

## Fat-Free™ Technical Information

### Product Description:

Fat-Free™ is an innovative formulation from Applied Nutraceuticals® that uses the latest scientific research to provide a completely unique product that can help users carve off body fat while maintaining lean body mass. Most fat burners are thinly - disguised energy pills; they pump you full of adrenaline, and then quit working as well after a few weeks. This leads to a massive barrier to fat loss, along with poor adrenal and thyroid function. Furthermore, it causes a huge additional problem of loss of lean body mass. This loss of lean body mass during dieting is counterproductive to further fat loss – sets you up for future weight re-gain and creates what is commonly known as “Yo-Yo Dieting”.

Yo-Yo dieting occurs when someone loses weight, but it is unable to maintain the weight loss over any period of time. One of the main reasons behind the lack of subsequent weight loss on future diets is the high percentage of loss of lean muscle mass versus fat during the weight loss phase. Dieting creates a catabolic (muscle-reducing) state, and the more lean muscle mass that is lost, the worse off a dieter is going to be in the long run (*see Figure 1 below*). Muscle tissue burns 20 times more calories than fat; therefore the more muscle that you lose while dieting, the less fat you can ultimately burn. Fat-Free™ stimulates a powerful muscle-sparing effect that stops the yo-yo effect cold, while kicking your body’s thermogenic mechanisms into high gear. **NO MORE YO-YO DIETING!** Strip away body fat, and keep it away with Fat-Free™.

**Figure 1: The Metabolic Response to Yo-Yo Dieting**



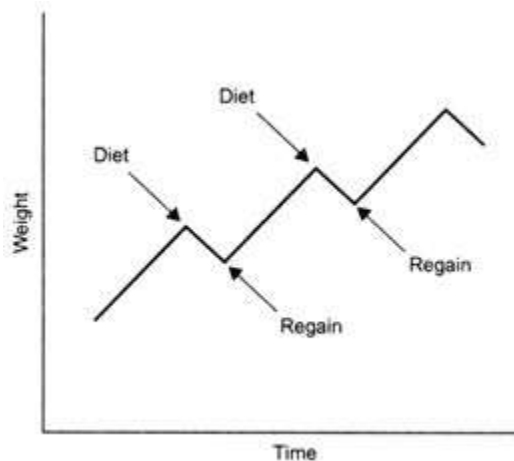
During dieting, the body undergoes multiple biochemical changes that begin to work against fat; however, many of these same metabolic changes can also begin stripping away lean muscle as well. When calories are reduced significantly during a diet, the body tends to go into a catabolic (*muscle-wasting*) state, meaning that certain processes associated with the maintenance of skeletal muscle essentially stop working. As these processes stop

occurring, rapid loss of lean tissue can occur (a process called *atrophy*), and **because of this loss of lean tissue, the body becomes much less metabolically active.** In summation, the more catabolism (muscle wasting) that occurs during a diet, the harder it becomes to lose fat. Unfortunately, most conventional fat loss products do not address this issue - they focus on “weight loss” rather than “Fat loss”. Typically they possess strong “thermogenic” properties, increase energy, and decrease appetite. These benefits only address half of the equation and in fact are setting you up for short-term success but long-term failure.

### The Tale of Two Fat Loss Products

Picture this scenario: “Susie” wants to lose 15 lbs. in 6 weeks, so she takes the leading fat loss product. Everything goes great for the first 3 weeks- she loses 8 lbs., has more energy, she is eating less, her clothes fit looser, and all of her friends are complimenting her. Great...but this is the stage where normal fat loss products normally begin to fail, and it is all downhill from this point on. You see, Susie has lost 8 lbs., but 5 of those pounds were lean muscle mass, so now she has a diminished capacity to burn calories. Her ratio of lean tissue to fat mass has decreased significantly; Plus, she is noticing her fat loss product just isn’t doing it for her anymore; she no longer gets the great energy boost, the weight isn’t coming off like it was (in fact, her progress has stopped), and she is now having to take twice the dose of her fat loss product to get the same effect. She has also developed a “Jekyll and Hyde” persona- the first 3-4 hours after she takes the fat loss product, she feels great, but by the time it starts to wear off later in the day, she crashes and becomes extremely irritable. By week 6, she has lost a total of 10 lbs. (an additional 2 lbs. of lean tissue), but her progress has all but stopped, even though she is spending more and more time in the gym. Soon she abandons the fat burner, and when she does, her appetite rebounds and she ends up gaining all of the weight back plus a few more pounds even though she is still working out. (see Figure 2). **Susie is trapped in the “yo-yo” effect!**

Figure 2: Post-Diet Weight Cycle Uptrend Without Fat-Free™



Picture a second scenario: “Jenny” wants to lose 15 lbs. in 6 weeks, so she takes Applied Nutriceuticals® Fat Free™- everything goes great for the first 3 weeks- she loses 6 lbs., has a lot more energy, is eating less, her clothes fit looser, and all her friends are complimenting her (sound familiar?). Jenny has lost 6 lbs., all of which are adipose tissue, and has not lost any lean muscle. Her amount of metabolic activity actually **increases**, because the ratio of lean tissue to fat mass has increased significantly as well. The weight is flying off, and the effects of the product continue to be very steady- she still has a good boost in energy. Fast forward to week 6, Jenny has now lost 10 lbs., but has actually gained some lean muscle in the process. The fat loss is extremely noticeable- she can fit in her skinny jeans, and is getting constant compliments. Week 10 rolls around, and she has lost an additional 2 lbs., but she now has a much higher lean tissue to fat mass ratio.

Which scenario do you want to experience? **The answer is obvious: Be Fat-Free™!**

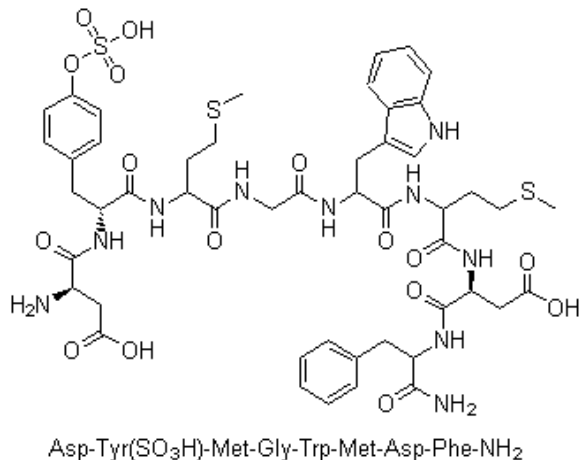
### **Basic Features and Benefits of Fat Free™:**

- A. Decreases both white and brown adipose tissue rapidly
- B. Allows for a significant sparing effect of lean muscle tissue
- C. Stops hunger in its tracks without destroying basal lean body mass and creating the “yo-yo” effect
- D. Provides a very pronounced “feel good” effect without an over-reliance on heavy stimulants
- E. The positive effects do not wear off within a matter of days or weeks

### **Technical Overview:**

- Fat Free™ induces a strong muscle-sparing effect during dieting and improves the lean muscle to fat ratio
- Increases the density and number of Beta Receptors, allowing for an increase in fat burning capabilities in white adipose tissue (WAT)
- Inhibits adenosine and phosphodiesterase (PDE), two biochemical markers that limit the effects of conventional fat burners
- Suppresses muscle-wasting biochemical pathways found during a dieted state, allowing for the greater retention of lean muscle mass
- Slows the “attenuation factor” that occurs with most conventional stimulant-based fat loss products by limiting or stopping adrenal fatigue- meaning that the product will continue to be effective for long periods of time
- Increases cholecystokinin (CCK), an enzyme that reduces appetite levels, and decreases catechol-O-methyltransferase (COMT), an enzyme responsible for down-regulating fat-burning catecholamines such as norepinephrine (NE)

**Figure 3: Cholecystokinin**



### **How Fat-Free™ is Different Than Other Fat Loss Products on the Current Market:**

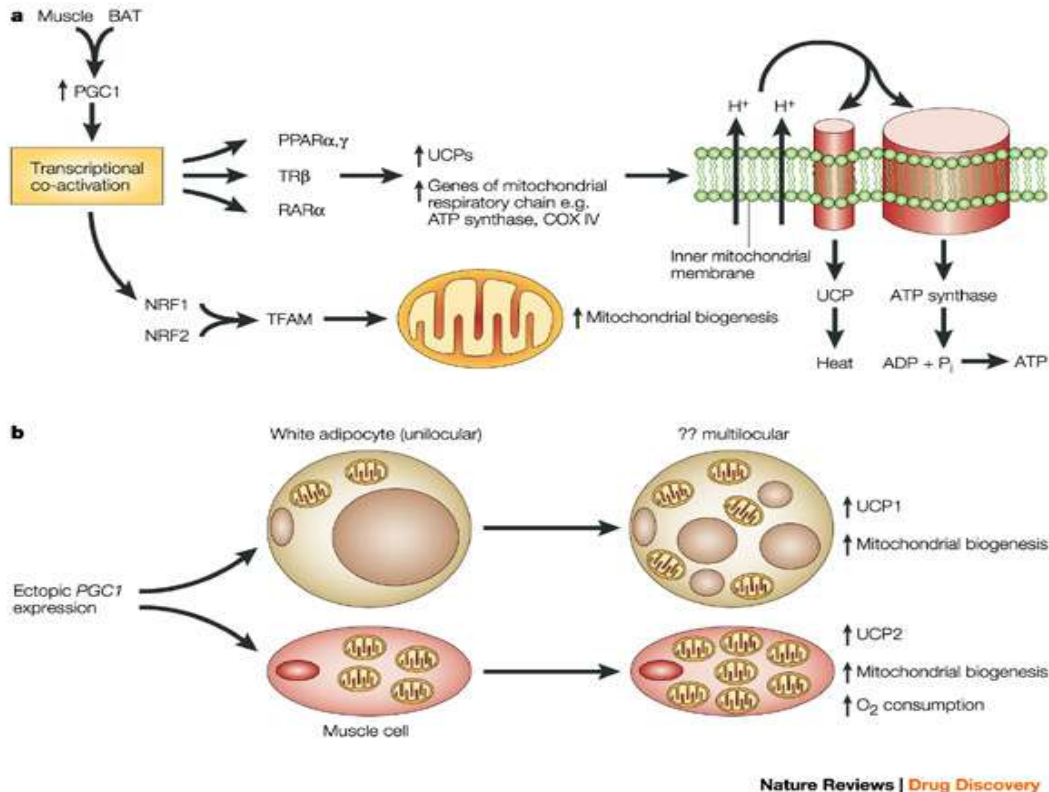
Many fat loss products tend to employ similar formulations and make similar claims - they claim to increase thermogenesis, energy levels, and kill hunger. Fat-Free™ also meets these criteria, but this is only part of what is necessary to have a truly effective product. What makes Fat-Free so different is it's the first product that effectively addresses the issues of lean muscle loss, which is one of the biggest reasons most diets ultimately fail.

However, it is crucial to accept the fact that there are several key success factors that cannot be ignored, regardless of what product you take:

1. Diet is still the single biggest factor when it comes to healthy weight loss
2. Substantial, sustained fat loss and weight maintenance requires regular exercise
3. Maintaining a healthy weight is a lifestyle, and can't come from just from taking a capsule

If these 3 simple rules are followed, Fat Free can play a huge role in helping you to accomplish your weight loss goals.

**Figure 4: Thermogenesis**



### What Does Applied Nutraceuticals Fat-Free™ Contain, and How Does It Work?

**Ligustrum Lucidum (Standardized to 25% Ursolic Acid)**- *Ligustrum Lucidum* is an extract that has been used for many years to treat a variety of maladies ranging from aches and pains to high cholesterol. Some of the newest scientific research available has found that Ursolic Acid, which is found in high amounts in *L. Lucidum*, has some major implications in the reduction of body fat and sparing of lean muscle tissue while dieting. Recent studies have found that ursolic acid can positively alter levels of certain biochemicals that become unfavorably misaligned while dieting.

**Coffea Arabica 95%**- a compound with strong anti-oxidant properties, *coffea arabica* can increase levels of the catecholamines norepinephrine (NE) and dopamine (DA), which are two components essential for burning fat and regulating mood. Coffea has also been shown to have a strong effect on increasing the activity of several enzymes responsible for fat metabolism.

**R-Beta MethylPhenylethylamine(R-Beta PEA)**- R-Beta PEA is a monoamine neurotransmitter that is derived from the amino acid phenylalanine. It has strong effects on fat loss, and is a “clean” stimulant that produces smooth energy without anxiety or a crash. Also known as the “love” component in chocolate- can have a strong positive effect on mood.

**Hordenine**- a compound that acts as a mild stimulant and MAO (monoamine oxidase) inhibitor. Hordenine can prolong and increase the action of R-Beta PEA substantially, and can also increase NE and DA levels.

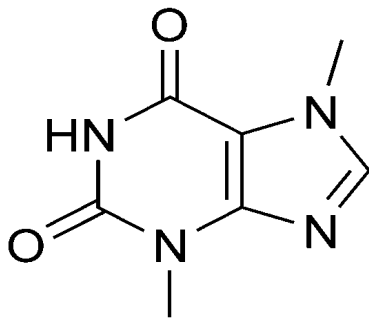
**Dehydroepiandrosterone (DHEA)**- a substance produced by the adrenal glands, DHEA has been shown to increase fat loss through several different mechanisms, and also can help mitigate adrenal fatigue, which is a common occurrence when dieting.

**Green Tea Extract 95%**- Green Tea is a versatile herb used for many centuries for a variety of ailments - Recent studies have determined Green Tea to be a strong fat burner that works through several different complementary mechanisms. Green tea is also a potent appetite suppressant with nutrient-repartitioning qualities, which means it has the ability to allow for the metabolism and utilization of macronutrients.

**Theobromine**- is part of the tri-methyl xanthine complex that makes up caffeine. Theobromine has the ability to act as a non-specific PDE inhibitor, which can prevent the breakdown of certain compounds that are crucial to fat loss.

**Quercetin Dihydrate 95%**- is a citrus bioflavonoid that has been shown in several clinical studies to work in concert with norepinephrine to reduce adipose tissue. Quercetin also can slow the breakdown of certain compounds such as caffeine in the bloodstream, rendering these ingredients more effective on a mg per mg basis.

**Figure 5: Theobromine**



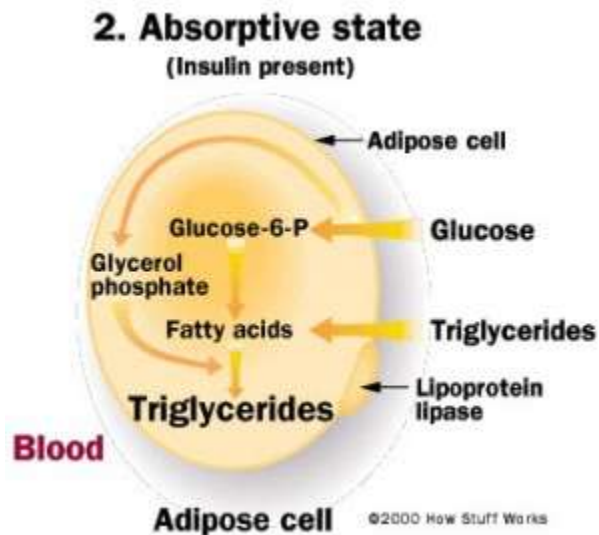
### **Using Ursolic Acid and Dehydroepiandrosterone (DHEA) to Solve the Biggest Issue Confronting Dieters- The Loss of Lean Tissue Due to Caloric Deprivation**

Recently, the mainstream media has been referencing multiple studies regarding recent research on dieting. Most of these relevant studies have been focused on the hormonal mechanisms that tend to become thrown out of balance when calories are reduced significantly while dieting. Many of these newly discovered hormonal mechanisms are centered around the signaling associated with IGF-1 and insulin on the cellular level, both of which are extremely crucial in the process of maintenance of lean tissue.

Caloric restriction that comes from dieting tends to disrupt the balance of several key mechanisms within the body, which is what is needed to commence fat loss. Plasma glucose and insulin levels become reduced, and the

body begins to rely on white adipose tissue (WAT) as a source of energy. WAT is subcutaneous fat, normally found in the layer beneath the skin, and is comprised of stored triglycerides (three fatty acid molecules attached to a glycerol backbone). As calories are reduced and glucose levels fall, available plasma glucose is shunted off as fuel for the brain and internal organs, and due to these low levels of plasma glucose, WAT is then used as a source of fuel. The utilization of WAT as fuel occurs via a biological cascade that frees up fatty acids from triglycerides, releasing them into the blood stream, where they are carried to different cells that are in need of energy (60).

**Figure 6: The Storage of Glucose and Triglycerides in Adipose (Fat) Cells**



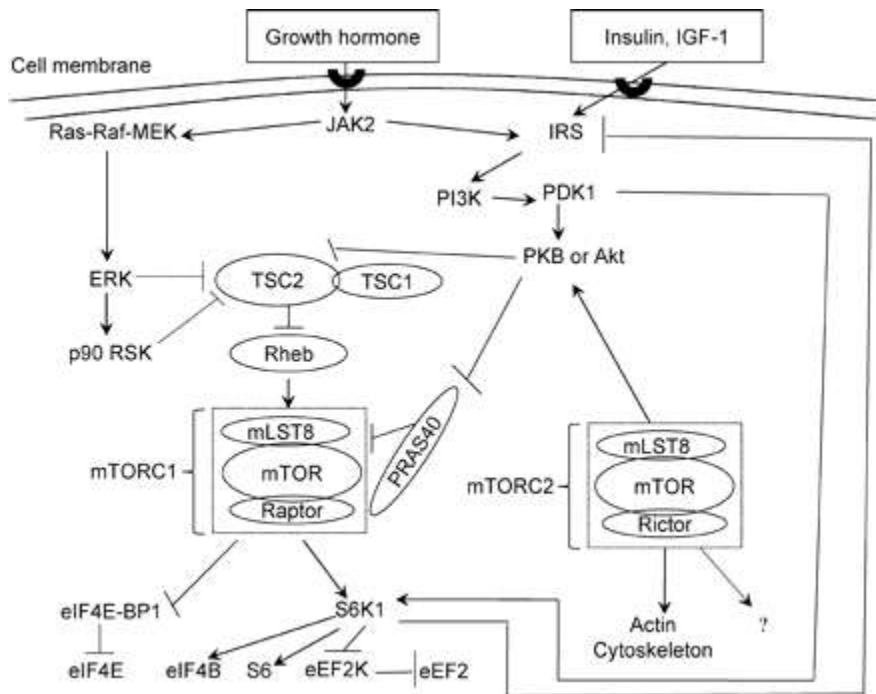
Insulin also plays heavily into the dieting equation. It is responsible for regulating blood glucose levels, and when blood glucose levels are high, the body releases insulin to lower blood glucose levels. Insulin is a storage hormone, and it stimulates certain enzymes involved in the increase of glucose and triglyceride deposition in adipose tissue (which results in fat gain- see figure 6 above), as well as the storage of glucose in skeletal muscle and the formation of glycogen (fuel for skeletal muscle). Lowered blood glucose is counterbalanced by another process involving the ATP:AMP ratio (which signifies energy homeostasis in the body). When blood glucose levels dip, the ratio drops, and AMPK is activated. AMPK is an enzyme that signals the mitochondria (the power plant of the cell) to begin utilizing fat as an energy source rather than glucose. At this point, free fatty acids can be liberated from WAT and be burned as fuel. (38,43).

The mantra of low carbohydrates and low calories during dieting is the cornerstone of many current weight loss programs. Too many carbs lead to too much insulin, insulin then allows for fat storage in the form of fat. Therefore fat can't be liberated to be used as cellular energy without a low-carbohydrate, low-insulin environment. While this is accurate to an extent, it becomes a double-edged sword - the reduction in calories creates a drastic reduction in IGF-1 and insulin levels, which results in a reduction of protein synthesis and an increase in muscle protein breakdown. Muscle protein breakdown occurs during dieting/fasting and exercise, and is associated with an overall catabolic state. Protein synthesis is a process where skeletal muscle cells repair the damage incurred from protein breakdown; skeletal muscle protein synthesis is a multi-step anabolic process in which genes for skeletal muscle proteins are expressed (the scientific term for when an individual cell manufactures a protein) via the transcription of DNA into mRNA. This process is essential for the maintenance of

lean body mass, and when there is a higher ratio of protein breakdown to protein synthesis, a loss of basal lean tissue can be expected (muscular catabolism) (6,8).

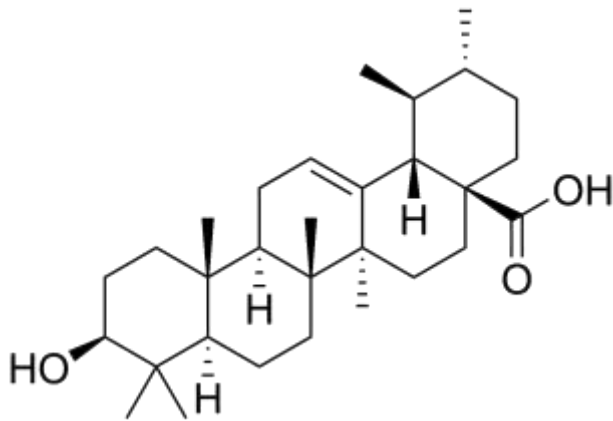
Fasting, low IGF-1 and low insulin levels tend to run hand-in-hand, and this produces a series of changes on the molecular level; multiple mRNAs/encoding proteins that have substantial roles in the maintenance of basal lean muscle and are downstream from the insulin and/or IGF-1 cascade tend to be altered in a negative fashion. Rapamycin (an inhibitor of Mammalian Target of Rapamycin or mTOR) and Wortmannin (an inhibitor of Phosphoinositide-3-Kinase or PI3K) tend to be much more heavily expressed during a low insulin/low IGF-1 state, and as the mRNAs from these two entities become more and more established, protein breakdown becomes predominant due to the suppression of mTOR by rapamycin. mTOR controls protein synthesis, and the suppression of mTOR by rapamycin can lead to extensive muscle loss. Similarly, the inhibition of PI3K by wortmannin (see below in Figure 7), can also lead to extensive muscular atrophy during dieting; this loss of basal muscle mass incurred during dieting can lower the lean muscle to fat mass ratio significantly, resulting in the decreased ability to maintain basal metabolism post-diet and on subsequent diets. (4,7).

**Figure 7: The IGF-1/Insulin Pathway**



You are probably thinking “If I can’t reduce my caloric intake or carbohydrate intake because I may lose lean muscle tissue, how am I ever going to lose weight?” This simple metabolic fact is something that has derailed diets for years, and is the underlying issue behind the yo-yo effect. You cut calories and carbohydrates to lose weight, and it works, but because you also lose a great deal of your underlying muscle mass, the weight is re-deposited, and then some. But what if there were a way to keep the insulin/IGF-1 pathway stimulated, and to override the muscle-wasting mRNA expression that occurs with dieting/fasting? This is where Ursolic Acid (UA) comes in.

**Figure 8: Ursolic Acid**



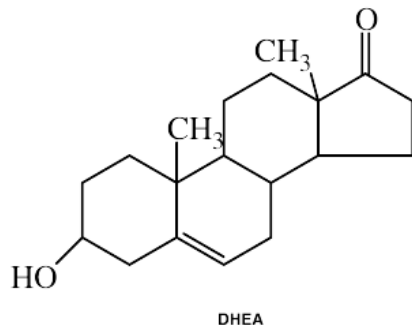
Recent research on ursolic acid uncovered something very startling: UA can completely reverse/override the catabolic mRNA expression that occurs during dieting! Researchers at the University of Iowa recently mapped out the genetic sequence that occurs during fasting, and recorded all of the different mRNAs that were expressed both in a fasted state, and also in a fully-fed state. Researchers then administered a series of compounds to subjects while they were fasted, to see if any of the compounds could reverse or override the mRNA that are expressed normally in a catabolic state. They found that UA could override many of the fasting-induced markers of catabolism associated with low insulin and/or IGF-1 levels, and that UA could also elevate these markers during a non-fasted state as well. Moreover, researchers found that UA worked optimally in conjunction with higher levels of IGF-1/insulin receptor stimulation, but UA did not actually increase IGF-1 or insulin blood levels. This is significant, because it means that UA works independently of binding the insulin/IGF-1 receptor, and instead works directly on some of the underlying (downstream) kinases/enzymes (1,3).

Also of note was that the expression of IGF-1 mRNA occurred only in skeletal muscle, and not in adipose tissue. This is important because it seems to mean that UA is only effective in skeletal muscle, and not in fat cells. IGF-1 mRNA expression is optimal in muscle cells, but not adipocytes- having these genetic markers in fat cells would mean that there was a storage component to the mRNA expression in adipose tissue from UA, which could lead to increased fat mass. Fortunately, this was not the case; researchers actually found that subjects treated with UA had a decrease in the size of fat cells, along with a decrease in plasma triglycerides and free fatty acids! UA accomplished this by decreasing plasma levels of leptin, which is a hormone associated with increased adipose weight. Normally, decreased leptin is associated with increased hunger, but this does not seem to be an issue when it comes to UA, as no increase in appetite was reported amongst the subjects (1,2,5).

As stated earlier, UA seemed to have no effect on plasma IGF-1 levels by itself, and only seemed to act on enzymes/kinases downstream of the IGF-1/insulin receptor when insulin or IGF-1 was already present. This is important because in a low endemic IGF-1/insulin environment due to dieting, UA may need some "assistance" due to low plasma IGF-1/insulin levels. This is where DHEA (Dehydroepiandrosterone) comes in. DHEA is a sulphated compound produced in the adrenal glands and is found throughout the human body. Supplemental DHEA has been shown to have a strong correlative effect at normalizing plasma IGF-1 levels in both men and women, even in a low-caloric or catabolic state. In this case, it is theorized that by adding supplemental DHEA in low doses to Fat Free™ will help users to recognize optimal levels of IGF-1, thus ensuring the optimal action of the ursolic acid (1,3,4,5,8).

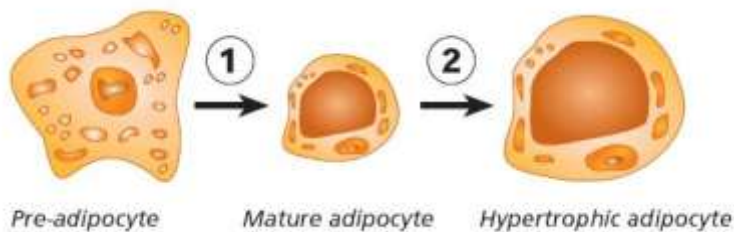
Another interesting quality of note with DHEA is that it has some strong lipolytic (fat burning) effects. DHEA accomplishes this in several different fashions. First and foremost, DHEA can increase thermogenesis (releasing energy from BAT stores to increase body temperature), through promoting the formation of brown adipose tissue (BAT) preferentially over the formation of white adipose tissue (WAT). This is significant, because BAT can actually contribute metabolically to burning body fat, via increasing thermogenesis through the expression of uncoupling protein (UCP). BAT sounds bad, but it actually can contribute to lipolysis substantially, via acting as its own fuel source, and through having the ability to uptake (and burn for energy) fatty acids released from WAT (9,10,17,18).

**Figure 9: DHEA**



DHEA also decreases levels of stearoyl-CoA desaturase (SCD1), an enzyme responsible in part for the synthesis of fatty acids and the development of obesity. SCD1 is heavily involved in body weight regulation and lipid partitioning; since it controls the rate-limiting step involved in fatty acid synthesis, high SCD1 levels have been correlated with hyperlipidemia and hypercholesteremia, as well as obesity. Similarly, DHEA has been shown to have the ability to slow the differentiation of pre-adipocytes to adipocytes, meaning that the compound can slow or stop the transition of fat cell-scaffolding material into full-fledged fat cells. This is extremely significant, in that it means DHEA can actually slow or stop the formation of mature fat cells via decreasing the activity of peroxisome proliferator-activated receptor gamma (PPAR gamma), a receptor whose subunit genes express lipid uptake and adipogenesis (fat formation) (10-13,16).

**Figure 10: Adipocyte Maturation**



So in summary, dieting/fasting causes some drastic alterations in metabolism and decreases levels of insulin/igf-1 levels. This can trigger a reduction in protein synthesis, and place the dieter in a catabolic state where they begin to lose lean muscle. This loss of lean muscle can significantly contribute to the “Yo-Yo Effect”, and as the ratio of lean muscle to fat mass decreases, the body becomes less metabolically active, even though a person may still be losing weight on the scale. This can lead to the person gaining fat dramatically once they cease dieting; However,

the DHEA and Ursolic Acid used in Fat-Free™, helps counteract (or even reverse) the loss of lean muscle mass while dieting- an effect no other fat loss product on the market can claim.

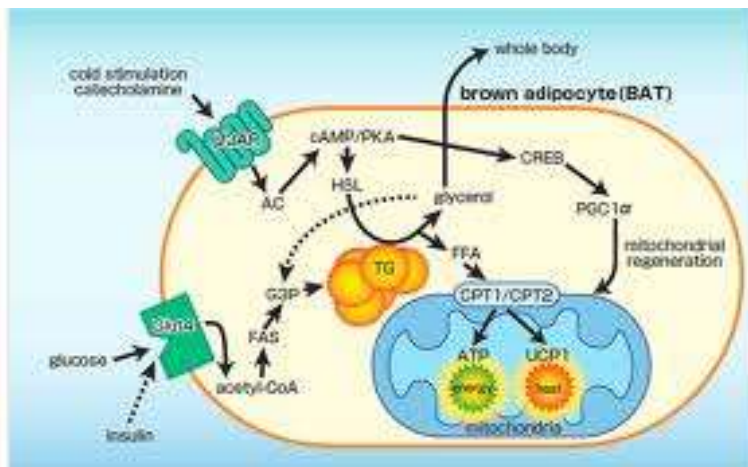
**The Role of R-Beta Methyl Phenylethylamine, Hordenine, and Coffea Arabica Extract in Producing Significant Adipose Reduction**

As mentioned earlier, fat loss tends to be a multi-tiered mechanism; we have explored the lean mass preservation component of Fat-Free™; now we will discuss how the product uses a system of biogenic amines to destroy fat and curb appetite. Biogenic amines are substances containing an amine group that act within the human body; the amine group denotes that the compound is an organic substance similar to ammonia, with a nitrogen atom and a lone pair, but with one or more of the hydrogen atoms being replaced by another substituent. In layman’s terms, this means that the substance can be readily used by the human body, and many substances sharing this type of structure can also be produced in the human body. Biogenic amine neurotransmitters play an extremely important role in fat loss from multiple angles; the catecholamine biogenic amines norepinephrine (NE) and dopamine (DA) as well as serotonin are of special importance to Fat-Free™. These biogenic amines are crucial for both fat loss and the maintenance of normal mood, both of which are important characteristics during any type of weight management undertaking. The goal of this section is to explain how these substrates allow for fat loss, and how Fat Free™ utilizes these biogenic amines to maximize adipose reduction.

Think back to the previous system, and how white adipose tissue (WAT) and brown adipose tissue (BAT) differ. BAT tends to be found more in the upper chest and neck, and contains much higher amounts of mitochondria and smaller lipid droplets than WAT. BAT is much more advantageous than WAT, at least from a metabolic standpoint, because:

- It is metabolically active, and can uncouple ATP via UCP and can generate thermogenesis (heat)
- BAT can be used readily as a source of energy
- BAT has its own capillary source, It can readily absorb fatty acids released from WAT (36,51,53)

**Figure 11: Brown Adipose Tissue and Cellular Processes**



WAT, however, is not so advantageous, and is what most of the bodies’ subcutaneous fat is composed of. WAT is structured differently than BAT, in that it is not metabolically active, and mainly stores triglycerides, like BAT. However, because WAT contains less fatty acid binding proteins than BAT, the triglycerides from WAT can be broken down and released into the bloodstream as free fatty acids (FFA) much more readily. Unfortunately, these

FFA can be easily recovered by WAT if they are not metabolized for energy promptly. WAT can be used for energy, but only when:

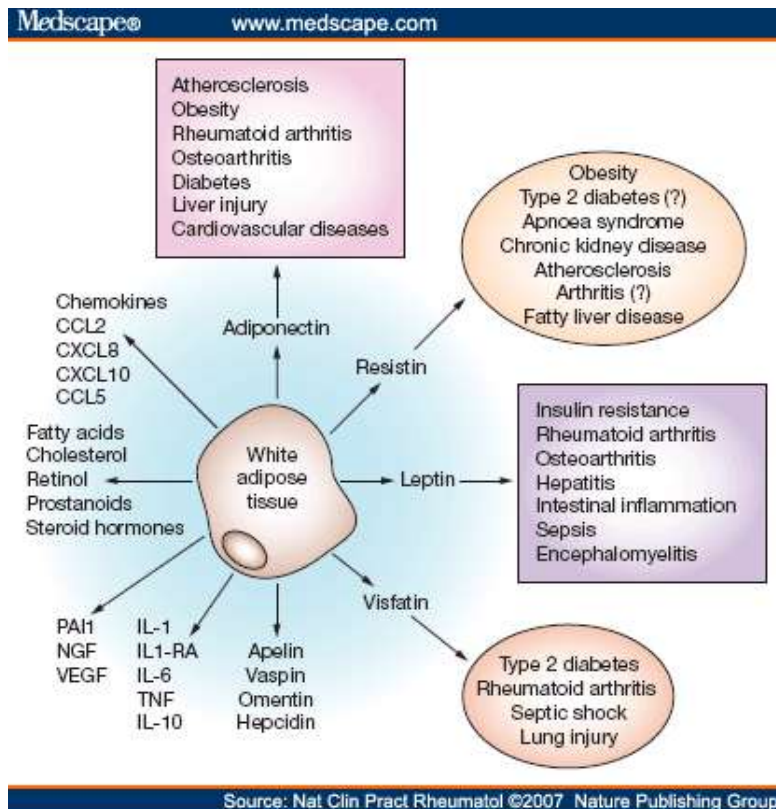
- the body is in a state of low blood glucose (hypoglycemia)/low caloric catabolic state
- certain types of Beta Adrenoreceptors (BAR) have been stimulated by catecholamine release (37,39,56)

As we discussed earlier, depletion of calories during a diet is normal, but not always advantageous due to the potential loss of lean tissue. However, this is only one of the ways to release WA; stimulating BAR is another way. Beta Adrenoreceptors (BAR) are found in many places throughout the body: on fat cells, cardiac, and smooth muscle, and are subdivided into three categories:

- Beta 1 Adrenoreceptors (B1AR) are found mainly in the heart, and influence heart rate and contractility
- Beta 2 Adrenoreceptors (B2AR) are found on smooth muscle and promote relaxation
- Beta 3 Adrenoreceptors (B3AR) are found mainly on fat cells and influence lipolysis (40-44)

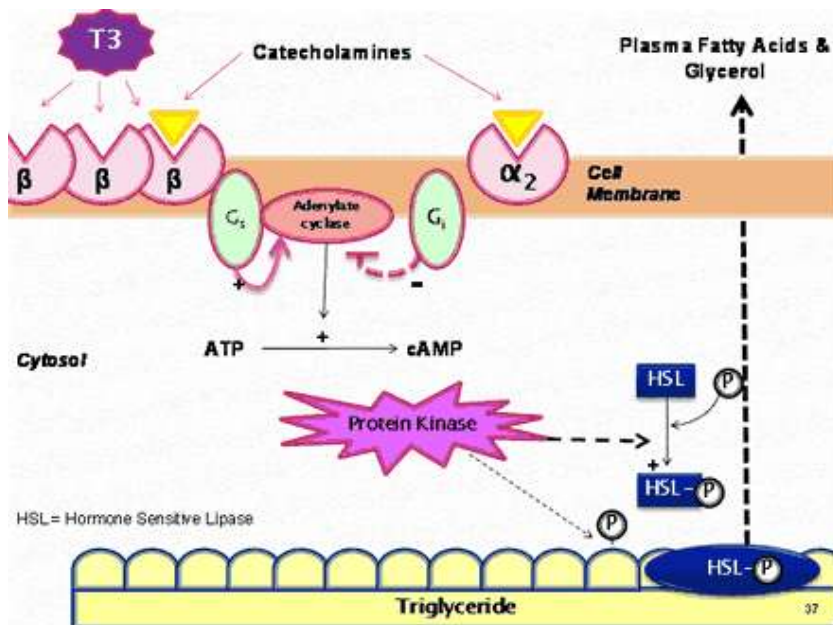
WAT contains mostly B2AR, BAT contains mostly B3AR; so the next logical question is: How do we stimulate B2AR and B3AR to attack WAT and stimulate BAT? The answer is the biogenic amine norepinephrine (NE). NE is produced from the neurotransmitter dopamine via dopamine Beta-Hydroxylase, and is released from the adrenal medulla of the kidney into the blood stream as a hormone; Interestingly, NE can also be released from noradrenergic neurons (nerve endings) as a neurotransmitter to serve a more localized function. When NE is released from the nerve endings, it can bind directly to the adrenoreceptor on the fat cell adjacent to the nerve ending, which begins lipolysis (40,41,50,52).

**Figure 12: The Processes Associated With An Overabundance of White Adipose Tissue (WAT)**



Fat Free™ uses a multi-tiered system of compounds that increase NE, prolong its action, prevent its reuptake, and prevent it from being broken down sequentially by monoamine oxidase or catechol-o-methyltransferase (COMT). R-Beta Methyl Phenylethylamine and Coffea Arabica Extract (extracted for chlorogenic acid and caffeine) have been shown to increase the release of dopamine (which converts to NE), and NE from nerve endings; Hordenine has been demonstrated to act as a monoamine oxidase inhibitor and a NE-reuptake inhibitor, meaning that it can prevent NE from being enzymatically deactivated by MAO, thus allowing it to build up in greater concentrations. Hordenine also decreases the activity of the norepinephrine reuptake transporter, which also allows NE to form a greater concentration around the beta receptors on the surface of adipose tissue. Similarly, Green Tea has been shown to inhibit the production of catechol-o-methyl-transferase (COMT). COMT is important in this process as well, because it is the enzyme that breaks down norepinephrine; therefore limiting the production of COMT allows NE to exert much stronger effects on the fat-burning cascade. The combination of these NE and dopamine-stimulating ingredients is nothing earth-shattering; it is a very simple way to accomplish the goal of dramatically increasing the amount of NE available to beta receptors for fat loss (23-35,39-42,45-47,57-59).

**Figure 13: NE and Thyroid-Based Lipolysis**



To summarize, Fat-Free™ allows for more NE to be released, and prolongs the action of NE by inhibiting its breakdown and reuptake. NE stimulates lipolysis by binding with BAT and triggering a cellular-signalling cascade begins on the sub-receptor level. To simplify, here is the process behind WAT-based lipolysis, both step-wise, and in a diagram:

1. Receptor binding of norepinephrine (marked "catecholamines" in the above diagram) to WAT or BAT beta adrenergic receptors on the cell membrane occurs (marked " $\beta$ " on the above diagram)
2. The binding of NE to BAR trigger a G-linked protein (messenger protein) located on the inside of the cell.
3. The G linked-protein activates another enzyme called adenylate cyclase

4. Adenylate Cyclase signals adenosine triphosphate (ATP, the main substrate for cellular energy; see above) inside of the cell to convert to a second messenger protein, cyclic adenosine monophosphate (cyclic AMP, or cAMP)
5. cAMP phosphorylates (activates) Protein Kinase A (PKA), an intermediary enzyme crucial to signaling within the cell
6. PKA activates Hormone Sensitive Lipase (HSL), an enzyme that breaks down triglycerides (stored fat, a molecule of 3 fatty acids with a glycerol backbone)
7. HSL liberates free fatty acids (FFA) and glycerol from triglycerides in a multi-step process
8. The liberated FFA and glycerol are released into the blood stream to be metabolized as energy (45-47,57-59,60-62)

The above demonstrates how the substantial norepinephrine increase from Fat-Free™ works to increase fat loss. Yet, there are still several other ways employed by Fat Free™ to increase the process on an intracellular level.

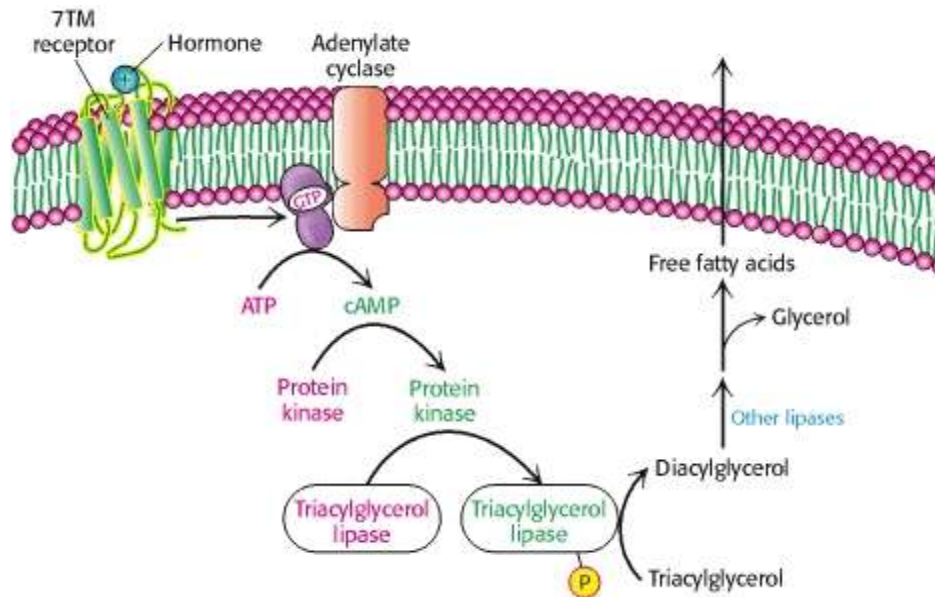
#### **The Role of Theobromine, Green Tea Extract, and Quercetin on Maintaining High Intracellular Levels of cAMP for Maximal Lipolysis**

Up to this point we have demonstrated how Fat Fat-Free™ has a strong muscle-sparing effect from Ursolic Acid, as well as a strong fat burning effect from increasing the release of catecholamines (chiefly NE). Now we are going to focus on a more direct mechanism through which the product destroys adipocytes (fat cells) by maintaining very high intracellular concentrations of cAMP by preventing the breakdown of the second messenger.

We have demonstrated that NE increases cAMP, but Fat-Free™ takes this process a step further by inhibiting the breakdown increased cAMP through the implementation of theobromine and green tea extract. NE-based lipolysis works well, but it does have some limitations; when the body senses high levels of NE, it will begin to fight back by increasing levels of phosphodiesterase (PDE) and adenosine (an anti anti-lipolysis agent) receptors. High levels of PDE will cause the breakdown of cAMP (and thus stopping lypolysis), and high levels of adenosine causes the fat cells to stop accumulation of cAMP, thus stopping the fat reduction cascade. The formulation of Fat Free™ has taken steps to prevent this.

This is where theobromine and green tea extract come in- this is important because it demonstrates the ability of the compound increases cAMP independently of NE, thus providing increased hormone sensitive lipase (HSL) levels in adipocytes and allowing for the greater liberation of free fatty acids into the blood (36-39,44-46,49).

#### **Figure 14: Hormone Sensitive Lipase and the Breakdown of Triglycerides into Free Fatty Acids and Glycerol**



Green Coffee Bean Extract (mostly due to its caffeine content) and theobromine have been shown in multiple studies to have the ability to act as phosphodiesterase (PDE) inhibitors, and Green Coffee Bean Extract has been shown to actually block adenosine, preventing adenosine from stopping the build-up of cyclic AMP in the fat cell. Theobromine has been shown to have the ability to inhibit PDE4, which is the PDE that breaks down cAMP, as well as having the ability to block adenosine receptors. By decreasing the enzyme that breaks down cyclic AMP, theobromine allows the adipocyte to become literally flooded with cAMP, providing a strong signaling base for HSL and its quest to destroy fat cells. Similarly, Green Tea Extract has also been shown to have some interesting characteristics, as it has not only been shown to have some effects on inhibiting PDEs in a non-specific manner, but has also been shown to significantly augment lipolysis in conjunction with NE in several animal studies, meaning that the compound will augment any type of NE-based lipolysis extremely well.

The inclusion of quercetin is important for several different reasons. Because it is a citrus bioflavonoid, quercetin has the ability to reduce certain liver enzymes that break down active components such as caffeine. This extends the half-life of these components in the blood stream, and can allow them to be much more effective, especially during lipolysis. More importantly, however, is the ability of quercetin to act in conjunction with available norepinephrine to dramatically increase fat loss, via increasing cAMP levels in adipocytes (41,44,54-56).

These MOAs demonstrate that even if negative feedback occurs on the NE-based component of lipolysis in Fat-Free™, there will still be an active source of cyclic AMP to continue the cascade. By maintaining high levels of cAMP, even independent of catecholamines, the product can continue to provide active substrates for fat loss on the intracellular level, even if the NE release is shut off and/or NE uptake occurs.

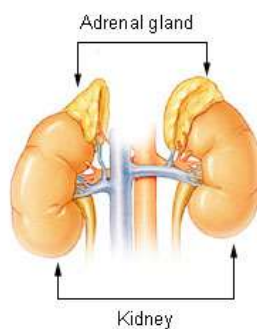
### Using DHEA (Dehydroepiandrosterone) to Enhance Adrenal Function

A critical factor in any lipolytic formulation is the availability of adequate endogenous epinephrine and norepinephrine (NE) from the adrenal medulla. The adrenal medulla is a disk-shaped gland that sits on top of each kidney that is responsible for the production of multiple hormones: cortisol, DHEA, epinephrine, norepinephrine, and aldosterone, just to name a few. When the body is exposed to certain situations (stress or certain supplements/medications), the adrenal medulla releases appreciable amounts of these hormones. As mentioned earlier, NE-based lipolysis is absolutely critical to the success of the product; however, the adrenal medulla tends

to be a limiting factor when taking any type of stimulant fat burner. Think back to Susie and Jenny- both were taking stimulant fat burners, but Susie continued to have to take more and more of the product she was taking, to get the same effect. This phenomenon is called attenuation, and it is extremely common with conventional fat burners. When a user takes a lipolytic (fat burning) compound that allows for the release of NE, its source is the adrenal medulla. As with any gland in the body, the adrenal medulla is regulated by homeostasis (the inherent need of the human body to stay within balance). When too much stimulation of the adrenal medulla occurs while taking traditional fat burners, NE and DHEA levels begin to become depleted and the user begins to build a tolerance to the effects of the fat burner, and a vicious cycle begins where the user must continue to take more and more of the product just to get the same effects as before (14-15,63-64) .

**Figure 15: The Adrenal Medulla of the Kidneys**

**Adrenal Gland**



However, there are ways to minimize or even prevent this entirely. Normally, when the adrenals are overtaxed, NE and DHEA levels tend to plummet significantly. DHEA can normalize plasma IGF-1 levels in both men and women, increase thermogenesis, and decrease levels of stearoyl-CoA desaturase (SCD1), an enzyme responsible in part for the synthesis of fatty acids and the development of obesity; NE enhances multiple processes at the cellular level to stimulate the breakdown of adipose. Low DHEA levels are associated with a variety of maladies associated with low adrenal output, and multiple studies have shown that supplemental DHEA can help to normalize markers associated with disorders related to adrenal insufficiency, such as chronic fatigue syndrome, and low norepinephrine levels (19-22):

Himmel, PB et al. (1999)

Supplementation with DHEA to CFS patients lead to a significant reduction in the symptoms of CFS: pain (improved by 18%,  $p = 0.035$ ), fatigue (decreased by 21%,  $p = 0.009$ ), activities of daily living (improved by 8.5%,  $p = 0.058$ ), helplessness (decreased by 11%,  $p = 0.015$ ), anxiety (decreased by 35%,  $p < 0.01$ ), thinking (improved by 26%,  $p < 0.01$ ), memory (improved by 17%,  $p < 0.05$ ), and sexual problems (improved by 22%,  $p = 0.06$ ) over the period of the trial.

Arlt, W. et al. (2000)

DHEA replacement improves well-being and sexuality in women with adrenal insufficiency. If this is due to a direct effect of DHEA on the brain, an indirect effect via increased androgen synthesis, or both, remains to be elucidated. Long-term studies in patients of both sexes are needed to further define the role of DHEA in standard replacement for adrenal insufficiency.

Barbetta, et al. (2004)

Our study confirms that DHEA may be beneficial for female patients with hypoadrenalism, mainly in restoring androgen levels. Concerning the health status, more sensitive and specific instruments to measure the effects of DHEA treatment could be necessary.

Zeilsen, et al. (2001)

DHEA also appears to have an affinity with certain receptors in the brain and can act as a neurosteroid. Patients with primary or secondary adrenocortical insufficiency exhibit a marked decrease in DHEA production and the added value of DHEA replacement in these patients has been investigated in three recently published trials. With a daily dose of 50 mg DHEA, the plasma levels of DHEAS (the sulphate of DHEA) increase to levels within the normal range and beneficial effects have been demonstrated for several psychological parameters such as mood, fatigue, general well-being and sexual function. The androgenic side effects on skin and hair appear to be both moderate and acceptable. For patients with adrenocortical insufficiency who function suboptimally despite adequate replacement therapy with glucocorticosteroids and (if indicated) mineralocorticosteroids, these results would seem to justify treatment with a replacement dose of DHEA.

These studies indicate that a strong link exists between DHEA supplementation and the attenuation of adrenal insufficiency. This is important due to the fact that any stimulant-based fat loss agent tends to be taxing to the adrenals. By including an effective dosage of DHEA in the formulation, Fat Burner™ may have the ability to normalize any type of adrenal burnout that could possibly occur due to increased adrenal medulla taxation.

### Stacks and Tips to Maximize the Product

- **For Women**, stack the product with Lipotrophin-PM™ and Omega Essentials™ to allow your body to become 24-hour-a-day fat-melting furnace! Product can also be stacked with Drive™ for further lean body mass gains.
- **For Men**, stack the product with Free Test™ and HGH♂ for dramatically increases in lean body mass and decreases in body fat.
- **For Men and Women:**
  - Take Bio-Mend™ Anti-Oxidant formula to minimize any harmful by-products caused by lipolysis.
  - **In general, maintain a healthy diet and lifestyle**
  - Drink Plenty of water; at least 64 oz. per day
  - Ingest at least 1 gram of protein per lb. of body weight daily
  - Avoid high-fructose corn syrup containing foods and other high-glycemic index carbohydrates
  - Use product for up to 10-12 weeks, and then take a 4-6 week break
  - Take product with or without food; taking the product without food will heighten the stimulant “kick”, while taking the product with food will tend to blunt this effect
  - Do not use this product in conjunction with MAOIs or Tri-Cyclic Antidepressants
  - Do not take this product within 6 hours of bedtime
  - Sleep at least 7 hours per night
  - Eat lots of fibrous complex carbohydrates such as fruits and vegetables
- Eat 5-6 smaller protein and carb-rich meals throughout the day

- Decrease calories to at least 500 Kcal/day under your normal intake
- Avoid alcohol and tobacco while taking the product

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