Biotics Research Corporation

# Technical Support

Products #3040

# ADB5-Plus™

## Nutritional Support for Adrenal Hypofunction

As a component necessary for survival, a dynamic equilibrium or steady state must exist in the internal bodily environment. As a constituent of this steady state equilibrium, the adrenals function to secrete specific neurotransmitters, including epinephrine (adrenaline), norepinephrine (noradrenaline), and cortisol in response to stress. Subsequently, with the release of these neurotransmitters, a series of physiologic effects ensues. These events may include for example a rapid heart rate or an increased alertness. Thus in these aspects stress represents a protective and restorative event. Alternatively, constant or excess stress may have negative consequences, manifesting as an assortment of symptoms and encompassing a multitude of emotional, behavioral, and even physical symptoms, which may include adrenal gland enlargement, gastrointestinal consequences, as well as immune dysfunction.[1] Although an adaptive process, when in excess, stress consequently results in adaptation, which in turn may result in bodily or organ damage. This process has been defined by Selye as the 'general adaptation (adjustment) or stress syndrome.' Selye, the first to coin the word "stress," further categorized it to represent the "mutual actions of forces that take place across any section of the body, physical or psychological."[2]

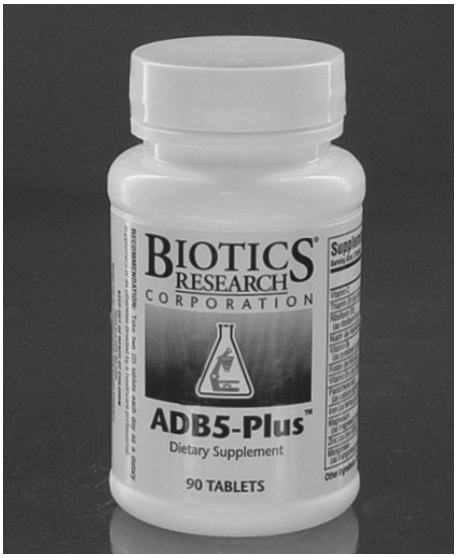
An excess production of stress may manifest in a variety of symptoms, varying enormously among different individuals. Stress related illnesses are a frequent occurrence, noted as one of the most common clinical patterns seen in healthcare clinics. As the degrees of stress vary broadly among individuals, four categories and degrees of stress have been categorized, which include; 1) physical stress, including overwork, lack of sleep, or athletic over-training; 2) chemical stress, such as environmental pollutants, diets excessively high in refined carbohydrates, food or additive allergies, and endocrine gland imbalances; 3) thermal stress, including over-heating or over-chilling of the body; and 4) emotional and mental stress.[3]

Hypoadrenia or adrenal fatigue is considered to be one of the most prevalent debilitating conditions of the past fifty years; however it is rarely diagnosed, and often it is misdiagnosed as other types of illnesses, including chronic fatigue conditions, fibromyalgia or serious food/inhalant allergies. Most patients describe their symptomatology as a 'fatigue that simply cannot be overcome.'[4] In addition to the adrenals acting alone, the combined hypothalamic-pituitary-adrenal axis also contributes to the body's ability to cope with stressors, which include among others infections, blood pressure fluctuations, and illnesses.

The adrenal glands play an essential part in many bodily functions, primarily as a consequence of the hormones they secrete. As such they supply components necessary for numerous biochemical reactions. As a consequence of these hormonal factors, they significantly effect the functioning of every tissue, organ and gland in the body. They also exert an effect on both mental processes and the overall feeling of wellness. Taking into account all of these actions, their primary function is to enable the body to cope with stress. In fact they have been subjectively classified as "the glands of stress."[4] Endurance, energy and resiliency, as well as life itself depends upon their proper functioning. In fact, the hormones secreted by the adrenal glands have been said to "influence all of the major physiological processes in the body."[4]

Adrenal dysfunction can take many forms, the most severe form being Addison's disease, which if left untreated is life threatening. Adrenal fatigue, although less serious, effects millions each year, and usually goes undiagnosed. Diminished function or adrenal hypofunction results from a deficiency in the function of the adrenal glands, and may present as a broad spectrum of disorders. Cortisol has a broad reaching effect in the body, as it not only affects glucose but also has an influence on both protein and fat metabolism. As a consequence of adrenal dysfunction, changes in carbohydrate, protein and fat metabolism may occur, as well as alterations in fluid and electrolyte balance, heart and cardiovascular system problems or a reduced sexual desire.[4] Nutrients, including vitamins, minerals and botanicals are known to provide valuable support for the adrenals, and can offer subsidiary and restorative components to overstressed adrenals.

Structurally, the adrenal gland is divided into two parts, an outer region called the adrenal cortex and an inner region called the adrenal medulla. The adrenal cortex, comprising the bulk of the gland, produces the mineralocorticoid aldosterone and the glucocorticoid cortisol, while the cells of the adrenal medulla produce epinephrine (adrenalin) and norepinephrine (noradrenalin). Androgens, including DHEA and testosterone are also produced by the adrenal cortex. Both epinephrine and norepinephrine have an effect on numerous organs or functions thereof, including the heart, the liver, blood pressure, blood vessels and airways.[5] The chief responsibility of the mineralcorticoids and glucocorticoids is to regulate the stress response, via the synthesis of corticosteroids (cortisol) and catecholamines (adrenaline).[6]




### Vitamins associated with Adrenal Support

**Vitamin C.** In the adrenal glands the concentration of vitamin C is among the highest in the body, being roughly 100 times that of blood plasma levels.[7] As such the adrenals are extremely sensitive to inadequacies in vitamin C. In catecholamine synthesis, vitamin C is required as a co-factor in the conversion of dopamine to norepinephrine.[8] In humans vitamin C secretion occurs as part of the stress response via hormone regulation, specifically in response to stimulation via the adrenocorticotrophic hormone (ACTH). Utilizing adrenal vein catheterization, it was demonstrated that following ACTH stimulation, the mean adrenal vein vitamin C level increased approximately four fold, and then subsequently returned to near pre-stimulation levels approximately 15 minutes thereafter. Peak adrenal vitamin C and cortisol concentrations have been strongly correlated ($r^2$=0.35, P<0.001), suggesting a local action of vitamin C on the adrenal glands. Additionally, it has been noted that, although being of unknown function, the increase in vitamin C secretion suggests that "adrenal vitamin C secretion is an integral part of the stress response."[9] Stress, fever and viral infections, as well as habitual actions, such as smoking and alcohol use, cause a rapid decline in the blood level of vitamin C,[10] and the vitamin C requirements tend to be higher in stressed or traumatized persons.[11]

**Thiamin ($B_1$) (as cocarboxylase)**. As a coenzyme thiamin plays central role in intracellular glucose metabolism,[12] making it a vital adjunct in adrenal dysfunction, as blood sugar fluctuations (hypoglycemia) are a known correlating symptom. Thiamin is required for the metabolism of carbohydrates, as part of the coenzyme cocarboxylase, also know as thiamin pyrophosphate (TPP). The energy produced from oxidation of glucose is highly dependent upon TPP,[13] and in the absence of thiamin a slowing or complete blocking of this enzymatic reaction occurs, due to a lack of TPP. An inadequate production of TPP has the potential to

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affect multiple enzymatic processes, particularly that of carbohydrate metabolism. Thiamin also participates as an active component in the citric acid cycle (Kreb's cycle), as a required cofactor for the decarboxylation of α-ketoglutaric acid to succinyl CoA, thus serves as an important component in energy production. Furthermore, a deficiency in thiamin has been correlated to selective neuronal death in the brain, possibly due to the induction of oxidative stress, as evidenced by the up-regulation of markers of endoplasmic reticulum stress. This type of stress has been associated with a range of neurodegenerative processes, including the obstruction of blood flow to the brain.[14] Decreased mental acuity is a correlating symptom of adrenal dysfunction, thus thiamin may play a beneficial role in this capacity.

**Riboflavin (Vitamin B2).** Riboflavin is found primarily in the body as a fundamental component of the coenzymes flavin adenine dinucleotid (FAD) and flavin mononucleotide (FMN).[15] In both adrenal and thyroid insufficiency the conversion of riboflavin into FAD and FMN is impaired.[16, 17] A deficiency in riboflavin has also been correlated to an increase in oxidative stress.[17] Along with other B vitamins, riboflavin is utilized to support energy transfer and production via its action in the metabolism of fats, carbohydrates and proteins. As such it plays a vital role in energy production. Additionally, riboflavin is required for red blood cell formation and respiration, antibody production, and in the regulation and production of growth hormone.

**Niacin (as niacinamide).** Niacin is an essential component of the coenzymes NAD and NADP, thus is essential to all living cells. NAD metabolism has been associated with a vital effect on biological entities, including the overall human lifespan.[19] NAD functions as both an electron carrier for intracellular respiration, and along with other enzymes, as a dehydrogenase, for the purpose of oxidizing energy providing molecules, including poly (ADP-ribose) polymerases, mono-ADP-ribosyltransferases, as well as the sirtuin enzymes.[19, 20] NADP on the other hand functions as a hydrogen donor in reductive biosynthesis. It has been estimated that approximately 200 enzymes require the coenzymes, NAD and NADP.[20] Nicotinic acid has also been associated with the glucose tolerance factor, implicating its importance in the insulin response, making it an extremely important entity in adrenal support, as adrenal fluctuations are associated with hypoglycemic symptoms. In niacin deficient DNA repair models, a dramatic inhibition in DNA repair has been demonstrated.[21, 22] A deficiency in niacin is commonly recognized by changes in the skin, including the mucosa of the mouth, tongue, stomach, and intestinal tract, as well as changes in the nervous system.[23]

**Vitamin B6 (as pyridoxal-5-phosphate).** Vitamin B6 serves as a coenzyme in well over 100 reactions, which makes it functionally important in both metabolism and health. The active coenzymes of vitamin B6 are pyridoxal 5-phosphate (PLP) and pyridoxamine 5-phosphate (PMP). PLP functions as a cofactor in lipid metabolism. Consequently with vitamin B6 deficiency, decreased body fat, decreased levels of liver lipids, as well as impaired lysosomal lipid degradation has been observed.[24, 25, 26] Both the nervous and immune systems require an adequate supply of vitamin B6 for efficient function.[27, 28, 29, 30] Vitamin B6 is also required for the conversion of tryptophan to niacin and serotonin,[31, 32] as well as for the conversion of tyrosine to dopamine. In one study a deficiency in vitamin B6 was correlated to a slower extracellular dopamine release (43% longer with deficiency).[33] Dopamine is known to be an active participant in the secretory modulation of both aldosterone and catecholamine from the adrenal gland,[34] and dopamine depletion is correlated with physical and/or psychological stress. In an animal study a single dose of B6 was demonstrated to stimulate the secretion of adrenal catecholamines.[35]

**Vitamin B12 (as cobalamin).** Fatigue is a common symptom in adrenal dysfunction, and a deficiency in vitamin B12 may be correlated to symptoms of fatigue. Vitamin B12 plays an integral part in the biosynthesis of pyrimidines and purines, making it an essential component in the synthesis of nucleic acids.[11] Vitamin B12 is required as a coenzyme for multiple enzymes, including $N^5$-Methyltetrahydrofolate homocysteine methyltransferase, which is a required component of L-methionine synthesis. A deficiency in vitamin B12 has been associated with neurological manifestations.[36] Additionally, vitamin B12 deficiency, in combination with a deficiency in other B vitamins, including vitamin B6 has a direct impact on the synthesis of neurotransmitters.[37] Subsequently with deficiency an impact on cognitive functions is possible. Alternatively, supplemental vitamin B12 may alleviate this deficiency and provide support for adrenal dysfunction, via its impact on improving decreased mental acuity.

**Folate (as folic acid).** Folate is a constituent of every living cell, both in plants and in animals. Like vitamin B12, folic acid is involved in the biosynthesis of purines and pyrimidines, and is utilized by the body to decrease homocysteine levels. Folate also plays a role as a coenzyme in numerous metabolic reactions, and deficiency has been correlated with generalized weakness, melancholy feelings, as well as disorders of the peripheral nerves.[11]

**Pantothenic Acid (as calcium pantothenate). (Vitamin B5)** Pantothenic acid, a water soluble vitamin, plays an essential role in the metabolism of carbohydrates, fats and proteins. It also participates in other essential bodily functions including the production of common neurotransmitters, for example hormones, and, as a factor in the synthesis and oxidation of fatty acids and pyruvate, it serves as an essential component of the citric acid cycle. As such it is an important factor in energy production.[38] A deficiency in pantothenic acid has been associated with adrenal atrophy.

Pantothenic acid forms the core of Coenzyme A (CoA), as the initial step in the synthesis of Coenzyme A is the phosphorylation of pantothenate. Coenzyme A is required in the synthesis of the important neurotransmitter, acetylcholine, a chemical required for nerve transmission. Thus, pantothenic acid plays an intricate role in the synthesis of isoprenoid-type compounds, including steroid hormones, cholesterol, and vitamins A and D.[39] Altered CoA homeostasis has been documented in certain conditions, including starvation, diabetes, alcoholism and vitamin B12 deficiency.[40] A close relationship exists between the tissue levels of pantothenic acid and adrenal cortex function, as pantothenic acid functions to stimulate the adrenal glands to produce additional cortisol. A deficiency in pantothenic acid has been correlated to disruptions in or abnormalities of neurotransmitter production, resulting in difficulty in dealing with stressful situations. Accordingly, pantothenic acid is sometimes referred to as the "anti-stress" vitamin. A deficiency in pantothenic acid has been shown to result in clinically prevalent symptoms of generalized malaise.[40]

## Minerals Associated with Adrenal Support

**Iron (as ferrous gluconate).** Iron is a major component of hemoglobin, the primary component of red blood cells, accounting for greater than 65% of iron in the body.[11] In addition to hemoglobin, other iron containing compounds include myoglobin and the cytochromes. Myoglobin's primary function is in the transport and storage of oxygen within the muscle, while the cytochromes, specifically cytochromes a, b and c, function in the mitochondrial electron transport chain, and thus are critical to respiration and energy metabolism. Significant iron deficiency has been correlated with depleted levels of cytochromes b and c, resulting in limited rates of oxidation by the electron transport chain.[41] Iron is also required as a cofactor in the synthesis of the neurotransmitters dopamine, norepinephrine and serotonin.[42] Epinephrine is derived from the amine norepinephrine, and epinephrine levels are known to be affected in adrenal fatigue, characteristically being decreased. Norepinephrine and epinephrine also act as aids in the maintenance of normal blood glucose levels by stimulating glucagon release, glycogenolysis and food consumption, and by inhibiting insulin release.[43] As a final point, iron deficiency is noted as the most common nutritional deficiency worldwide, affecting predominately women and children.[44, 45]

**Magnesium (as magnesium malate).** As a cofactor in over 300 metabolic reactions, including those involved in the production of metabolic energy, magnesium serves as an extremely important mineral *in vivo*. A deficiency in magnesium is characterized by diverse symptomatology, including muscle spasms, personality changes, and neuromuscular symptoms,[11] as well as 'impairments in emotional memory,[46] and central nervous hyperexcitability".[47] Magnesium is a necessary component in the adrenal hormone cascade, thus magnesium status is closely correlated to the ability of the adrenals to recover from stress. Additionally, the absorption capacity of magnesium decreases with increasing age, emphasizing the need for added magnesium with increasing age.[48]

**Zinc (as zinc citrate).** Zinc performs many diverse actions in the body; however three are considered vital, those being its function as a structural component, as a catalyst, and as a cocatalyst. An added role is its function as a regulatory factor. Zinc is an essential component of the zinc containing metalloenzymes, which includes alkaline phosphatase and lactate dehydrogenase, and in this role may have dual functions, for example playing both a functional and a structural role. Consequently, a depleted zinc status affects the function of these enzymes, resulting in either diminished or complete loss of enzymatic activity.[49] Proper functioning of the adrenal glands relies on adequate zinc status. Thus it is not surprising that zinc deficiency has been correlated to 'adenohypophyseal-adrenal cortex function' as well as to an increased

stress response. The adrenocorticotropin response was demonstrated to be positively correlated with serum zinc status.[50] Also, with zinc deficiency an increase in neuronal damage has been observed, which was associated with an increase in the formation of free radicals.[51] Supplemental zinc has demonstrated to be an efficient means of improving zinc status.[52]

**Manganese (manganese glycinate).** Manganese functions as a component of the mitochondrial manganese containing superoxide dismutase (SOD), which plays a critical role in protecting the cell from damage due to oxidative stress. Manganese deficiency in animals has been reported to downregulate the mitochondrial manganese SOD, at the level of gene transcription. Manganese-activated enzymes also play important roles in the metabolism of carbohydrates, amino acids, and cholesterol.[53] Both manganese-containing and manganese-activated enzymes play critical roles in gluconeogenesis.[54]

**Copper (as copper gluconate).** Copper is an essential trace element for both humans and animals, as it plays a critical role in the oxidation/reduction reactions of the body, primarily due to its ability to easily accept and donate electrons. This capacity also makes it an important mineral in the scavenging of free radicals. In addition to being a vital component of the copper containing enzymes, known as the cuproenzymes, it is also involved in multiple enzyme processes, including the production of cellular energy, via its vital function as part of the enzyme cytochrome *c* oxidase. As a result it may be viewed as a vital component for adrenal support.

**Malic Acid (as magnesium malate).** A deficiency in malate, an essential component of the Citric Acid Cycle, has been linked to physical exhaustion.[55] Exogenous Malate in very small amounts is required to increase ATP production and mitochondrial oxidative phosphorylation. Additionally, Malic Acid, known to be an aluminum chelator, may support aluminum detoxification.

## Botanicals Beneficial for Adrenal Support

***Rhodiola rosea* (extract) (root).** In many parts of the world *Rhodiola* has been utilized for decades to alleviate everyday symptoms of anxiety, despair, and insomnia, and is a popular adaptogen and anti-stress plant in both Europe and Asia.[56] Its use has been correlated to mood improvement, and the alleviation of both depression and fatigue.[57] In one study the use of *R. rosea* was demonstrated to significantly improve symptoms of general apprehension, as indicated by a reduction in the Hamilton Anxiety Rating Scale (HARS) score.[58]

**Tyrosinase (from mushroom)**. Mushroom derived Tyrosinase is a valuable source of amino acids, containing all of the essential amino acids, along with most of the nonessential amino acids.[59] Tyrosinase is a copper-binding transmembrane glycoprotein, which catalyzes the hydroxylation of tyrosine, the first step towards melanogeneisis; the biochemical pathway for melanin biosynthesis.[60] Tyrosinase also catalyzes the hydroxylation of tyrosine to dihydroxyphenylalanine (DOPA), as well as the subsequent oxidation of DOPA to further bioactive derivates, including 5,6-dihydroxyindole (DHI).[62, 63] DOPA plays a significant role in adrenal function as it is the precursor of dopamine, noradrenaline, and adrenaline, as well as the rate-limiting step in catecholamine biosynthesis.[64] In addition to its presence in epidermal melanocytes, tyrosinase is also a component of the eye, as part of the pigment epithelia of the retina, iris, and ciliary body.[61]

## Additional Components Providing Support for Adrenal Function

**Citrus Bioflavonoids.** The adrenals are known to be concentrators of vitamin C, with the level of vitamin C in the adrenals typically around 100-fold that of blood plasma levels.[65, 66] In animal studies a depletion of vitamin C was shown to reduce the vitamin C content of the adrenals to 1/20$^{th}$ of the normal concentration, which was correlated with a lower secretion of aldersterone, compared to those animals with no vitamin C depletion. Additionally, in animals exhibiting vitamin C depletion, an impaired plasma aldosterone response to sodium depletion has been demonstrated.[67] As such antioxidants such as bioflavonoids may provide support to stressed adrenals.

**N-acetyl-L-cysteine (NAC).** NAC is a potent antioxidant that functions in intracellular glutathione synthesis,[68] in which it serves as a scavenger of reactive oxygen intermediates. As an antioxidant NAC functions to inhibit glutathione-induced cytochrome *c* release, to reduce elevated levels of intracellular hydrogen peroxide ($H_2O_2$), and to prevent the loss of mitochondrial membrane potential. These actions are particularly important during increased oxidative stress, as under these conditions various intracellular components, including polyunsaturated fatty acids, lipids, proteins, as well as DNA may suffer extensive damage.[69] NAC has also been demonstrated to be a potent blocker of the induction of TNF-alpha, IL-1 beta, IFN-gamma and iNOS,[70] implicating an additional beneficial action via its ability to quench these proinflammatory activators.

**Choline (as choline bitartrate).** Choline is recognized as an essential nutrient in humans, primarily due to its role as the precursor of phospholipids, as well as to the neurotransmitter acetylcholine.[72, 73] Acetylcholine functions as a crucial component for the structural integrity of the cell membrane. The phosphorylation of choline, via the Kennedy pathway, yields phosphatidylcholine, the major form of cellular choline.[74] Over 1,000 genes associated with neural precursor cells, including those involved in cell proliferation, differentiation and apoptosis require choline for activity, thus choline is an essential factor in gene expression.[75] In addition to other functions, choline participates in lipid and cholesterol metabolism, cholinergic neurotransmission, and transmembrane signaling.[76]

**Superoxide Dismutase and Catalase (vegetable culture sources).** Superoxide dismutase and Catalase both function as potent antioxidants, shown in human studies to decrease both oxidative damage, as well as other types of damage to DNA.[77] Since adrenal dysfunction may potentially result in an increased production of reactive oxygen species, antioxidants may be an important adjunct for adrenal support.

## Glandular Support

**Adrenal Gland Concentrate (porcine), Lamb Pituitary/Hypothalamus Complex (ovine), Parotid Tissue (bovine).** Glandular components serve to provide raw materials which aide in the functional support of the respective organ. Glandular components also contain vital chemical messengers, which are potentially lacking in those with adrenal dysfunction. They function in supporting the adrenals by relieving the burden of underfunctioning adrenal glands, which may be particularly important in the initial phases of adrenal repair. They have also been demonstrated to speed recovery of the organ, and specifically with the adrenals may lead to increased energy.[78]

In addition to a good diet, natural adrenal support utilizing vitamins, minerals, botanicals and glandular components serves to aid in promoting the restoration of healthy adrenal function.

# Supplement Facts

**Serving Size: 2 Tablets** — **Servings Per Container: 45**

| | Amount Per Serving | % Daily Value |
|---|---|---|
| Vitamin C | 75 mg | 125% |
| Thiamin ($B_1$)(as cocarboxylase) | 5 mg | 333% |
| Riboflavin ($B_2$) (as riboflavin-5-phosphate) | 5 mg | 294% |
| Niacin (as niacinamide) | 25 mg | 125% |
| Vitamin $B_6$ (as pyridoxal-5-phosphate) | 5 mg | 250% |
| Folate (as folic acid) | 200 mcg | 50% |
| Vitamin $B_{12}$ (as cobalamin) | 6 mcg | 100% |
| Pantothenic acid (as calcium pantothenate) | 75 mg | 750% |
| Iron (as ferrous gluconate) | 0.5 mg | 3% |
| Magnesium (as magnesium malate) | 35 mg | 9% |
| Zinc (as zinc citrate) | 2.5 mg | 17% |
| Manganese (as manganese glycinate) | 1 mg | 50% |

| | Amount Per Serving | % Daily Value |
|---|---|---|
| Proprietary Blend | 733 mg | |
| Malic Acid (as magnesium malate)* | | |
| Adrenal gland concentrate (porcine)* | | |
| Rhodiola rosea (extract) (root)* | | |
| Citrus bioflavonoids* | | |
| Choline (as choline bitartrate)* | | |
| Superoxide dismutase (vegetable culture)* | | |
| Catalase (vegetable culture)* | | |
| N-acetyl-l-cysteine* | | |
| Lamb Pituitary/Hypothalamus complex (ovine)* | | |
| Parotid tissue (bovine)* | | |
| Copper (as copper gluconate) | | <2% |
| Tryosinase (from mushroom)* | | |

***Daily Value not established**

**Other ingredients:** Stearic acid (vegetable source), cellulose, modified cellulose gum, silica and food glaze.

**RECOMMENDATION:** Take two (2) tablets each day as a dietary supplement or as otherwise directed by a healthcare professional.

**WARNING:** Accidental overdose of iron-containing products is a leading cause of poisoning in children under 6. Keep this product out of reach of chidren. In case of accidental overdose, call a doctor or poison control center immediately.

**Caution:** Not recommended for pregnant or lactating women.

**KEEP OUT OF REACH OF CHILDREN**

Store in a cool, dry area.

Sealed with an imprinted safety seal for your protection.

NDC #55146-03040 Rev. 6/08

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