

DEFEND™

white paper provided by Archmore Botanical Research Group, LLC

*A Javita
International
product*



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Defend™, an ActiveBlendz product

a Javita International product

- A technical overview outlining the safety and efficacy of Defend™, a dietary supplement designed to support healthy immune function*
- This technical white paper will include:
 - Formulation breakdown
 - Synopsis of health benefits associated with the proprietary ingredients
 - Safety
 - In vitro and in vivo trials demonstrating safety of ingredients in Defend™ at recommended levels
 - A review of any adverse events associated with the ingestion of the proprietary ingredients
 - Efficacy
 - A description of the mechanism of action for each proprietary ingredient
 - Cellular, animal, and human trials demonstrating immune support
 - Recommended guidelines for use
 - Dosing recommendations for immune support
 - Potential adverse events and warnings

**These statements have not been evaluated by the Food and Drug Administration and are meant for research purposes only.*



Overview

The immune system is defined by the National Institute of Health (NIH) as a network of cells, tissues, and organs that work together to protect the body from infection. It can do this by directly targeting and destroying foreign invaders (antigens) when they enter the body or by recognizing and remembering previous invaders to prevent future infections. This is done through a complex array of proteins and specific immune cells, the main ones being phagocytes, lymphocytes, NK cells, and cytokines. To stimulate the immune system, increasing the proliferation and activity of these cells is crucial. Defend™ was designed to do just that.

By combining a complex mixture of mushrooms with a blend of superfruits and vitamin C, Defend™ stimulates the immune system to increase the production and activity of these immune cells. It includes compounds that improve fatigue as well, helping the body improve energy levels to better fight off infections. Finally, it includes strong antioxidants such as vitamin C that help with the inflammatory immune response, reducing it through free radical scavenging.

This white paper will review the available scientific evidence to support the formulation and use of Defend™ for both existing infections as well as prevention. It will provide an overview of how the botanical ingredients work in the body as well as a more detailed analysis of each ingredient's mechanism of action. For those wishing to pursue information on these ingredients further, a list of citations is available. This paper is meant to assist in the education of consumers. It is not meant to diagnose, treat, or be used in place of medical advice.



Formulation

Defend™ was designed to be an easy to consume, great tasting powdered beverage that could easily be mixed with water on the go to help support a healthy immune system. This formulation contains two key complexes. First is the renowned mushroom complex known as Immune Assist, comprised of six powerful mushrooms that support healthy immune balance. The second is a blend of powerful superfruits known to stimulate the immune system and also protect from inflammation through antioxidation, a key mechanism for fighting infection. Both complexes have been supplemented with vitamin C, a critical ingredient for maintaining optimal immunity.

- Formulation includes two herbal complexes for immune support
 - Immune Assist Mushroom Complex
 - Contains six mushroom products well-researched and used for immune support
 - *Agaricus blazei*
 - *Lentinula edodes* (Shiitake)
 - *Grifola frondosa* (Maitake)
 - *Coriolus versicolor* (Turkey tail)
 - *Ganoderma lucidum* (Reishi)
 - *Cordyceps sinensis*
 - Fruit Complex
 - Contains a blend of elderberry, acai, and blueberry to stimulate the immune system and provide antioxidant protection for beneficial intestinal microbiota
- Formulation includes vitamin C from acerola fruit which has been shown to support immune function while also providing antioxidant protection from inflammatory conditions



Immune Assist Mushroom Complex- overview

Immune Assist is a blend of six well-known mushrooms that have been used for centuries as health tonics throughout much of Eastern Asia. These mushrooms include *Agaricus blazei*, *Lentinula edodes*, *Grifola frondosa*, *Coriolus versicolor*, *Ganoderma lucidum*, and *Cordyceps sinensis*. At first glance, these may appear to be foreign herbal products; however, they have become more widely known throughout the globe in recent years. Mushrooms naturally contain a high level of polysaccharides including beta glucans, which provide some of the immune stimulation we see in Defend™. These compounds increase the production of immune cells including phagocytes, lymphocytes, NK cells, and cytokines.

When developing Immune Assist, researchers discovered that when dealing with the immune system, it is often necessary to utilize more than one compound to fight infections. This is because of the rapid adjustment viruses and bacteria are able to make in their reproductive process. They are able to adjust their genetics to become new strains of infection that can bypass immunities. Therefore, by supplementing the immune system with more than one ingredient, Immune Assist provides a more complex weapon to fight these brilliant invaders.

Agaricus blazei, also known as the mushroom of the sun or the almond mushroom, is an edible mushroom cultivated through much of Brazil, China, and now Japan, and has a rather sweet taste and aroma, similar to almonds.

Lentinula edodes may seem like an unfamiliar botanical name; however, it is one of the most commonly consumed mushrooms in East Asia. Referred to by its common name, the shiitake mushroom can now be found in most markets throughout the West as well. It is used in Asian cooking in both its fresh and dried forms and is readily seen in the commonly consumed Japanese miso soup.

Grifola frondosa, known as the maitake mushroom, is used readily as a medicinal plant in Asia, yet it is grown prolifically in the northeastern United States as well. This mushroom grows for many years in the same place, allowing its fruiting body to cluster, in some cases growing up to one hundred pounds. It, too, is edible when young, becoming inedible over time simply due to the hard exterior that occurs with age.



Coriolus versicolor is also known as the turkey tail mushroom due to the multiple colors radiating throughout this polypore mushroom. Although used for thousands of years throughout Asia to stimulate the immune system, Turkey Tail is gaining renowned credibility due to its approved use in clinical trials by the US FDA as well as the Japanese government for cancer research.

Ganoderma lucidum, the reishi mushroom, has been a medicinal remedy in China for more than 2,000 years. It is known there as the lingzhi mushroom and is also a polypore mushroom, meaning that it releases its spores through fine pores, not through gills. Although edible, this mushroom is highly bitter, and is usually administered as an extracted product in capsule or powder form. In addition to its immunologic properties, reishi is also highly valued as an anti-allergen, showing positive effects against asthma and contact dermatitis.

Cordyceps sinensis is sometimes referred to as the caterpillar mushroom due to the method in which it grows in the wild. This fungus germinates inside the living larva of ghost moths, kills and mummifies the larva, and then the fruiting body emerges from the dead larva. Although it has a very strange life cycle, this fungus has been prized for over 2,000 years in Tibet and Nepal for its medicinal benefits, including lung and kidney health, anti-aging, cancer, and even erectile dysfunction.

Immune Assist is a 100% USDA-certified organic, certified kosher, non GMO blend of these six mushrooms cultivated in a biotech lab to insure no contamination occurs and only the highest quality product is produced. Immune Assist Mushroom Complex has been refined physically to reduce the particle size of the product without negating or removing any of the beneficial compounds. Through this non-destructive process, developers are able to achieve a particle size of less than 40 microns. This extremely small size allows for the improved bioavailability of the product when it enters the digestive system. While eating whole mushrooms delivers the compounds found in Defend™, albeit at much lower doses than this concentrated form, it takes significantly longer for these beneficial compounds to be broken down in the digestive system and absorbed into the body. By processing the material before it is consumed, Immune Assist allows for the ease of digestion and enhanced bioavailability one is seeking when looking to enhance immunity in a timely manner. This small micron size also allows it to dissolve more easily when mixed with water, making for an easy to consume beverage.



Fruit Complex- overview

Although there is not a set criteria used to define a superfruit, many fruits have been classified as such due to the immense medicinal properties they possess. A number of these superfruits were used in Defend™ for their ability to stimulate the immune system while simultaneously providing antioxidant protection a mechanism necessary to maintain proper immune balance.

Acai fruit is probably the quintessential superfruit. Although there are several palms that have an edible palm heart, this native Brazilian palm is the most well-known and most widely appreciated as a functional food. An evergreen of the rainforest, acai has been well-documented for its potent antioxidant power, scoring higher than any other fruit in free radical scavenging tests. This antioxidation plays a very strong role in intestinal inflammation, a body system that must be maintained to achieve optimal immunity.

Blueberry, although commonly consumed in the everyday diet, is considered a superfruit, just one that is much more widely known and utilized. Blueberry not only contains powerful antioxidants similar to acai, but it also has the ability to directly influence the immune system by increasing the proliferation of lymphocytes, the cells that allow for the creation of antibodies.

Elderberry is also included in Defend™, although it is not normally classified as a superfruit per se. However, this botanical has been used for hundreds of years to boost immune responses and aid in infection prevention. Recently it has been studied for its ability to prevent or shorten the duration of the flu, and has been shown just as effective in other devastating viruses as well.



Vitamin C- overview

Vitamin C, or more accurately L-ascorbic acid, is an essential nutrient necessary for human life and development. Although it is naturally produced by the body, in compromised situations, a deficiency of this nutrient can occur. Since vitamin C is a cofactor in several essential enzymatic reactions, when it is deficient, negative conditions result. Vitamin C is found in high concentrations in immune cells, and in situations of illness, can be easily and quickly depleted. Although it may not directly prevent infection, vitamin C has been known to decrease the duration of the common cold. It is hypothesized to regulate the activity of immune cells, including phagocytes, lymphocytes, and cytokines. Because of its crucial role in many reactions throughout the body, the US FDA has issued a North American Dietary Reference Intake of 90 milligrams per day simply to maintain its presence in the body. However, under conditions of stress due to infection, disease, or even rigorous exercise, this amount should be increased. Most international government agencies have set an upper limit of vitamin C intake to no more than 2 grams per day.



Safety

- Defend™ was designed such that a single cup daily could produce results, but in cases where a stronger immune boost is needed, two cups daily would maintain safety parameters.
- All safety studies outlined below are relevant to the dosages recommended for Defend™
- Adverse safety and toxicity trials are also reviewed



Immune Assist Mushroom Complex- safety

The six mushrooms included in Immune Assist have been consumed as functional foods for thousands of years throughout much of East Asia; however, when moving from a food product to a supplement, safety evaluations must be carried out. In acute, subacute, and chronic toxicity studies, all of these six mushrooms have shown no adverse effects, including no anaphylactic reactions and no effects in mutagenicity, genotoxicity, and blood chemistry tests. In animal and human trials utilizing these mushrooms, researchers found little to no negative side effects (1, 2, 3). In some instances, lethal doses for the mushrooms were evaluated and found to be significantly higher than possible to consume even with multiple cups of Defend™ per day (4).

Adverse Events in Clinical Trials: A Review

Cordyceps has been shown to be safe and effective in humans; however, there have been minimal side effects in clinical trials including dry mouth, nausea and diarrhea. As cordyceps functions via a different mechanism than the other mushrooms in the study, it has effects on testosterone levels not seen with the other mushrooms. These have been shown to be beneficial in instances of erectile dysfunction, but should be avoided by pregnant or lactating women (5).

There is a condition known as shiitake dermatitis, which is a skin eruption that resembles whiplash marks and occurs after consumption of raw shiitake mushrooms. It is caused by a reaction to the compound lentinan found in the mushroom. There have only been two documented cases of this rare condition, and both instances resolved themselves following the onset after only 10 days (6).



Fruit Complex- safety

The four fruits included in the fruit blend of Defend™ include elderberry, acai, acerola, and blueberry. Acai and blueberry are edible fruits consumed regularly throughout the world (7). Although very rare, allergies may occur with these fruits, as with any product known to have a protein component. These allergies are rare, but if known, Defend™ should not be consumed.

Elderberry is less well known in the western world but has been used for hundreds of years in traditional medicine throughout the rest of the world. This long history of use has resulted in little to no negative side effects. In a clinical trial involving sixty patients suffering from influenza, elderberry was shown to be safe and effective with minimal side effects (8). However, elderberry is a powerful immune-stimulant. Some research has alluded to an indirect interaction with those being treated for autoimmune disorders, as elderberry stimulates the immune system, while treatments for these conditions are meant to reduce immune function (9).

Acerola is known to be one of the best fruits rich in vitamin C and polyphenols. As a potential natural supplier of vitamin C, acerola has been studied extensively to determine its safety for delivering this essential nutrient. In animal trials, it was found to have little to no toxicity, with a lethal dose of more than 2000 mg/kg body weight in mice (10). In human trial, not only was vitamin C derived from acerola well tolerated, but it was also found to be slightly more absorbable than vitamin C alone (11). When it comes to vitamin C, this essential nutrient has an established daily intake requirement of 75 mg to 90 mg in the United States, with similar requirements established for other developed countries. Upper limits have been set to 2 grams daily, otherwise, potentially negative consequences may occur, namely gastrointestinal distress (12).



Adverse Events in Clinical Trials: A Review

A single cellular trial showed that acai has mutagenic abilities, meaning it may be able to alter genetic material. This was demonstrated using *Salmonella typhimurium* as the testing medium. Acai pulp was found to have positive mutagenicity in this particular species. In all other safety assessments including mass spectroscopy analysis, blood biochemistry, bacterial reverse mutation, and genotoxicity, acai showed no negative results (13). However in a second safety evaluation, acai was not found to have these mutagenic abilities, leading to conclusions that there may have been a compounding factor involved in the previous study (14). In addition, its long history of regular use and lack of negative outcomes suggest that there is not a genetic risk with the ingestion of acai, particularly at the levels found in Defend™.



Formulation Efficacy

Defend™ contains two botanical complexes combined with vitamin C to target multiple immune cells for optimal enhancement. By combining a wide array of mushrooms, fruits, and essential nutrients, Defend™ activates these different classes of immune cells while simultaneously providing antioxidant protection from inflammation, aiding in further immunity. These mechanisms will be discussed for each of the complexes in detail. Should any potentially negative outcomes from clinical trials be discovered, they are presented here as well along with a rationale for said outcome.

- Immune Assist Mushroom Complex
 - Activates a full spectrum of immune cells through a diverse blend of numerous mushroom species
 - Contains an adenosine-like compound to increase cellular energy to fight infection
- Fruit complex with vitamin C
 - Activates phagocytes, lymphocytes, and cytokines for optimal immune balance
 - Prevents inflammation through antioxidation, protecting various body systems to enhance immunity



Immune Assist Mushroom Complex- efficacy

Mechanism of Action: Activates a full spectrum of immune cells through a diverse blend of numerous mushroom species

Mushrooms naturally contain very high levels of polysaccharides, large carbohydrate molecules that play different roles in our cells, from building structural walls to acting as storage containers. In the case of immunity, polysaccharides activate specific immune cells depending on the type of polysaccharide. Immune Assist Mushroom Complex includes six different types of mushrooms containing a diverse array of polysaccharides to activate all different classes of immune cells, including NK (natural killer) cells, phagocytes, lymphocytes, and cytokines. One of the most potent polysaccharides found in Immune Assist is beta-glucan, a powerful activator of these specialized immune cells. Beta-glucan has been found in all six mushrooms included in this complex.

Agaricus has an additional type of polysaccharide that not only activates natural killer cells like beta-glucan but also increased activity of macrophages. Macrophages are a type of white blood cell that absorbs and removes foreign bodies, including microbes, debris, and even cancer cells. When tested, agaricus increased cytotoxic T-lymphocyte activity in tumor-bearing mice, showing not only its role in immunity but also its potential as an aid for cancer treatment (15).

Shiitake mushroom (*Lentinula edodes*) contains another well-known polysaccharide called lentinan ([1,3] beta-D-glucan). Lentinan is one of the most abundant compounds in this mushroom and is believed to house most of the immunological benefits for this mushroom species. Lentinan has demonstrated a wide range of immune enhancement, from antifungal effects to suppressing the activity of HIV-1 reverse transcriptase (16). This diverse polysaccharide has also demonstrated anti-cancer benefits on colon cancer cells in vitro, a mechanism believed to be through its ability to suppress cytochrome P450 1A enzymes that are known to activate cancer cells (17, 18).

Maitake (*Grifola frondosa*) has received much funding for research since it was approved in 1997 as an Investigational New Drug by the US FDA. Since then, it has been involved in many in vitro and clinical trials. One such trial was the ground breaking clinical trial in 2009 conducted at Memorial Sloan-Kettering Cancer Center. In this Phase I/II clinical trial, researchers demonstrated conclusively that maitake can stimulate the immune systems of breast cancer patients. It does this by stimulating NK cells



as well as other immune system cells, demonstrating its ability to improve both the innate immune system as well as the adaptive immune system (19, 20, 21, 22.). This could have powerful ramifications in cancer treatment, if not directly impacting the proliferation of the cancer itself, but by helping the body naturally ward off secondary infections during cancer treatments.

Turkey Tail mushroom (*Coriolus versicolor*) contains components hypothesized to induce cytokine expression, small proteins that are important in cell signaling (23). In the immune system, cytokines regulate the balance between antibody-mediated immunity and cell-based immunity (phagocytes and lymphocytes) and can also regulate the growth and responsiveness of cell populations. It also has been shown to selectively promote apoptosis, or programmed cell death, specifically on leukemia cells and cells that had been treated with chemotherapeutic agents (24). In addition, compounds from this mushroom were shown to lessen some of the side effects from chemotherapy and radiation therapy through the enhancement of the immune system itself as well as its strong antioxidant activity (25, 26).

Reishi mushroom (*Ganoderma lucidum*) balances the immune system by insuring it is effective when stimulated but not over effective when it does not need to be, a condition known as auto-immunity. Reishi not only contains the powerful beta-glucans that activate immune cells but also has a high concentration of triterpenes, a class of chemical compounds necessary for life including steroids. Reishi has been shown to stimulate macrophages to aid in removing toxins, microbes, and debris from the body as well as increasing interleukins, a specific group of cytokines (27, 28, 29).

Cordyceps sinensis is unique among these mushrooms as it contains a nucleoside not found in the other species known as cordycepin (3'-deoxyadenosine). This is a derivative of the nucleoside adenosine that plays a crucial role in energy transfer through the ATP pathway. Cordycepin is so similar in structure to natural adenosine that the body has a difficult time differentiating between the two. Therefore, when it is faced with cordycepin, the body will incorporate it just as it would adenosine, increasing bio-energy via the ATP pathway. This has been shown to increase the utilization of oxygen and improve endurance while reducing fatigue in the body. Taken a step further, research has shown these benefits to alleviate symptoms of respiratory illness including bronchitis and asthma (30). Cordyceps has also been shown in trials to promote NK cell activity, improving the production of immune cells (31).



Fruit Complex-efficacy

Mechanism of Action: Activates phagocytes, lymphocytes, and cytokines for optimal immune balance

The fruits included in this complex were specifically selected for their stimulatory effects on the immune system. They accomplish this through the activation and proliferation of specific immune cells, including phagocytes, lymphocytes and cytokines. Each fruit has a slightly different mechanism, allowing for an additive effect when combined in Defend™.

Elderberry has been shown in vitro to have beneficial effects on both bacterial and viral proliferation, namely with the incidence of both colds and flus (32). In an animal trial evaluating its effects on treating human influenza A virus, elderberry was shown to suppress viral replication in the bronchoalveolar lavage fluids while simultaneously increasing the levels of antibody in the serum. This was concluded to not only aid in reducing the viral infection itself but promoting the prevention of reoccurrence (33).

Elderberry has also been shown to be a stimulant for cytokine production and activity. In a trial evaluating the effects of elderberry extract on various types of human cytokines, elderberry was shown to increase the production of five different cytokines involved in the inflammatory pathway of the immune system, stimulating the immune system during infection. However, because the researchers utilized healthy cells and were still able to achieve results, they concluded that elderberry may also activate the immune system even in healthy individuals, thus assisting in a preventative manner as well as for treatment (34). These results were applied in a double-blind, placebo controlled, randomized study where elderberry extract was administered following flu infection to determine if this is a viable treatment option for infection. Because of its ability to increase cytokine production, elderberry was found to significantly shorten the duration of the flu infection by several days (35).

Acai has been shown to activate NK cells, which enhances the proliferation of T-cells. In a study evaluating acai's effects on two strains of gram negative bacteria, it was shown to impair replication of both bacteria through the production of NK cells. Although only two bacteria were used in the trial, researchers saw such powerful results that they concluded that acai may have broad-spectrum activity against virulent intracellular pathogens (36). Acai is very well known for its polyphenol content particularly with relation to antioxidation. However, when researchers evaluated its polysaccharide fraction instead, they found it induced robust T-cell stimulatory activity in human cell cultures. When



tested in human peripheral blood mononuclear cells (such as lymphocytes or monocytes), they found it enhances innate immune responses (37).

Blueberry has been shown to be beneficial on cellular immune function. In an animal trial, T-lymphocyte production in the spleen was evaluated after administration of blueberry. Researchers found a significant increase in the proliferation of these lymphocytes following blueberry administration, leading to beneficial conclusions for both immune stimulation as well as hepatoprotection (38). An interesting finding has been the discovery that prolonged, rigorous exercise increases susceptibility to viral infections. In a human clinical trial involving long distance runners, researchers found that by supplementing with blueberry during the intensive training period, runners were able to delay an exercise-induced increase in viral replication. They concluded that blueberry may have the potential to protect athletes from viral infections following rigorous exercise due to its immune-stimulatory effects (39). A second human clinical trial involving well-trained athletes found similar results, yet they were able to determine that the mechanism by which blueberry reduced viral replication was through the promotion of NK cell counts as well as cytokines (40).



Mechanism of Action: Prevents inflammation through antioxidation, protecting various body systems to enhance immunity

In addition to directly stimulating the production and activity of immune cells themselves, many of the fruits found in the fruit complex of Defend™ are powerful antioxidants, targeting inflammation of the intestines, a body system directly involved in the immune response.

Acai is currently the highest scoring free radical scavenger of all the known fruits or vegetables tested (41). In just one of the hundreds of trials involving acai and antioxidant capacity, it demonstrated significant increases in total antioxidant capacity of plasma attenuation where muscle damage was induced through exercise (42). However this antioxidant capacity is also important for the immune system, as inflammation in the body can negatively impact the immune system. Elderberry, for example, was shown to stimulate the immune system by modulating various inflammatory responses, such as those involved in wound healing, angiogenesis, and blood pressure modulation (43). Blueberry has also been shown to have anti-inflammatory benefits through antioxidation, specifically targeting inflammation of the gut. Researchers demonstrated that by protecting the gut via anti-inflammation, blueberry aided in the colonization of beneficial microbiota, improving gut health, which ultimately aids in immunity (44).

The fruit complex includes acerola standardized for vitamin C, a strong antioxidant that occurs naturally in the body but may be deficient in instances of illness or stress. By including this natural antioxidant, the free radical scavenging abilities of Defend™ are enhanced. Because oxidative stress plays an important role in host innate immune response to foreign pathogens, having this very well-known and highly utilized antioxidant brings further protection and prevention from infection (45).



Usage Guidelines

Defend™ may be used to help shorten the duration of an existing illness or to boost the immune system prior to exposure to infection. For the purposes of prevention, a single dose daily prior to exposure may be consumed. However, if an illness is already being experienced, it may be necessary to consume a second dosage of Defend™ daily during the course of the illness. The ingredients included in Defend™ allow for this second dosage with little to no negative side effects. However, should you be under the care of a physician for an illness, you should notify them of your desire to supplement your treatment plan with Defend™.

In addition, should you be under the care of a physician for an auto-immune disorder, notify them prior to the use of Defend™.

Defend™ contains vitamin C. Although overdosing with this particular vitamin is highly unlikely, care should be taken if you are already following a vitamin C regimen. No more than 2 grams per day of vitamin C should be consumed, as recommended by the US FDA as well as other international government bodies.

Defend™ may be consumed with food or on an empty stomach. Should intestinal distress be experienced, it may be better to consume with food. If discomfort persists, discontinue use, and contact your health care professional.

As always, pregnant and nursing women should consult their health care professional before beginning any supplement program.

Should adverse effects be felt when consuming any new supplement, discontinue use, and contact your healthcare professional immediately.



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