FLEX™

A Dollar Coffee Club product

white paper provided by Archmore Botanical Research Group, LLC
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Flex™, an ActiveBlendz product

a Dollar Coffee Club product

- A technical overview outlining the safety and efficacy of Flex™, a dietary supplement designed to support healthy joints*
- 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 the safety of the ingredients in Flex™ at recommended levels
        - A review of any adverse events associated with the ingestion of the proprietary ingredients
    - Efficacy
        - Cellular, animal, and human trials demonstrating joint health benefits
        - A review of any negative outcomes found in clinical trials using the proprietary ingredients
        - Potential secondary health benefits outside the scope of joint health
    - Recommended guidelines for use
        - Dosing recommendations for joint 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.*

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Overview

Arthritis and joint pain are serious conditions that will affect at least half of the population by the age of 85 years. It may be in the form of osteoarthritis, rheumatoid arthritis, symptoms from obesity, gout, lupus, or even fibromyalgia. An estimated 52.5 million adults in the United States alone have been diagnosed as having one of these conditions, with an estimated 67 million expected to be diagnosed by 2030 (1). This is in addition to those experiencing reduced motility, decreased flexibility, and joint pain upon normal and strenuous activities or exercise.

Arthritis, specifically, is a form of joint disorder characterized by inflammation of the joints. There are two main types of arthritis: osteoarthritis and rheumatoid arthritis. Osteoarthritis is a degenerative disorder that breaks down the joint cartilage and underlying bone. This can cause joint pain and stiffness, with symptoms occurring initially following exercise but becoming constant in the long term. Rheumatoid arthritis, on the other hand, is an autoimmune disease that carries with it detrimental side effects, such as pain, stiffness, and swelling in the joints. Severe damage may also result from this progressive disease. It afflicts more than 1.6 million Americans, with the vast majority being women.

Flex™ was designed to address both the symptoms and the main underlying cause of joint pain: inflammation. It was designed with an anti-inflammatory natural ingredient in order to address the primary cause of joint pain and swelling; however, it contains a second ingredient to reduce the joint pain itself while increasing motility and flexibility. This two-fold approach allows for more pronounced results for a variety of joint health concerns.

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Formulation

Flex™ was designed to be a convenient and great tasting beverage for on the go use as a joint health supplement. Flex™ contains two powerful natural ingredients to help reduce the underlying causes of inflammation and joint cartilage damage, while reducing pain and increasing motility of the joints. It was formulated in a blend of natural fruit juices which have high antioxidant levels; however, by combining them with lemon, Flex™ enhances their antioxidant capacities naturally (2). By providing this additional antioxidant protection, Flex™ protects joints further from free radical stress and damage.

Formulation includes two main natural ingredients as part of a joint support beverage:

- *Boswellia serrata*, providing boswellin/boswellic acids
    - Boswellic acids reduce inflammation that may be the source of joint pain and swelling
- UC-II, naturally derived undenatured type-II collagen
    - Prevents T-cell damage of joint cartilage
    - Reduces joint pain and improves joint mobility and flexibility

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Boswellin- overview

Boswellin is a term used to describe the resin extracted from various species of Boswellia, a genus of tree from which the biblical incense frankincense is derived. *Boswellia serrata* is the species most extracted for its use in pharmacological applications. It is a moderate to large size tree that grows in the dry mountainous regions of India, Northern Africa, and the Middle East. Workers extract the oleo gum-resin by tapping the trunk of the tree, through an incision, and then storing the resin in a specially made bamboo basket. It is then divided to remove the oil portion from the solid resin. The resin and oil have been used since historical times as folk remedies to treat various conditions, including chronic inflammatory diseases. The oil portion may contain up to 60% resin, while the remainder consists of essential oils and polysaccharides. The resin possesses many compounds including several pentacyclic triterpenic acids, which are responsible for the inhibition of pro-inflammatory enzymes. Of these, acetyl-11-keto-β-boswellic acid, referred to as boswellic acid, is the most potent and is therefore the most researched for anti-inflammation.

Joint health may be impeded by the inflammatory response, either due to stress from use or through inflammatory conditions such as arthritis. Arthritis is usually a chronic disease that results from a dysregulation of pro-inflammatory cytokines and enzymes that assist in the production of prostaglandins, such as COX-2, leukotrienes, and other such compounds. These factors are regulated by the activation of NF-kappaB. Research has found that by suppressing the activation of NF-kappaB, COX-2, or one of these other factors, they may be able to identify treatment options for inflammatory conditions. Both animal and clinical trials have demonstrated the potential of boswellin for the treatment of both rheumatoid arthritis and osteoarthritis, as well as a variety of other inflammatory diseases, including bowel disease and even asthma.

Boswellin has been shown to be a powerful anti-inflammatory agent; however, it works differently than an NSAID (non-steroidal anti-inflammatory drug). It most likely functions by inhibiting specific biological pathways associated with the inflammatory response; however, because it functions differently than an NSAID, it has none of the negative side effects on the digestive system normally found with NSAIDs.

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UC II- overview

UC-II is an undenatured type-II collagen manufactured from chickens to support joint health and function. Although it is a relatively new ingredient, having been isolated and studied extensively in just the past few decades, it is supported by several successful animal and human trials for use in joint health products. These studies demonstrate the powerful effect this ingredient has for alleviating pain associated with inflamed joints, while simultaneously increasing range of motion, overall joint function, and even quality of life. These results have been compared to well-known joint health supplements, such as glucosamine and chondroitin, and UC-II has far exceeded performance in all cases. In addition, it accomplishes more significant results than other supplements, yet only requires a very small amount of material. This makes UC-II highly tolerable for consumers, who had near perfect compliance levels with very minimal if any side effects.

UC-II is manufactured in a GMP-certified facility (Good Manufacturing Practices). This means that only the highest quality processes are utilized in the production of this natural ingredient. It is an FDA-notified and published New Dietary Ingredient (NDI). Its safety is unsurpassed, which affords it the highly sought GRAS status (generally recognized as safe) for food and beverage use, making it a perfect ingredient for Flex™.

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Safety

- Flex™ was designed such that a single cup daily could produce results, but that multiple cups would maintain safety parameters
- All safety studies outlined below are relevant to the dosages recommended for Flex™
- Adverse safety and toxicity trials are also reviewed if applicable

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Boswellin- safety

Boswellia serrata, or more specifically, the resin from Boswellia, has been used since historical times as an anti-inflammatory agent. In recent times, the major compounds responsible for anti-inflammation have been identified as boswellic acids. In an early toxicity trial conduced on both small animals and primates, boswellic acids were found to be non-toxic when administered both orally and intraperitoneally at extremely high doses (nearly 100 times higher than those used in Flex™). Researchers then provided daily oral administration of boswellic acids at low, medium, and high doses to both types of animals and noted that there were no significant changes in general behavior, nor in clinical, chemical, or pathological parameters. Therefore, this initial safety study concluded that boswellic acids are safe for clinical studies (3).

To further corroborate these findings, researchers used different cytogenetic assay systems to evaluate the genotoxic potential of boswellic acids in vivo. Using visual chromosomal aberration evaluations, sperm morphology, micronuclei and comet assays, researchers determined that boswellic acids are quite safe and did not show any genotoxicity at any dose level up to almost 10 grams, more than 50 times the amount used in Flex™ (4). These findings are corroborated by clinical trials, where limited if any reports of intolerance were noted by human subjects. A detailed discussion of these clinical trials and their outcomes can be found later in this white paper.

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UC-II- safety

As UC-II is a relatively new compound derived from animals, rather than a botanical with a long history of use, it has undergone rigorous safety evaluations necessary for the FDA to regard it as a new dietary ingredient (NDI) and also to award it GRAS status for use in foods and beverages. These safety studies involve a battery of tests, including acute oral toxicity, acute dermal, primary dermal irritation, primary eye irritation, genotoxicity, and dose-dependent 90-day sub-chronic toxicity.

The acute oral LD(50) is the amount of substance necessary to provide a lethal dose to more than half of the subjects. Although a lethal dose was not established in this study due to the extremely high amount of material required, researchers estimated that it must be greater than 48.6 grams in adult humans. (This is more than 1000 times greater than the therapeutic dose recommended for UC-II). They did not observe any changes in body weight or any adverse effects following necropsy. The acute dermal LD(50) was determined to be greater than 19.4 grams in adults, as it was not observed at this high dosage either. They did note that UC-II is slightly irritating to the skin and eyes and thus should not be applied to these body areas. In the genotoxicity studies, UC-II performed well, not causing mutagenicity in several types of standard assays. Finally, in the dose-dependent 90-day sub-chronic toxicity study, UC-II showed no pathologically significant changes in organ weights or brain weight. There were also no observed chemical changes. Therefore, researchers concluded the broad-spectrum safety profile for UC-II, allowing it to be used in clinical trials (5).

While extensive in and of themselves, these results have been corroborated in animal and human clinical trials. Subjects responded well to treatments, noting no adverse events nor changes in body chemistry. The amount of material required to achieve successful results is extremely small, making this product easy to consume with no gastrointestinal distress. These trials will be discussed in depth later in this white paper.

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Formulation Efficacy

Flex™ contains two potent ingredients for use in joint health. Outlined below are the mechanisms of action defined by the available published literature. In some cases, these mechanisms may have benefits outside the scope of joint health. These additional secondary benefits will be discussed briefly. Should any potentially negative outcomes in clinical trials be found, they will be presented and discussed as well.

- *Boswellia serrata*
    - Interferes with biological pathways important for inflammatory reactions
        - Reduces inflammation in the joints
        - Reduces inflammation in other organ systems (i.e. bowels, bronchioles)
- UC-II
    - Suppresses auto-immune pathologies that lead to T-cell attacks on joint cartilage
        - Reduces pain in the joints and improves mobility and flexibility

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***Boswellia serrata*- efficacy**

Mechanism of Action: Interferes with biological pathways important for inflammatory reactions

Although it has been shown repeatedly to be a potent anti-inflammatory agent, boswellin and specifically boswellic acids, do not have a single definable mechanism of action. Researchers have set out to determine the molecular basis for its anti-inflammatory action and have established several hypotheses. In most instances, it has been concluded that boswellic acids interfere with signal transduction pathways related to functional cellular processes important for inflammatory reactions (6). These were shown to be dependent upon the structure of the boswellic acid itself as well as the cell type it was acting upon (7). Some examples are outlined further for their direct relevance to inflammation of the joints.

Leukotrienes: Leukotrienes are a family of inflammatory mediators produced by the oxidation of arachidonic acid (8). They use lipid signaling to regulate immune responses, and their production is usually accompanied by the production of histamine and prostaglandins; these compounds also act as inflammatory mediators. Boswellic acids have been shown to suppress leukotriene formation, which has led to the anti-inflammatory response they have become known for. In both animal and pilot clinical trials, boswellic acids have demonstrated this suppression (9). Although these were the results of oral supplementation with boswellic acids, additional studies have shown a significant reduction in the amount of leucocytes themselves when boswellic acids are injected directly into the knee. In this case, the boswellic acids changed the electrophoretic pattern of the synovial fluid proteins found there and thus reduced inflammation in the knee (10).

PGE(2): Another study found that in human cells, boswellic acid suppressed the transformation of prostaglandin (PG)H(2) to PGE(2). By selectively inhibiting PGE(2) generation, boswellic acids reduced lipopolysaccharide-induced PGE(2) biosynthesis without affecting the formation of COX-derived metabolites and thromboxane B(2). Although this pathway seems complicated, it essentially demonstrates another avenue for suppressing inflammation by boswellic acids (11).

Cat G: An earlier study found boswellic acids suppress the proteolytic activity of lysosomal protease cathepsin G (cat G). This is important for anti-inflammation because cat G participates in connective tissue remodeling at sites of inflammation. By suppressing the protease responsible for cleaving this

enzyme, boswellic acids help to protect it, allowing it to be present for future repairs at inflammatory sites (12).

NF-kappaB: Many familiar with the ailment of arthritis are familiar with NF-kappaB. This is because NF-kappaB is a protein complex that controls many aspects of cell survival. Incorrect regulation of this protein has been linked to inflammatory diseases, as well as viral infection, improper immune development, and even cancer. In a study evaluating the role boswellic acids play in the regulation of this protein complex, researchers found that these acids significantly inhibited NF-kappaB specifically on atherosclerotic lesions. This means that they worked against them, reducing them and actually assisting in suppressing this detrimental inflammatory response in the body (13).

Clinical Evidence Supporting Boswellic Acid for Anti-Arthritic Purposes

In a double-blind, placebo controlled clinical trial published in 2008, researchers compared boswellic acid daily against a placebo for potential benefits in osteoarthritis of the knee. Utilizing seventy subjects over a 90 day trial, they showed anti-inflammation of the knee in as little as seven days. This was confirmed by measuring a significant reduction in pro inflammatory modulators, including those cited above in cellular trials. In addition, they cited a significant reduction in cartilage degradation that accompanies osteoarthritis. Side effects were mild including minor GI distress and diarrhea; however, these side effects were evenly distributed among both the treatment and the placebo groups. Those subjects in the treatment group reported reductions in pain and joint stiffness as well during the course of the trial (14).

In a second trial evaluating mobility and function in osteoarthritic subjects using boswellia, researchers enlisted sixty subjects for a thirty day trial. Again, benefits were seen in as little as one week in the treatment group. These benefits included significant reductions in pain scores using the WOMAC scale, the industry standard for clinical pain trials. They also showed significant improvement in joint function. Minor GI distress was the only reported side effect, and it was once again seen evenly in the treatment and placebo groups, with only a single case reported for each group. To confirm safety, all hematological and urinary profiles were compared, and no differences were seen before and after treatment (15).

Secondary Effects of Boswellic Acids

As boswellic acids have been shown to be powerful anti-inflammatory agents, their use for joint health is guaranteed. However, these same inflammatory pathways affect many other body systems outside the scope of joint health. One key body system negatively affected by inflammation is that of the digestive system, in particular the bowels. Inflammatory bowel disorders afflict a number of individuals, and seem to be on the rise. Boswellic acids have been shown to reduce this inflammation in the bowels following similar mechanisms to those described above for joint health, in particular by affecting NF-kappaB (16). This mechanism allows for the reduction of ulcers in instances of ulcerative colitis and a significantly higher and prolonged anti-inflammatory effect in the bowels (17, 18).

Combination Therapy with Curcumin

In a clinical trial to assess the potential synergy between boswellia and another known natural anti-inflammatory, curcumin, researchers tested the stand-alone curcumin, as well as the combination of curcumin and boswellia, against the known published trials using just boswellia. On its own, curcumin showed no significant improvement in osteoarthritis over placebo. However, when combine with boswellic acid, there was significant improvement. No adverse events were reported between any of the groups. These results showed that it was the benefits from the boswellic acid that were having the most pronounced effects on treating osteoarthritis, and that there are not necessarily synergies between curcumin and boswellia for anti-inflammation. (19).

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A Review of Negative Outcomes from Clinical Trials: Boswellin

While boswellin has immense research demonstrating its benefits for inflammation, its pharmaceutical development has been severely hampered due to its historical limited bioavailability. A number of trials in decades past had reported little to no bioavailability in plasma levels after supplementation. Researchers have investigated this and found that the limited bioavailability has been due to the composition of the resin hindering gastrointestinal absorption (20). Many different researchers have attempted to modify the composition of the resin to improve bioavailability with much success. By creating a water-soluble version of boswellin, they significantly improved bioavailability, which then translates to significant improvements in inflammatory biomarkers (21, 22, 23). In fact, when tested both orally and topically, boswellic acid was measured in the plasma and determined to be bioavailable via both delivery methods (24). These findings conclude that in a water-soluble form, such as found in Flex™, boswellin is bioavailable and should produce the results seen in the trials cited above.

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***UC-II* -efficacy**

Mechanism of Action: Reduces T-cell attacks on joint cartilage

While many supplements used for joint health address only inflammation, UC-II targets one of the underlying causes of the inflammation itself, directly in the immune system; it protects joint cartilage from T-cells attacks. T cells are a type of lymphocyte that has been shown to play a role in the development of rheumatoid arthritis. It is believed to do this by orchestrating the inflammatory processes responsible for the disease through the immune system. UC-II has been shown to alter the configuration of glycoproteins responsible for the recognition/response signaling that catalyze T-cell attacks. This then suppresses autoimmune pathologies, including antigen-induced rheumatoid arthritis. (25). By lessening the internal attack on joint cartilage and the inflammatory response of the immune system, UC-II alleviates symptoms of arthritis and may help to prolong the onset of the disease.

This mechanism was put to the test in well-designed animal and human clinical trials. Initially, UC-II was tested in obese-arthritic dogs against a placebo. Two doses were used to determine if there was a dose response. Blood samples were taken to determine safety during the course of the 120 day study. Both the high and low doses of UC-II significantly improved overall pain, pain during limb manipulation, and lameness after physical exertion over placebo, with the higher dose showing a greater improvement. This suggests that the higher dose is more beneficial for achieving greater results. In addition, the dogs were taken off of the intervention for 30 days and retested on all parameters. They all experienced a relapse in overall pain, lameness, and pain upon limb manipulation. As there were no adverse events reported and tolerability was high, it is assumed that UC-II is safe and effective with continual use (26).

In two separate studies, researchers evaluated the effectiveness of UC-II in arthritic dogs as a stand-alone therapy or in combination with the well-known joint supplements glucosamine and chondroitin. Their objective was to determine if there was an additive effect when these natural products are combined. They tested varying levels of all natural products against a placebo group. Although all groups showed improvements compared to placebo, only the UC-II group showed a significant reduction in overall pain within the first 30 days of the trial, with maximum reductions in pain shown at day 120. The glucosamine/chondroitin group alleviated some pain compared to placebo, but only when they were combined with UC-II did it have statistically significant reductions in pain (27). These findings were

duplicated in the second trial nearly five years later, citing the benefits of UC-II as a powerful stand-alone ingredient for joint health (28).

Research has also been conducted on much larger mammals. In a study on performance horses, varying levels of UC-II were tested against glucosamine/chondroitin or placebo. The horses given the placebo showed no change in arthritic condition. However, all of the UC-II and the glucosamine/chondroitin groups showed significant improvements in all parameters tested. When compared, the efficacy of the glucosamine/chondroitin group was less than that of the UC-II groups, with the higher doses of UC-II providing significantly more benefits than glucosamine/chondroitin alone (29). These doses have been translated into human doses based on body surface area calculations and are the doses tested in human clinical trials and recommended for human consumption.

An initial pilot human clinical trial measured the efficacy of UC-II at the recommended dose for reducing joint pain and swelling in subjects diagnosed with rheumatoid arthritis. After 42 days, a significant reduction in pain was noted, including morning stiffness, stiffness following periods of rest, pain that worsens with the use of the affected joint, and loss of joint range of motion and function. These results suggested that UC-II could be a novel tool in treating joint inflammatory conditions and symptoms associated with arthritis (30).

These conclusions were put to the test against glucosamine/chondroitin in human subjects suffering from osteoarthritis (OA) of the knee. The Western Ontario McMaster Osteoarthritis Index (WOMAC) score, a standard measure of pain associated with OA, was calculated before and after treatment. UC-II treatments were shown to significantly decrease this score compared to glucosamine/chondroitin. This was seen in as little as 90 days, with some results reported earlier. Subjects in the UC-II groups also showed significant enhancement in daily activities, suggesting an improved quality of life following treatment (31).

To evaluate UC-II in healthy individuals who experience joint stress and pain due to activity and exercise, researchers conducted a double-blind placebo-controlled trial using fifty-five healthy subjects. All subjects reported knee pain after a step mill performance test, yet did not exhibit signs of inflammatory disease, such as arthritis. UC-II was administered against a placebo for 120 days, after which joint function was measured as well as joint pain. Those in the UC-II treated group exhibited a statistically

significant improvement in average knee extension compared to placebo. They also exercised longer before experiencing joint discomfort compared to baseline. Results were so dramatic by the end of the study that five subjects reported no pain during or after the step mill protocol following 120 days of UC-II treatment (32).

In a broad spectrum research study, comparisons of different functional foods were made to determine the benefits on synovial fluid. Arthritic disorders involve the suppression of inflammatory mediator production from synovial cells. If you can stop this suppression, you could potentially rebuild synovial fluid, helping to buffer the joints and prevent the arthritic conditions and pain. Among the functional foods tested was UC-II. It was found to successfully suppress the IL-1β-stimulated IL-8 production by human synovial MH7A cells, thus keeping them active and creating synovial fluid effectively (33).

Because of successes such as these, where UC-II has been shown to rebuild synovial fluid, many researchers and finished product companies have successfully combined it with other natural products that help with anti-inflammation, including boswellia such as in ActiveBlend Flex (34).

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Usage Guidelines

Joint health comes in varying degrees. Whether looking to improve overall flexibility and motility for exercise purposes or suffering from a debilitating disease such as rheumatoid arthritis, a joint support product should be considered. For general everyday use, it is advised to consume one cup of Flex™ per day to achieve results. This is based on the available research and proven efficacy of the active ingredients at recommended dosages.

As noted in this white paper, safety studies were conducted using doses of the herbal ingredients much higher than those provided in Flex™, even when multiple cups are consumed per day. Therefore, consuming even 1-2 cups of this beverage should yield health benefits without negative safety concerns. However, should you be under the care of a physician for any ailment, consult your physician before consuming Flex™ to insure there will not be any detrimental interactions with other medications or supplements.

Although not seen in clinical trials, should gastrointestinal distress be experienced when consuming this product, you may consume it with a meal. This should minimize any potential upset of the stomach without reducing efficacy.

As always, pregnant and nursing women as well as children 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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