high altitude thrombosis though, as will be discussed, this connection has been contradicted.
N-acetylcysteine supplementation significantly increases erythropoiesis at both sea-level and during acute altitude exposure. An argument could be made that enhancement of red cell production could increase blood viscosity and contribute to an increased risk chronic mountain sickness. Assuming high hematocrit is an actual risk factor for high altitude thrombosis, NAC could theoretically enhance this risk. We therefore assessed the available evidence regarding NAC supplementation and its effects on thrombosis, chronic mountain sickness, and the underlying physiological factors contributing to these conditions. This information should be reviewed with a physician prior to Mountain Might supplementation during exposure to extreme altitude or prolonged exposure to high altitude.

**Does NAC Increase the Risk of Chronic Mountain Sickness?**

Chronic mountain sickness (CMS) is a rare condition characterized by abnormally elevated hematocrit levels in subjects chronically exposed to high altitude. According to the Chinese Medical Association for high altitude medicine, key diagnostic indicators for CMS include hematocrit levels above 65% and oxygen saturation below 85% (Chines Medical Association 1996). Theoretically, an argument could be made for chronic NAC supplementation increasing CMS risk in highlander populations due to its ability to enhance red blood cell production during acute exposure to altitude. However, a closer examination of the prevailing pathophysiological mechanisms underlying CMS and the preliminary findings of a recent clinical trial that examined NAC for CMS treatment suggests that this risk is minimal.

The prevailing pathophysiological explanation for CMS is that it results from hematological compensation for varying forms of cardiopulmonary insufficiency or hypoxic ventilatory depression that hinder blood oxygen saturation at altitude (Castillo et al. 2006). NAC has been shown to enhance the hypoxic ventilatory response and may actually prevent the ventilatory depression that is thought to trigger CMS (Hildebrandt et al. 2002). Furthermore, a recent study was conducted on NAC as a CMS treatment due to its antioxidant and chelation properties. Preliminary findings have also shown that 600 mg/d does not exacerbate CMS and may enhance CMS outcomes when combined with Acetazolamide (Hurtado et al. 2012). This suggests that NAC does not increase the risk of chronic mountain sickness or excessive erythropoiesis at high altitude.

**Does NAC Increase the Risk of High Altitude Thrombosis?**

High altitude thrombosis is a rare condition involving the formation of blood clots that can obstruct circulatory flow and manifest as pulmonary embolism, cerebrovascular hemorrhage, and deep vein thrombi (Kumar 2006; Hussain & Niaz 2002). High altitude exposure has been suggested to increase the risk of this condition due to its effects on the blood that promote a hypercoagulant state. These effects include reduced red cell flexibility secondary to cell membrane damage, activation of coagulant and immune response cascades secondary to endothelial cell damage, circulatory stasis associated with prolonged sedentary activity, cold exposure, and high hematocrit secondary to dehydration and erythropoiesis (Kumar 2006; Hussain & Niaz 2002).

A recent meta-analysis of 28 high altitude thrombosis case studies demonstrated that no patients had abnormally high hematocrit (Kumar, 2006). This suggests that excessive hematocrit levels do not contribute significantly to high altitude thrombosis risk. It is also important to note that dehydration has been shown to play a considerably larger role than erythropoiesis in the development of high hematocrit levels at extreme altitude (Markus et al. 2010). The effect of NAC supplementation on thrombosis at high altitude has not been examined. However, NAC has been assessed in numerous clinical studies for its ability to reduce the hypercoagulation of blood and thrombosis risk. NAC supplementation has been shown to reduce thrombosis risk in type II diabetics by enhancing platelet antioxidant concentrations (Gibson et al. 2011). In vitro NAC administration also significantly reduced coagulation factors in blood taken from healthy subjects (Jang et al. 2013). NAC infusions have also been shown to reduce prothrombin time, an indirect measure of blood coagulant status, in healthy subjects (Jepsen & Hansen 1994). In conclusion NAC may theoretically contribute to high altitude thrombosis risk by increasing hematocrit. However, due to the secondary role of erythropoiesis in the development of abnormally high hematocrit at altitude, evidence suggesting no relationship between high hematocrit and high altitude thrombosis, no direct evidence of NAC mediated increased risk of thrombosis at altitude, evidence suggesting NAC does not contribute to excessive hematocrit during chronic altitude exposure, and evidence suggesting its anticoagulant and antithrombic properties, NAC supplementation likely does not significantly raise the risk of high altitude thrombosis.

**3. Interactions with High Altitude Medications**

It is unclear whether N-acetylcysteine may interact with certain medications used for the treatment and prevention of high altitude pulmonary edema (HAPE). The PDE5 inhibitors tadalafil and sildenafil have recently become prescribed for the treatment and prevention of HAPE. Neither tadalafil nor sildenafil are listed as contraindicated with NAC in any medical databases we reviewed. However, NAC is contraindicated with, nitroglycerin, a medication that shares a similar mechanism of action to both sildenafil and tadalafil.
The potential concern originates from NAC’s potentiation of the vasodilation effect of nitroglycerin. Nitroglycerin is a potent vasodilator that is no longer used for the treatment and prevention of HAPE due to hypotensive effects as well as case reports regarding its potential to aggravate high altitude cerebral edema by increasing cerebral blood flow (Mazzuero et al. 2008). Nitroglycerin’s vasodilation properties are exerted through the activation of guanylate cyclase by nitric oxide. Guanylate cyclase activation, which is also dependent on sulfhydryl availability, increases the production of cyclic guanosine monophosphate (cGMP), which in turn-induced vasodilation. Since NAC is a sulfhydryl donor it increases sulfhydryl availability and has been shown to potentiate the vasodilatory effect on nitroglycerin and increase the associated risk of hypotension with this medication (Horowitz et al. 1988).

Sildenafil and tadalafil also effect guanylate cyclase mediated vasodilation by inhibiting the breakdown of cGMP and are currently used for the treatment and prevention of HAPE. Though no potentiation has been demonstrated in clinical research the combination of NAC with sildenafil and tadalafil could produce a more substantial vasodilation effect. This potential interaction should be discussed with a physician before combining these substances or engaging in a high altitude excursion where HAPE treatment may be necessary.

**Legality:**
WADA and other banned substance and anti-doping agencies govern the legality of training practices and performance supplements. None of these organizations have illegalized any of the three altitude training techniques. Furthermore, none of the ingredients in Mountain Might or any of their derivatives are listed on any of these organization’s banned substances lists. Mountain Might specifically does not contain any form of the banned substance erythropoietin (EPO).

In addition to not containing any banned substances, Mountain Might is manufactured by the most reputable nutraceutical manufacturer in the industry. This manufacturer complies with all standards set by the GMP and FDA, which include measures to eliminate banned substance cross contamination. There have been absolutely no reports of failed drug tests as a result of Mountain Might supplementation.

**Ethicality:**
There are clear ethical principles that anti-doping and banned substance organizations use to determine legality. Specifically, a substance or form of training is added to a banned substance list if it matches two out of these three criteria: 1) it can potentially improve performance, 2) it is potentially unsafe or harmful to one’s health, and 3) it violates the spirit of sport.

High altitude training, specifically LHTL techniques that utilize artificial altitude simulation, have undergone scrutiny by WADA and the Olympic Committee because of their performance improving capability and potential violation of the spirit of sport. Arguments regarding this technique potentially violating the spirit of sport center around it giving athletes an unfair advantage over their competitors. This is because access to high altitude training is highly variable and dependent on an athlete’s financial and geographical situation. Though WADA and the Olympic Committee have ultimately rejected these arguments, they do highlight the fact that altitude training is a performance advantage that only elite athletes and those lucky enough to live in high altitude regions possess.

Mountain Might is a breakthrough performance supplement that ends the exclusively privileged access to high altitude training. By expanding the geographic and personal financial scope of access to this training technique, it effectively makes high altitude training itself a more ethical practice.

“Mountain Might levels the playing field by expanding altitude training access to those who are not geographically or financially privileged”
Altitude Training Replacement Diagram

High Altitude

Blood Oxygen

NAC Activates
Sodium Phosphate Activates
Hawthorne Berry Sodium Phosphate Activates

Hypoxic Response System
Oxyhemoglobin Affinity
Peripheral Altitude Adaptations

Blood O₂ Saturation
Blood O₂ Carrying Capacity
O₂ Delivery
Cardiac Output
Buffering Capacity

Iron Vitamin Support

↑ VO₂ Max
↑ Aerobic Power
↑ Endurance

Experience the Benefits of Altitude Training Faster and Longer ♦ www.mountainmight.com
Preparations and Unit-Dose Packaging Requirements.

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