

**A New *Champion* To Defeat *Inflammation!***

**PARACTIN**  
CLINICALLY PROVEN  
HEALTH BENEFITS  
**Bone, Joint &  
Muscle Health**  
YOUR  
**BRAND**  
60 | 150

Chondroitin  
Glucosamine  
Boswellia  
Curcumin  
Eggshell Membrane

**PARACTIN**<sup>®</sup>  
*Bone, Joint & Muscle Health*

**HPI**  
**HP Ingredients**  
Delivering Herbal Science • Since 2001

**Clinically Proven • Highly Effective • Anti-Inflammatory Agent • [www.ParActin.com](http://www.ParActin.com)**



# It's only natural, and that's the way we plan on keeping it.

~ Annie Eng, Founder, HPI

*Taking a peaceful respite  
in a Malaysian rainforest*



**Naturally...** when we started in 2001, our founder, Annie Eng, set out to create a company that would not only deliver herbal science for health products that people all over the world could rely upon, but also support the indigenous peoples who provide the raw botanical materials for our ingredients. We strive for enduring sustainability of all our products.

Today we manufacture and supply safe, patented, clinically proven natural botanical extracts that are used by hundreds of companies to produce successful health products. Our mission is to maintain a reputation as a pioneer in the global natural

health industry while we continue to deliver unique ingredients backed by rigorous scientific research.

**Proven Clinical Results** – At HP Ingredients we work closely with patent-awarded researchers to provide ongoing clinical evidence that supports our formulations and patented ingredients. These botanicals are then used to create some of the most effective nutraceuticals on the market today.

***It's only natural, and that's the way  
we plan on keeping it.***

*We provide unique ingredients that address common health and aging concerns such as support for...*

Metabolic Syndrome • Cholesterol, Blood Glucose Balance • Weight Management • Skin Care  
Men's Testosterone Health • Enhanced Physical Performance • Sports Nutrition • Neuronal Health  
Bone, Joint and Muscle Health • Cognitive Function, Mood, IQ Performance • Antioxidant Support

LJ100<sup>®</sup> PARACTIN<sup>®</sup> BERGAMONTE<sup>®</sup> CitrusSlim<sup>®</sup> NQMax<sup>®</sup>  
MAQUIBERRY<sup>®</sup> NeuroActin<sup>®</sup> IQ200<sup>®</sup> MaquiCare<sup>®</sup> ProteoActin<sup>®</sup>

\* The products and the information provided have not been evaluated by the Food and Drug Administration.  
The product is not intended to diagnose, treat, cure, or prevent any disease.

**HPI**

**HP Ingredients**  
Delivering Herbal Science • Since 2001

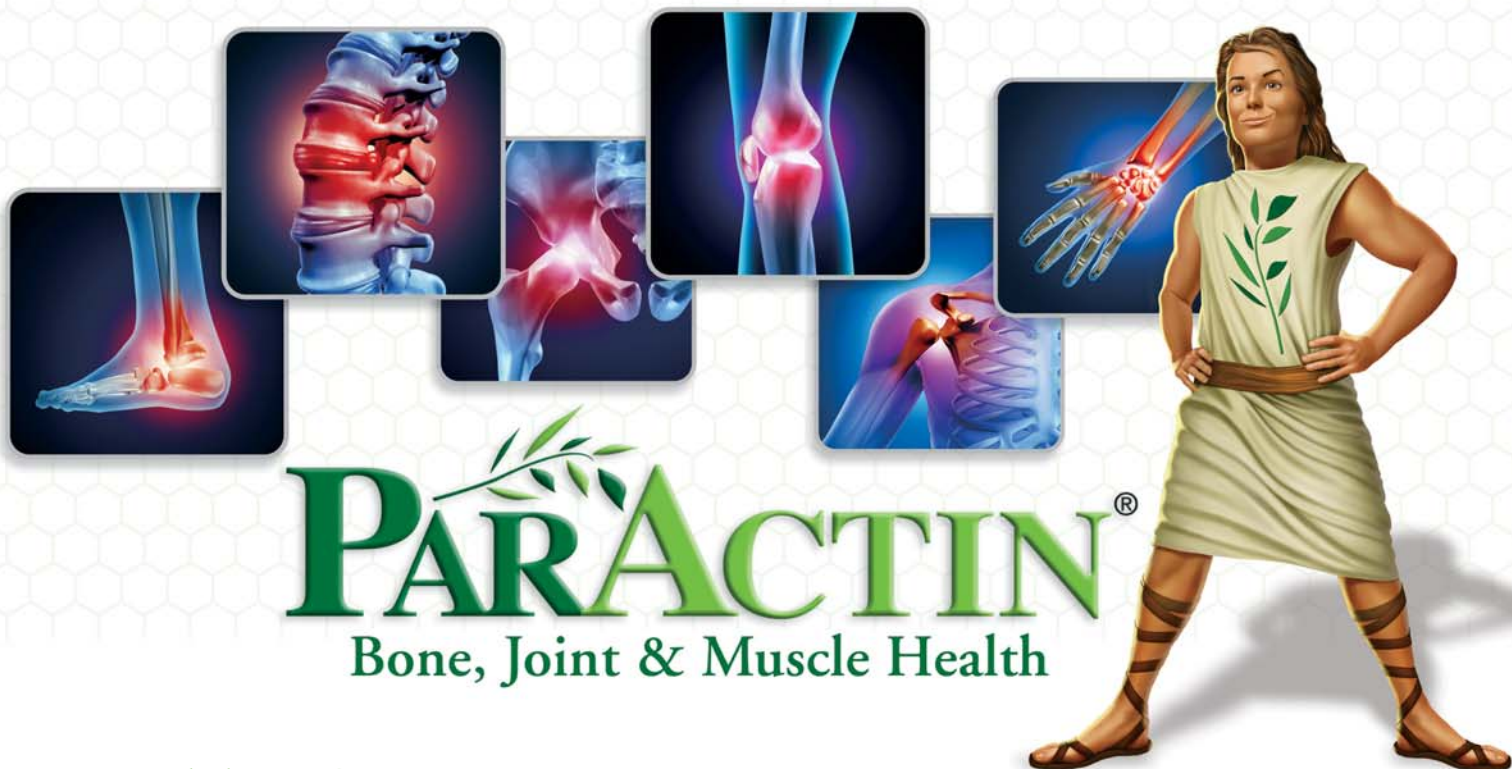
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# PARACTIN®

## Bone, Joint & Muscle Health

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# David & Goliath

## How To Make A Super-Selling Product With ParActin® That Beats Inflammation!

It's an epic tale that is extrapolated in many ways – but at its core, David and Goliath is all about unseating, vanquishing, eliminating the fearsome foe. Beating the top dog. And everyone loves the underdog.

But wait, you say, that's what curcumin does to inflammation and everyone seems to just love it.

So, what if you had a natural faster acting, smaller dose and therefore *less expensive* formulation than curcumin to offer consumers who want to control inflammation and keep moving to enjoy a fuller, more active life at any age?

### *You'd want to know about it, wouldn't you?*

If you haven't heard of "**ParActin**®" before, you will be hearing much more about this potent, multi-tasking herb. And if you are familiar with David and Goliath, **ParActin**® is like David, a more powerful anti-inflammatory-and-more herb than the current curcumin in fighting the Goliath inflammation.

We believe, and the science shows, that **ParActin**® is poised to become the dominant botanical ingredient for managing inflammatory response and related health conditions.

In fact, this patented extract of *Andrographis paniculata* is the next new anti-inflammatory agent, which is faster and more effective, with more biologically beneficial abilities.

Yes, we are here to say (and show) it: andrographolides are more powerful for health than curcuminoids.



# Haven't Got Time For The Pain

When joint discomfort begins to arise, potentially signaling a deteriorating condition, today's active adults simply do not have time to wait for their chosen joint-health supplement to work. **ParActin®** is right there, right now. It crosses the blood-brain barrier and is therefore highly absorbable – meaning that your consumers will feel the difference within an hour!

## Here's how other ingredients stack up:

**Chondroitin:** According to a Cochrane review, studies after 2000 showed that there were no statistically significant differences in pain scores than those in the placebo group.<sup>1</sup>

**Chondroitin & Glucosamine:** A meta-analysis of 10 trials of 3803 individuals measuring arthritis pain intensity found that this combination did not reduce joint pain.<sup>2</sup>

Furthermore, the combination at 1,200 mg daily was shown not to confer statistically significant results until

six to eight weeks of habitual consumption.<sup>3</sup> Do your target consumers have two months to wait for improvement?

In addition, chondroitin and glucosamine require large doses, and in an age of pill fatigue, this is not attractive. For the growing number of individuals who want to avoid any substance that may cause sensitivities or allergies, shellfish is not an option. For the growing number of vegans, cow cartilage (or shark, porcine and poultry), is absolutely verboten.

**Curcumin:** Although Curcumin can be effective in some pathways, individuals need high doses, typically about 1,500 mg, because by nature it is not easily absorbed, and there are many sources claiming to have overcome this flaw.

**Chicken sternal collagen:** Other than the fact that is not suitable for vegans or vegetarians, it provides discernible relief of joint discomfort in seven days.<sup>4</sup>

	ParActin®	Glucosamine	Chondroitin	Curcumin	Chicken Collagen	Egg Shell Membrane
Time to Work	4 hours	45-60 days	45-60 days	30-60 days	7-14 days	10 days
Effective Daily Dose	300 mg	1500 mg	1200 mg	1,500 mg	40 mg	500 mg
Allergen-free	✓					
Vegetarian	✓			✓		



*It would appear that inflammation may still topple those other challengers.*

*But wait...*

*There is something new that may prove victorious.*

**ParActin®** is a joint health ingredient that:

- *Is exceptionally efficient at a daily dose of only 300 mg*
- *Has superior bioavailability because it crosses the blood brain barrier*
- *Has human clinical studies demonstrating clear efficacy*
- *Perfectly suitable for vegans and vegetarians as it is a botanical source*
- *Contains no allergens*
- *Available in organic and conventional*
- *Is non-GMO*
- *Reduces pro-inflammatory cytokines such as COX-2, interleukins 2 and 6, and prostaglandins*
- *Has multiple clinical trials showing reduction of swollen joints*
- *Reduces C-reactive protein*
- *Inhibits NF-κB (the master switch of inflammation)*
- *Supports healthy bone function*
- *Supports healthy cartilage*
- *Supports skeletal muscle strength*
- *Is non-irradiated, TSE free*
- *Is certified kosher and halal*

As a botanical, **ParActin®** is a clean ingredient consumers can trust will work to support joint – and bone, cartilage and muscle – health while not having to be concerned with side effects.

*Clearly, ParActin® is for anyone who doesn't have time for the pain!*



## Introducing the Challenger:

# PARACTIN<sup>®</sup>

**Bone, Joint & Muscle Health**

**ParActin<sup>®</sup>** gets its name from what it does – activating PPAR-gamma, which shuts down the master switch of inflammation (nuclear factor-kappaB or NFkB).

**ParActin<sup>®</sup>** is a patented extract from *Andrographis paniculata*, standardized to andrographolide, 14 deoxyandrographolide and neoandrographolide. These naturally occurring phytochemicals in *Andrographis paniculata* have been shown by researchers to support healthy joints, bones and muscles; this is so important in today's active lifestyle.

**ParActin<sup>®</sup>** was awarded U.S. Patent #8,084,495 B2 (Dec. 27, 2011), titled, "Composition of Labdane Diterpenes Extracted from *Andrographis paniculata*, Useful for the Treatment of Autoimmune Diseases, and Alzheimer's Disease by Activation for PPAR-Gamma Receptors."

Andrographis has a long and rich history of use in Asia where it is called the "King of Bitters." In the venerable medicinal systems of Ayurveda and Traditional Chinese Medicine, practitioners provide or recommend this herb for many maladies and for adaptogenic (i.e., to help the body adapt, balance) support. Interestingly, its traditional uses are what modern medicine now knows as the source of unhealthy inflammatory response.

In fact, wrote researchers in one study...

***"andrographolide and its analogs have great potential to be the next new class of anti-inflammatory agents..."***<sup>5</sup>





# Fighting the Silent Killer – Inflammation

Cancer. Alzheimer's. Autoimmune diseases. Depression. What do all these conditions have in common? They have been linked to chronic inflammation. It seems impossible that one thing can be responsible for so many problems, but a growing body of medical research is revealing that long-term, systemic inflammation that occurs when one's immune system goes into overdrive – sending out cells that attack unhealthy and healthy tissues – may be at the root of many prevalent diseases.

The medical and nutraceutical research communities are highly aware how chronic inflammation damages the human organism in many ways. *In vivo* research has outlined and clarified the cascade of reactions causing unhealthy inflammation.

Inflammation, however, is not an unjustified biological response. It is critical for our survival and is the body's natural mechanism to defend against a diverse variety of pathogens including bacteria, viruses, fungi, tumors and other harmful agents (e.g., chemicals, radiation, burns and wounds). Inflammation is a complex reaction of the body in response to cellular injury (such as a bruise). It is marked by tissue swelling, capillary dilation, antihistamine activity, redness, heat and pain. It serves as a mechanism initiating the elimination of noxious agents and of damaged tissue. (see Figure 1)

Two types of inflammation are associated with imbalanced immunity. Classical inflammation is usually associated with pain and may result from an overactive immune system that is constantly "turned on." This causes the self-attack mode that can lead to several disorders such as irritable bowel syndrome, psoriasis and rheumatoid arthritis, among others. Silent inflammation happens when the immune system continues its self-attack mode at the cellular level, affecting certain organs such as the heart or brain without the individual perceiving pain or discomfort. He or she may experience fatigue, muscle stiffness and headaches, however.

Aging slows down the effective functioning of the immune system, causing an ever-smaller reservoir of cells capable of responding to the increasing amount of damage inside the body and tissues. It's a sad story. The body hurts itself by trying to fix problems it can't resolve.

Most people reach for common non-steroidal anti-inflammatory drugs (NSAIDs) like acetaminophen and ibuprofen to ease aches and pains when we bang up muscles or joints or experience headaches and colds. Unfortunately, NSAIDs can rip the stomach lining and gastrointestinal tract, contributing to even more inflammation in the long run. COX-2-inhibitor drugs were designed to block just the inflammatory functions of the COX-2 enzyme, leaving the stomach-protecting functions of COX-1 intact. However, research has shown an increased risk of heart attack and stroke among users.

The current hot theory suggests that depression may be caused by cytokine-driven inflammation in the brain. A study published in *JAMA Psychiatry* found that people with clinical depression had levels of brain inflammation 30% higher than those in a control group.<sup>6</sup> This may be one reason why half of clinically depressed people don't respond to antidepressants; these drugs cannot tackle inflammation levels.

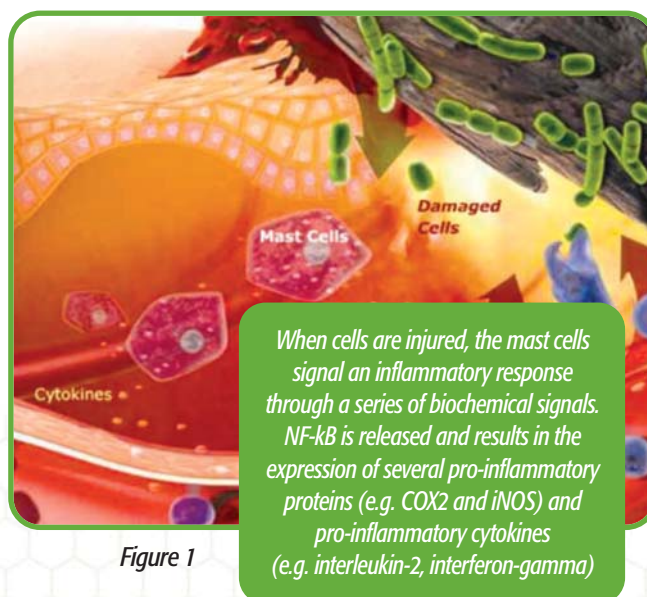


Figure 1



# Activating PPAR- $\gamma$ : The Key to ParActin's Incredible Strength

**ParActin's**<sup>®</sup> mechanism of action is activating PPAR- $\gamma$ . Activated PPAR- $\gamma$  then inhibits nuclear factor-kappaB (NFkB) – the key regulator of the immune and inflammatory response system. When you can turn off NFkB you can reduce inflammatory cytokines and proteins that cause pain and inflammation, such as COX2, prostaglandins, interleukin 6, and other pro-inflammatory compounds.

Although there are some studies showing the opposite, researchers of one study adamantly declare that curcumin does *not* bind to or activate PPAR- $\gamma$ . They conclude that their results show “these multiple lines of evidence conclusively demonstrate that curcumin is *not* a PPAR- $\gamma$  ligand and indicate the need for further investigation of the mechanisms through which the compound acts.”<sup>7</sup>

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily. PPAR- $\gamma$  was originally characterized as a regulator of fatty acid synthesis, glucose metabolism, and is a known factor promoting differentiation of adipocytes. Due to its involvement in regulation of many physiological processes such as lipid metabolism, response to insulin, and proliferation, PPAR- $\gamma$  became an attractive therapeutic target for the treatment of metabolic disorders.

PPAR- $\gamma$  also plays a pivotal role in the immune system. Moreover, PPAR- $\gamma$  exerts anti-inflammatory properties that can modulate the immune inflammatory response. Recent studies have linked PPAR- $\gamma$  with inflammation – implicated as a key causative factor in the development of atherosclerosis, cancer, and fibrosis.

Continuing research validates the danger that nuclear factor-kappaB (NFkB) poses to maturing individuals, as it kicks off the inflammation cascade – and you don't feel this happening.

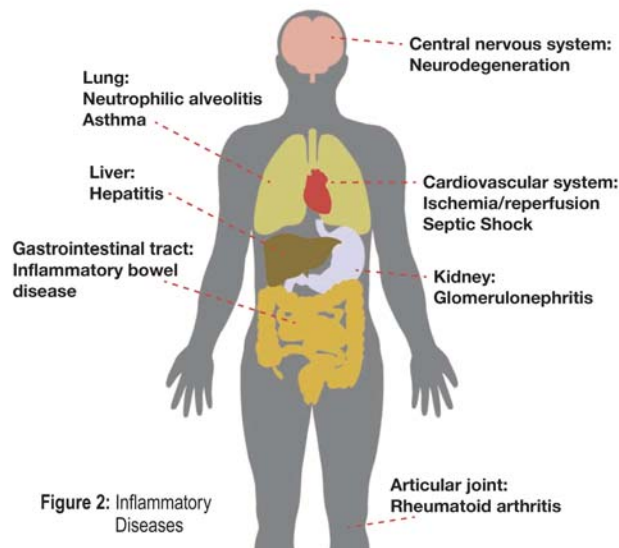


Figure 2: Inflammatory Diseases

NF-kB is a protein that acts as a switch to turn inflammation on and off in the body. Scientists describe NF-kB as a “smoke sensor” that detects dangerous threats like free radicals and infectious agents. In response to these threats, NF-kB “turns on” genes that produce inflammation. As we age, NF-kB expression in the body increases, provoking widespread chronic inflammation and setting the stage for diseases ranging from atherosclerosis and diabetes to Alzheimer's. Evidence from recent research suggests that by inhibiting NF-kB, a wide range of diseases and conditions in which inflammation plays a critical role can be treated. (see Figure 2)

**ParActin**<sup>®</sup> helps modulate overactive immune cells. Andrographolides in **ParActin**<sup>®</sup> can exert their beneficial effects through PPAR gamma activation (i.e., PPAR gamma agonist), which effectively turns off the “master power switch” NF-kB, responsible for igniting the over-reactive inflammatory response. By deactivating NF-kB, the hyper-expression of cytokines, pro-inflammatory proteins and enzymes such as COX-2, PGE2, interleukin-2 and interferon gamma is reduced. (see Figure 3)

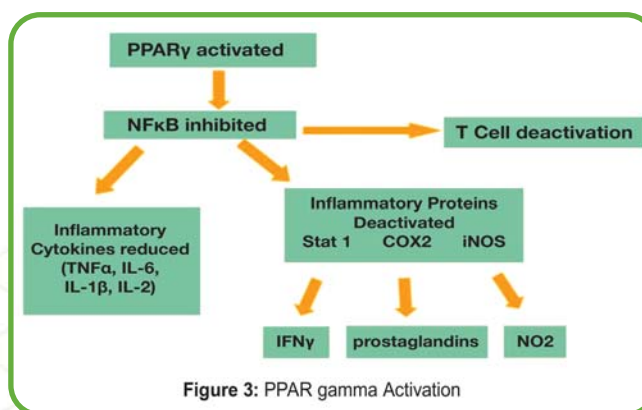


Figure 3: PPAR gamma Activation



## New, Better MOA for ParActin®

In 2018, a new major mechanism of action of andrographolide, the bioactive compound in **ParActin®**, was published in *Biochemical Pharmacology*. The new mechanism proposed for andrographolide is the increase in the Nrf2-Keap1-antioxidant response element (ARE) pathway, which involves an acceleration in expression of the antioxidant proteins expression.

### Free Radicals

Most compounds and molecules in our bodies exist in a relatively stable state. However, cellular energy production and environmental stressors may lead to the formation of damaging molecules called free radicals (reactive oxygen species ROS, peroxides, hydroxyl radical, nitric oxide radical). These free radicals are chemically unstable, and highly reactive. The normal stable form of oxygen is O<sub>2</sub> but it forms O<sub>2</sub><sup>-</sup> (superoxide) when involved in some reactions in the body. The little - sign means that an extra electron has been added. Superoxide is highly reactive as it is trying to find a way to lose that extra electron, and the only way to do that is to transfer it to another molecule or compound.

This is where antioxidants step in – it's their function to mop up these highly reactive species to ensure they don't interact with any of the important molecules in a cell. This mopping up occurs constantly in the body, however, oxidative stress can occur when antioxidant function becomes overwhelmed by free radicals.

### Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production of free radicals and the body's ability to counteract their damaging effects through neutralization with antioxidants. Many lifestyle factors and environmental stressors can contribute to oxidative stress. During inflammation, for example, the body produces toxins that can cause oxidative stress in the cells.

In the short term, oxidative stress is unlikely to be harmful, as while the body may be temporarily overwhelmed it will usually respond to clear any harmful compounds. Increased levels of ROS (reactive oxygen species) cause oxidative stress which in turn may severely damage lipids, proteins, and DNA. Oxidative stress also activates a variety of pro-inflammatory transcription factors such as NF-κB, AP1, HIF-1α, PPAR-γ, β-catenin/Wnt, and Nrf2. Continuous and chronic oxidative stress can accelerate the aging process, lead to chronic inflammation, damage or even destroy healthy cells in different parts of the body, which in turn could contribute to the development of various health conditions.

### Enter the Nrf2-KEAP1-ARE Pathway

At the center of the day-to-day biological response to oxidative stress is the Nrf2–Keap1– ARE pathway. This pathway plays a key role in the maintenance of cellular homeostasis under stress and inflammation by activating the many antioxidant and detoxification genes to help process and eliminate toxins before they can cause damage.

Nrf2 (nuclear factor erythroid 2-related factor 2) is a major regulator of cellular defense mechanisms against environmental stressors, and plays a key role in the resolution of inflammation. Activation of Nrf2 is believed to provide many health benefits including reducing systemic inflammation, oxidative stress, cellular DNA, RNA and protein damage, while also improving mitochondrial function (cellular energy production). Under normal conditions, Nrf2 exists in the region outside of the nucleus where it cannot interact with DNA. It is held here by another protein called KEAP1 (Kelch ECH associating protein 1), which prevents it from moving into the nucleus.

KEAP contains several sensors for ROS and other cell proteins associated with cell stress. If KEAP1 is inhibited, these receptors are activated, then Nrf2 is released, and can pass into the nucleus.



Once within the nucleus, Nrf2 binds to a region of DNA known as an antioxidant response element (ARE). These AREs are closely associated with the genes for NQO1 [(NAD(P)H Quinone Dehydrogenase 1], glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD), and catalase (CAT), among other genes. When Nrf2 binds to ARE, it induces the production of these active proteins and enzymes that exhibit potent antioxidant capacity and can rapidly clear oxidative stress.

Superoxide dismutase (SOD) is an enzyme that catalyzes the dismutation of the superoxide radical into either ordinary molecular oxygen or hydrogen peroxide. Superoxide is produced as a byproduct of oxygen metabolism and, if not regulated, causes many types of cell damage.

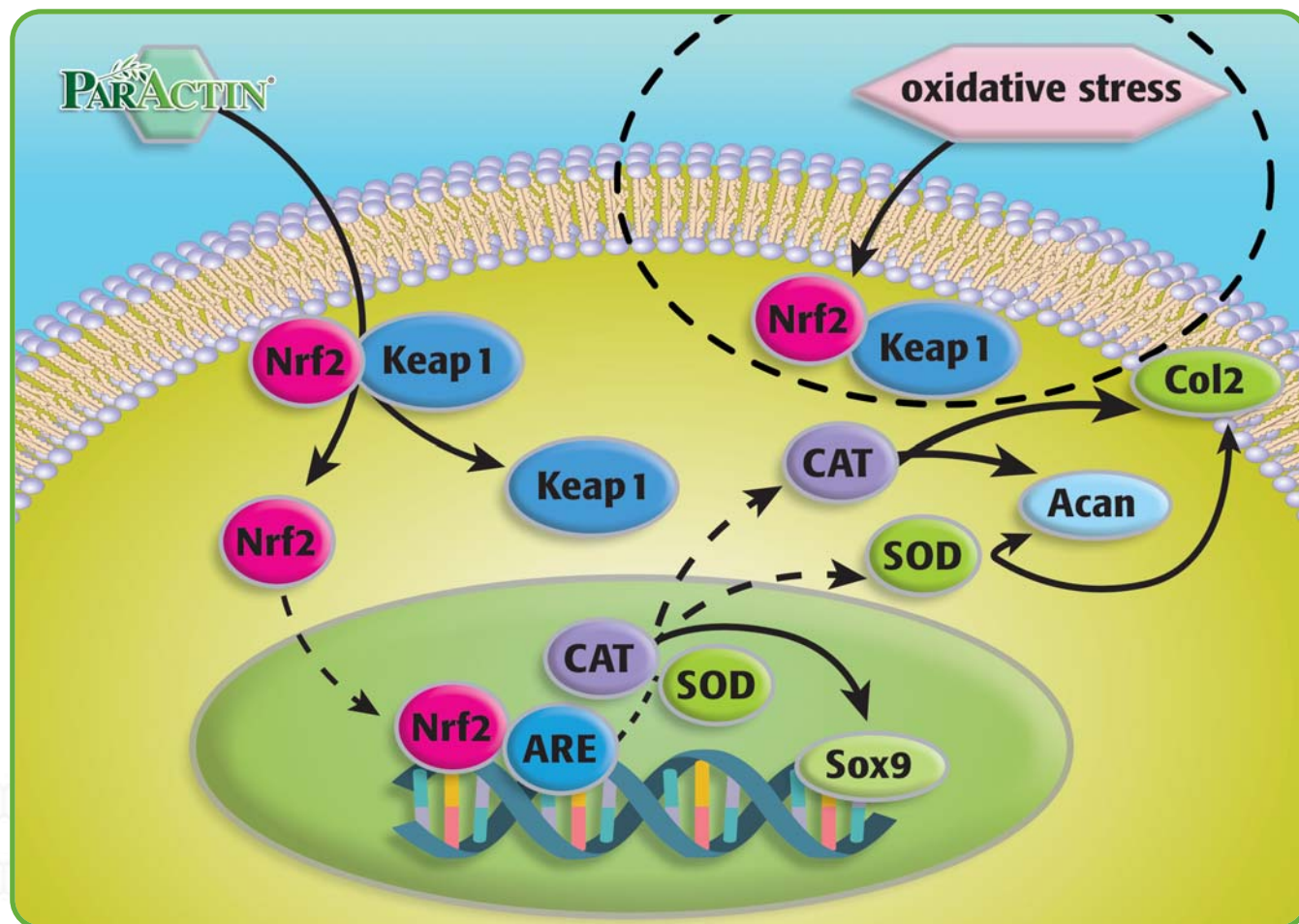
Catalase is a common enzyme found in nearly all living organisms exposed to oxygen (such as bacteria, plants, and animals). It catalyzes the decomposition of hydrogen peroxide to water and oxygen. It is a very important

enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS).

***The Nrf2-KEAP1-ARE is an important pathway for maintaining healthy anti-inflammatory, antioxidant, detoxification, and autophagy actions. It is essential for cardiovascular health, blood glucose regulation, maintenance of autophagy in pancreatic, liver, and kidney function, as well as to protect against neurodegenerative disorders.***

### **ParActin® Increases Nrf2 Activity And Activates Antioxidant Response Element**

**ParActin®** inhibits the KEAP1 protein, thereby unbinds the Nrf2 from KEAP1, and activates the ARE signal pathways. These cause an increase in antioxidant proteins and enzymes such as SOD and CAT, thereby reducing oxidative stress and inflammation, normalizing mitochondrial metabolism, restoring redox balance, and suppressing proinflammatory cytokines.





## ParActin® ~ Healthy Joint Support

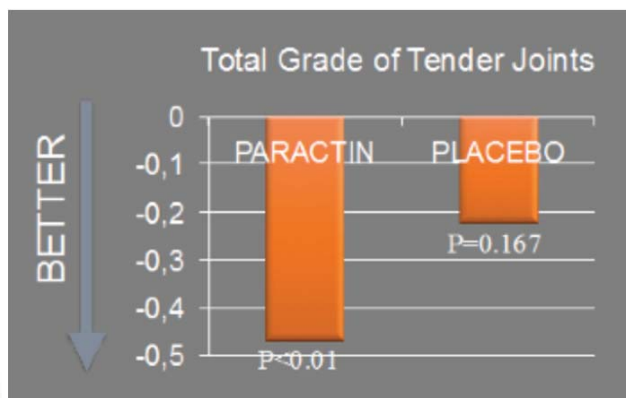
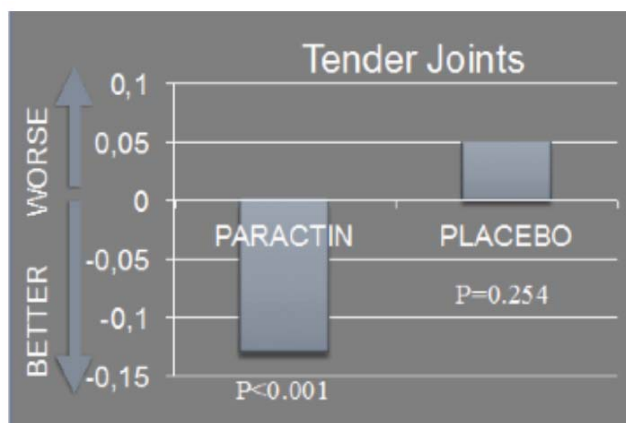
Rheumatoid arthritis (RA) results from the immune system mistakenly attacking healthy joints for a prolonged duration, causing a great deal of inflammation. Individuals with RA typically have high levels of C-reactive protein (CRP), which is involved in acute and chronic inflammatory activity in unhealthy joints. Rheumatoid factors (RFs) are antibodies detectable in the blood of approximately 80% of adults with RA. RFs are produced by an immune system that can attack healthy tissue in your body. Tumor necrosis factor-alpha (TNF- $\alpha$ ), another key driver of inflammation, is a cytokine that stimulates an acute reaction. Research has found TNF- $\alpha$  to be present in the synovial fluid of RA patients. Andrographolide is known to reduce TNF- $\alpha$ , which leads to a significant reduction in RFs.

In a 2009 randomized, double-blind and placebo-controlled study published in *Clinical Rheumatology*, 60 individuals with RA were given 100 mg of **ParActin®** or placebo in conjunction with methotrexate (MTX), three times a day for 14 weeks.<sup>8</sup> MTX, a standard therapy for RA, relieves tender and swollen joints, pain and improves functional status, but long-term use of MTX may cause serious infection and liver damage.

**ParActin®** was effective in reducing the number and total grade of swollen joints, the number and total grade of tender joints, as well as improving scores on HAQ-52, and SF-36 health questionnaires.

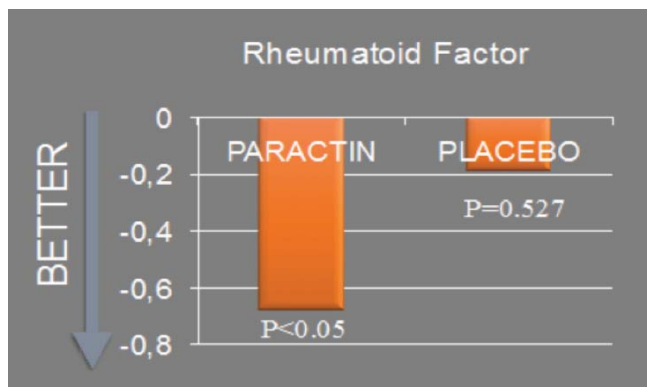
The **ParActin®** group showed significant improvement compared to the placebo (with MTX) group in the following scores:

- **Number of swollen joints: 9 in the ParActin® group vs 13 in the placebo group**
- **Total grade of swollen joints: 11 in the ParActin® group vs 16 in the placebo group**
- **Total grade of tender joints: 14 in the ParActin® group vs 17 in the placebo group**
- **HAQ: 19 in the ParActin® group vs 24 in the placebo group**
- **Reduction of RF: 119 in the ParActin® group vs 130 in the placebo group**
- **Reduction in IgA: 293.7 in the ParActin® group vs 335 in the placebo group**

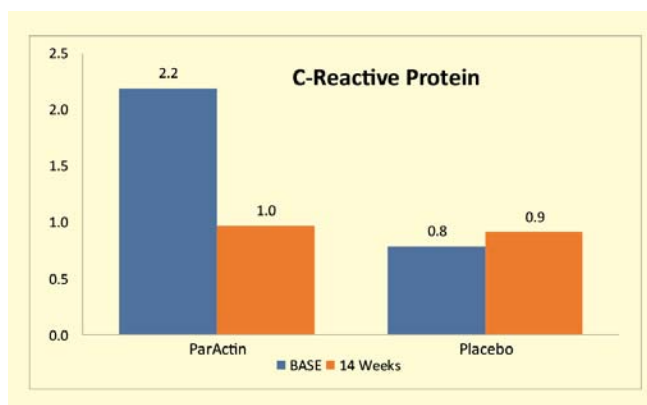




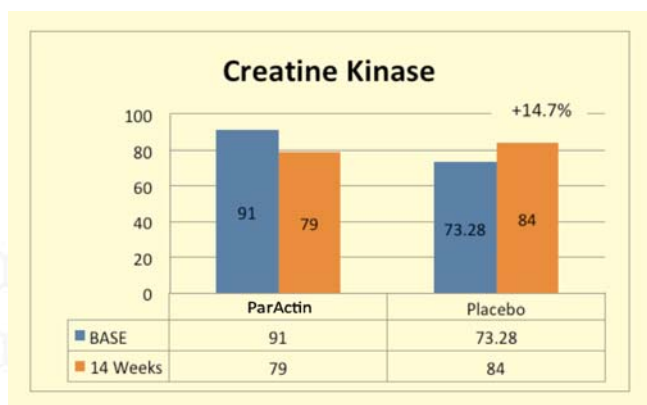
The beneficial effects of **ParActin**<sup>®</sup> in reducing the clinical symptoms of RA is tied to its ability to decrease rheumatoid factor (RF), creatine kinase, hemoglobin, IgA and IgM. MTX reduces rheumatoid factor, which is collated to the reduction of clinical symptoms of RA. The complementary therapy of **ParActin**<sup>®</sup> additionally reduced rheumatoid factor. The reduction of immunoglobulins, such as IgM and IgA, is also beneficial because of their correlation with cartilage damage.



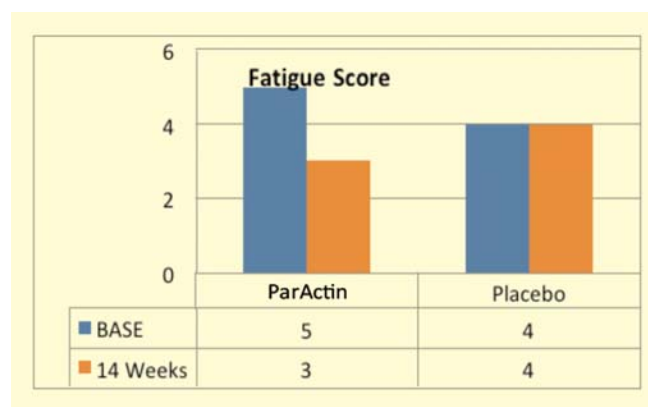
**ParActin**<sup>®</sup> significantly reduced pro-inflammatory C-reactive proteins by 55.7% compared to a 16.1% increase in the placebo group.



**ParActin**<sup>®</sup> significantly reduced creatine kinase by 13.3% compared to a 14.7% increase in the placebo group.



**ParActin**<sup>®</sup> significantly reduced the Fatigue Score compared to no changes in the placebo group.



The clinical efficacy of **ParActin**<sup>®</sup> could be explained by the anti-inflammatory properties of andrographolide, a potent inhibitor of NF- $\kappa$ B, which is linked to several pro-inflammatory proteins and cytokines such as COX-2, iNOS, and TNF- $\alpha$ , and IL-6. **ParActin**<sup>®</sup> may have an additional therapeutic effect over the drug prednisone and MTX in reducing pain, via inhibiting COX-2 and reducing PGE2 production.

The study concluded that **ParActin**<sup>®</sup> is significantly effective at reducing inflammatory symptoms and serological parameters and therefore is useful as a complementary natural treatment for rheumatoid arthritis.





In another human clinical trial published in *Innovative Rheumatology*, eight individuals with various arthritis conditions were given 300 mg of **ParActin**<sup>®</sup> daily for four years. Supplementation with **ParActin**<sup>®</sup> showed significant improvements in the number of swollen joints, total grade of swollen joints, total grade of tender joints and quality of life.

Also noted were significant reductions in RF, erythrocytes sedimentation rate and CRP. Furthermore, serum immunological parameters of inflammation were reduced progressively during 48 months of **ParActin**<sup>®</sup> supplementation.<sup>9</sup> (see Figure 5a)

**ParActin**<sup>®</sup> may also have additional therapeutic effects over prednisone and MTX in easing pain and fatigue. Research suggests that Andrographolide inhibits the COX-2 enzyme and reduces prostaglandin production tied to pain and inflammation. (see Figure 5b)

After 24 months of taking **ParActin**<sup>®</sup>, six individuals progressed to supplementing with **ParActin**<sup>®</sup> as their only therapeutic. No side effects were observed, indicating **ParActin**<sup>®</sup> was safe, nontoxic and well tolerated.

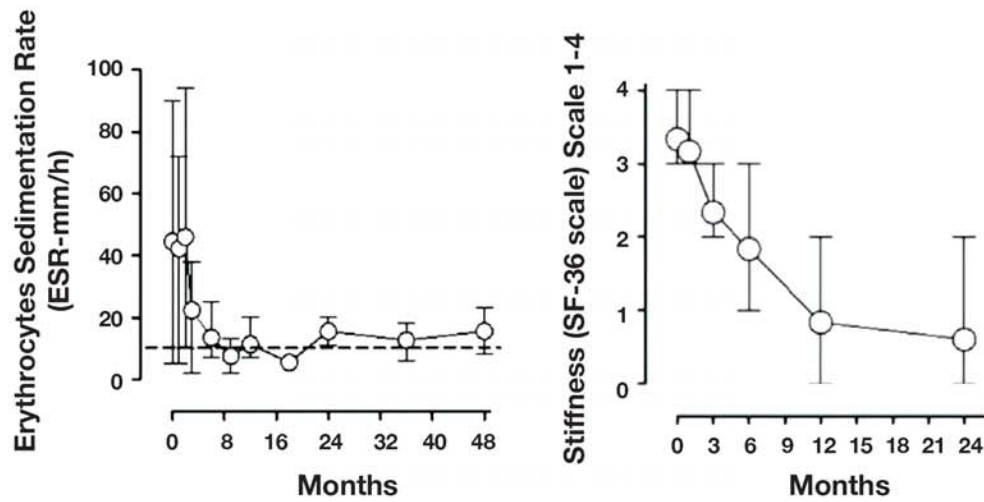
(see Figure 5c)



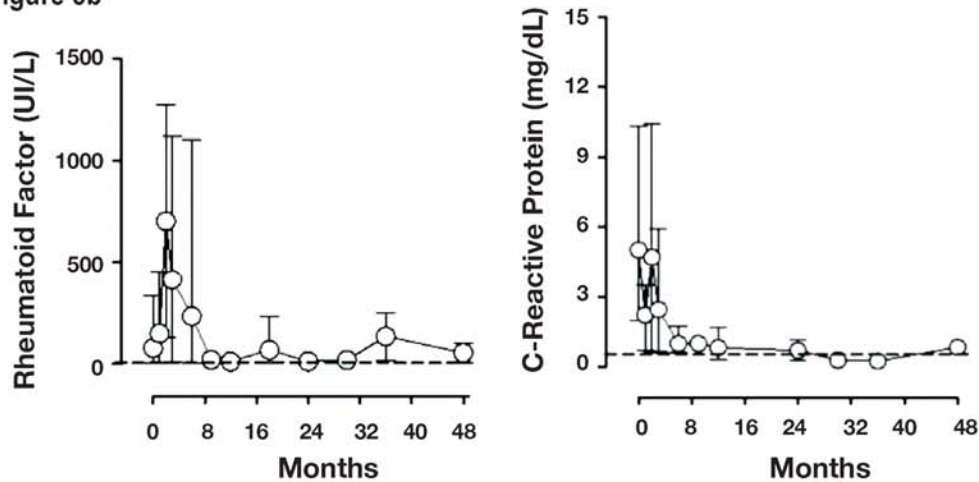


**Figure 5: Effect of ParActin® in Patients with Chronic Rheumatoid Arthritis.**  
Adapted from Hildalgo *et al.* (4).

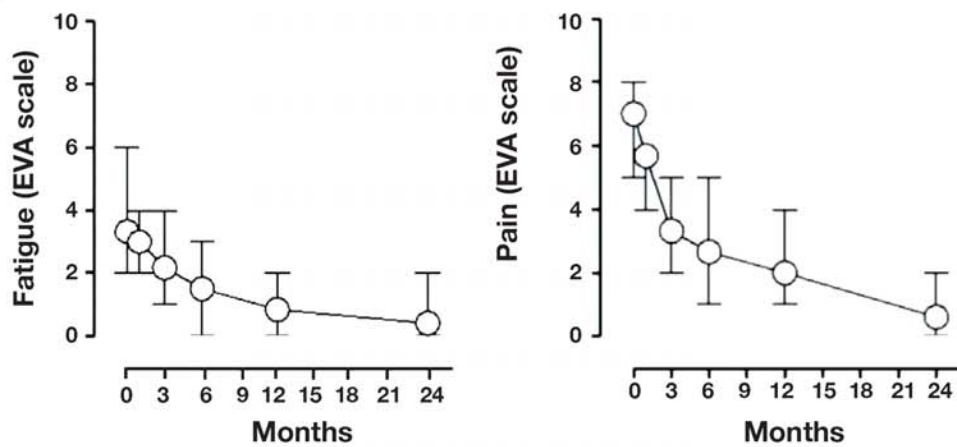
**Figure 5a**



**Figure 5b**



**Figure 5c**



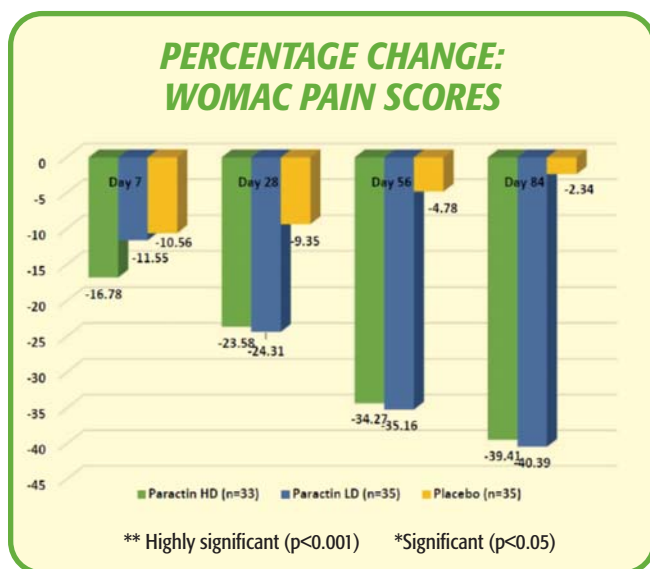


In a new double-blind, randomized, placebo-controlled study published in *Phytotherapy Research* May 2019, **ParActin**<sup>®</sup> was shown to provide benefits in individuals with knee joint discomfort.

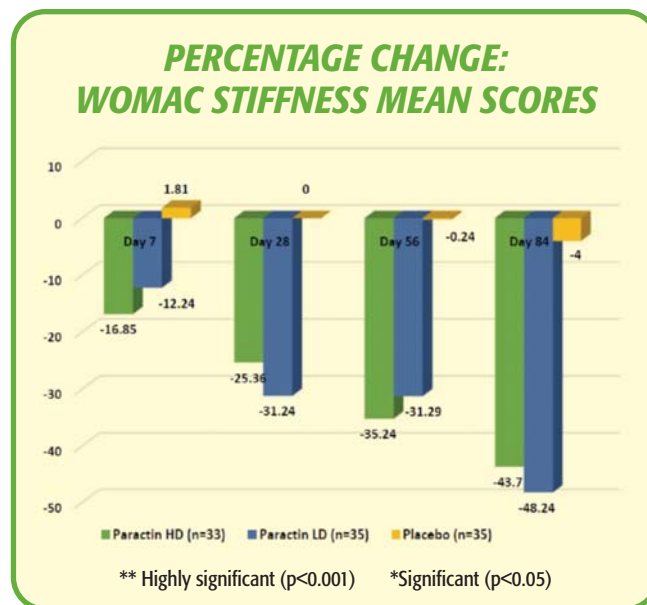
The 84-day study examined the efficacy of daily doses of 300mg (LD) and 600 mg (HD) **ParActin**<sup>®</sup> or placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores of pain reduction in 103 adults with mild to moderate knee osteoarthritis. Parameters tested were joint stiffness, changes in the SF-36 quality of life questionnaire, physical function and fatigue scale.

Among the study findings, the WOMAC pain scores showed a highly significant reduction in HD **ParActin**<sup>®</sup> and a significant reduction in both LD and placebo group at day 7.

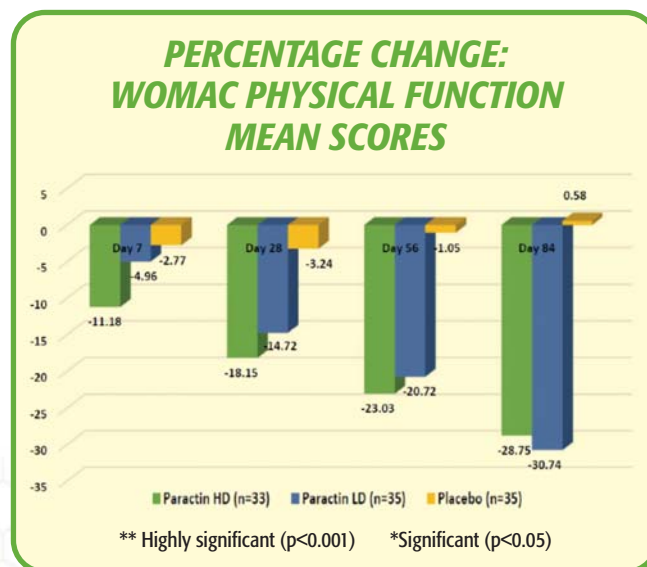
Beginning on day 28, the reduction in WOMAC pain scores become highly statistically significant in both **ParActin**<sup>®</sup> groups compared to placebo ( $p = 0.013$ ). The reduction in the placebo group reversed and showed an increase in score after day 7.



In the WOMAC stiffness score, both **ParActin**<sup>®</sup> group showed significant reduction starting day 7 and become highly statistically significant by day 28 in both groups. There was no improvement in this area in the placebo group.



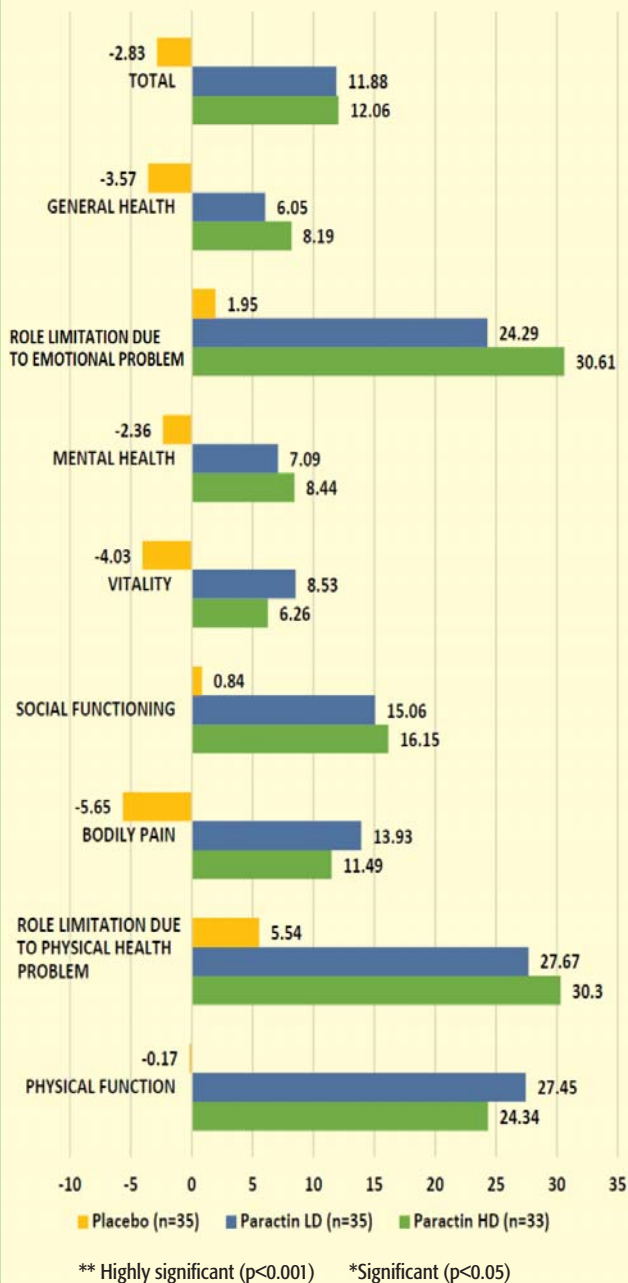
In the WOMAC physical function scores, all 3 groups showed significant improvement at day 7. Both **ParActin**<sup>®</sup> groups showed highly statistically significant improvement starting day 28 and continued to see improvement throughout the trial. The placebo group began to show a reversal trend on days 56 and 84.





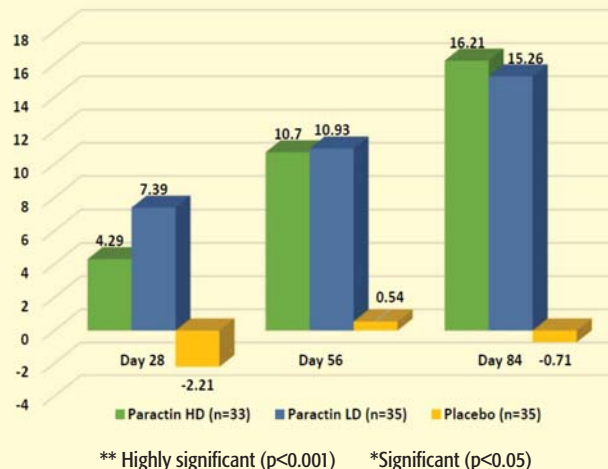
In the quality of life scores, from baseline to day 84, both **ParActin**<sup>®</sup> groups showed highly significant improvement in physical function score, Role Limitation due to Physical Health Problem Score, Role Limitation due to Emotional Health Problem Score, bodily pain score, and general health score. The total WOMAC score showed significant reduction in both **ParActin**<sup>®</sup> groups compared with the placebo.

### SF-36 MEAN PERCENTAGE CHANGE

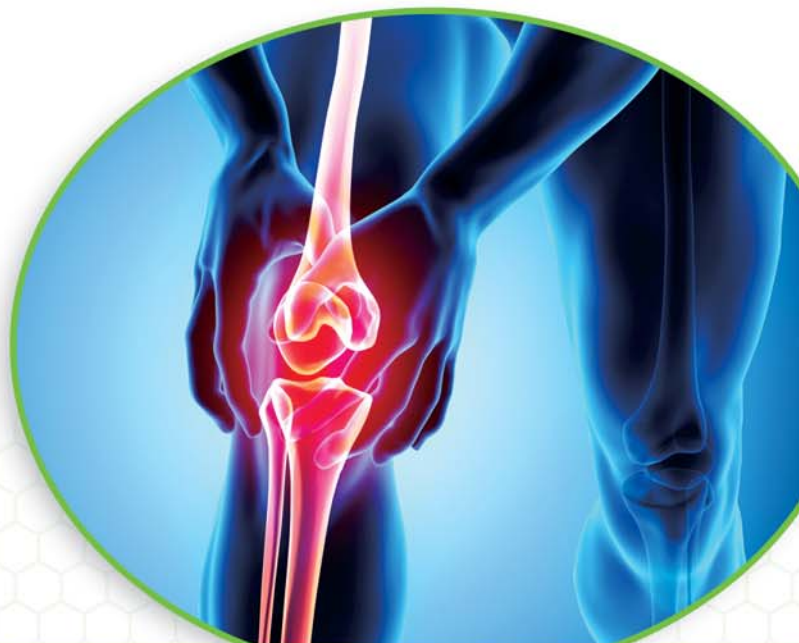


The FACIT–fatigue scale comprises 13 different factors and was used to record the level of fatigue experienced by the patients. The FACIT fatigue scores were statistically significant higher for both **ParActin**<sup>®</sup> groups compared with the placebo.

### PERCENTAGE CHANGE: FACIT FATIGUE MEAN SCORES



The researchers concluded, *“Overall, our study is the first clinical placebo-controlled trial that supports a potential use of **ParActin**<sup>®</sup> in knee OA patients. We propose that **ParActin**<sup>®</sup> can decrease the pain and discomfort of knee osteoarthritis and improve the patient’s general condition and quality of daily life, with no major adverse events.”*





## ParActin® ~ Healthy Bone Support

Fluid, comfortable movement isn't only the job of the joints. It requires bones strong enough to withstand bursts of physical activity or prolonged routine movement.

Healthy bones require two coordinated actions: bone formation (by osteoblasts) and bone reabsorption (by osteoclasts). In the process of bone formation, osteoblasts produce a calcium and phosphate-based mineral that is deposited into bones. Almost the entire bone matrix is mineralized by the osteoblasts. An osteoclast is a type of bone cell that resorbs or breaks down bone tissue. (see Figure 6)

However, this healthy balance of bone formation and bone resorption tends to decline with age, particularly in postmenopausal women. Osteoporosis is the most common bone disorder and is caused by excessive bone resorption by osteoclasts without adequate bone formation by osteoblasts. Increased bone resorption, among other actions, are predominantly caused by the decline of estrogen production in postmenopausal women, who tend to develop porous bones more often than aging men.

**ParActin®** has been shown to help support healthy bone function. In research published in the *International Journal of Molecular Sciences*, a group of mice whose skeletons mimic postmenopausal osteoarthritis were treated with andrographolide.<sup>11</sup> The use of these ovariectomized (OVX) animals is a typical experimental model for the investigation of postmenopausal osteoporosis due to estrogen deficiency in women. The **ParActin®** group showed a significant increase in bone mass, trabecular thickness and number, and a decrease in trabecular separation compared to control mice. (see Figure 7)

NF-κB activation is essential for RANKL (receptor activator of NF-κB ligand)-induced osteoclast formation. Andrographolide found in **ParActin®** – a natural NF-κB inhibitor -- significantly decreased osteoclast formation in the bone marrow by suppressing RANKL, which are responsible for making osteoclasts. (see Figure 8)

The authors concluded that Andrographolide inhibits estrogen deficiency-induced bone loss in mice and may have supplemental potential for osteoarthritis.

In an *in vitro* study published in the *European Journal of Pharmacology*, andrographolide from **ParActin®** inhibited nuclear factors of activated T-cells (NFAT) activity, which regulates the expression of osteoclast genes and is linked to bone erosion.<sup>12</sup> In another unpublished study, Andrographolide induced osteoblast mineralization via COX-2 expression, showing a mineralizing effect on the bones with the increase of calcium deposits, thereby suggesting that **ParActin®** may have other supplemental effects for osteoarthritis. (see Figure 9)





Figure 6: Osteoclast and Osteoblast

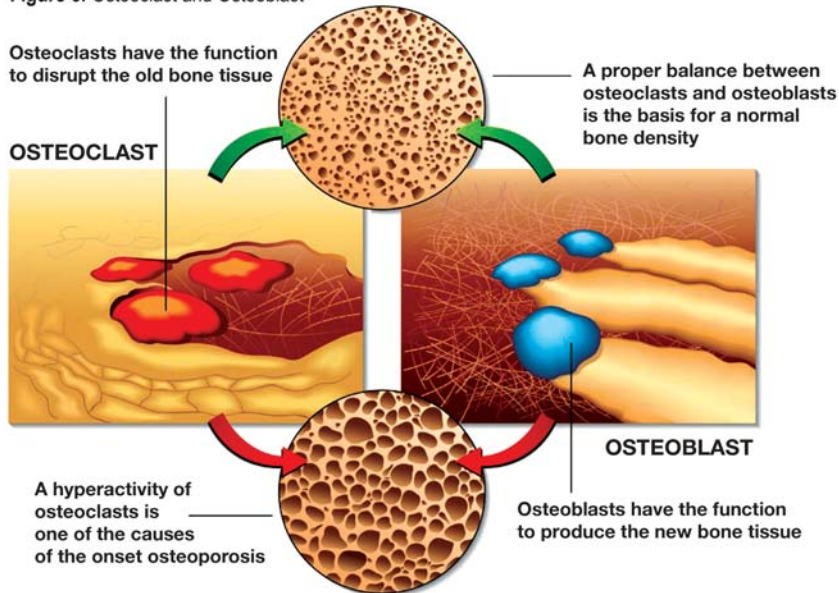


Figure 7: Micro-CT Scanned 3D Image of Mice Tibias Showing that Andrographolide Inhibits OVX-induced Bone Loss Compared to Vehicle. Adapted from T. Wang *et al.* (5).

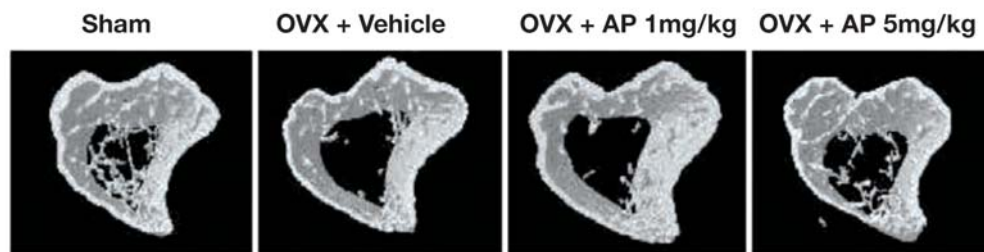


Figure 8: Effect of Andrographolide on Osteoclasts. Adapted from T. Wang *et al.* (5).

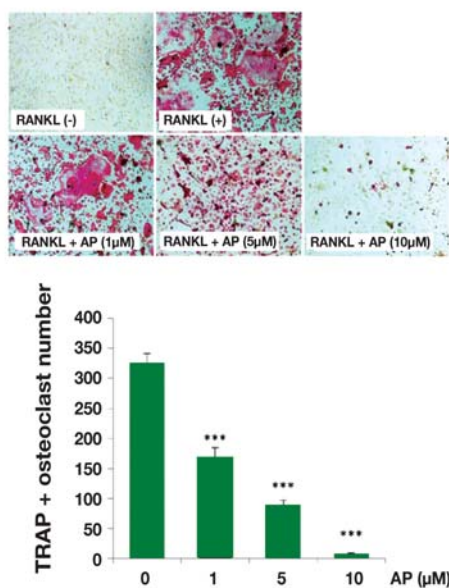
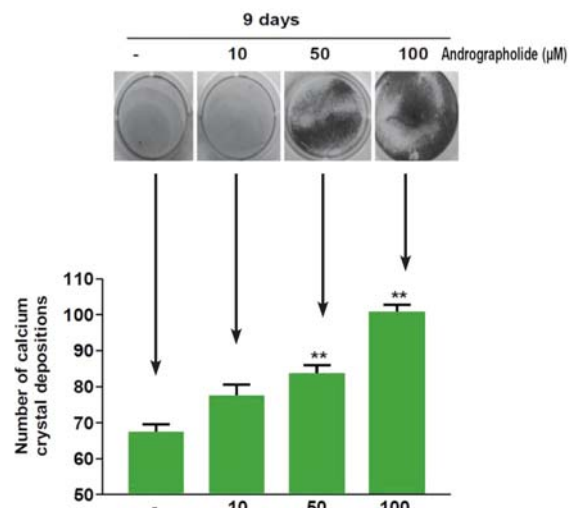


Figure 9: Effect of Andrographolide on Calcium Deposits. Adapted from M.D. Carretta *et al.* (6).





## ParActin® ~ Healthy Cartilage Support

Osteoarthritis is characterized by progressive and permanent cartilage degradation. Cartilage erosion can cause inflammation and pain, decreased mobility and reduced athletic performance. (see Figure 10)

This degradation is caused by interleukin-1 $\beta$  (IL-1 $\beta$ ) cytokines, which trigger the over-production of cartilage-degrading enzymes called matrix metalloproteinases (MMPs) in the synovial cells and the chondrocytes. This leads to a progressive loss of the cartilage matrix, which is composed of biochemicals aggrecan, hyaluronan (HA) and collagen.

Recent research has shown that Andrographolide inhibits MMPs in IL-1 $\beta$ -treated human chondrocytes while increasing the natural inhibitors of these enzymes via the NF- $\kappa$ B pathway. A study published in *International Scholarly Research Notices* found that andrographolide suppressed MMPs that were induced by IL-1 $\beta$  in equine cartilage.<sup>13</sup>

Andrographolide further slows cartilage degradation by dramatically reducing the loss of collagen, uronic acid, HA and sulfated-glycosaminoglycans (s-GAGs) caused by IL-1 $\beta$ , a key inducer of cartilage degeneration. The research not only demonstrated the potent cartilage-protecting activities of andrographolide, but also showed the ability of andrographolide to increase the production of cartilage biomolecules including collagen, aggrecan and HA. (see Figure 11)

In RA, aggressive fibroblast-like synoviocytes (FLSs) are found in the synovial tissues. These FLSs invade and destroy joints and cartilage by actively releasing pro-inflammatory cytokines. They also produce massive amounts of cartilage-degrading enzymes, especially matrix MMPs, which contribute to the invasive growth of FLSs and subsequent joint destruction.

Researchers at the La Jolla Institute for Allergy and Immunology, in collaboration with colleagues from the University of California, San Diego (UCSD), identified FLSs as the target of a potential new RA drug that focuses on

cells responsible for the cartilage damage in affected joints. Current RA treatments focus on intercepting the immune system's misdirected attack on the lining of affected joints to alleviate the debilitating symptoms, reduce inflammation and slow the progression of the disease.

"Unfortunately, for around 40% of patients, immune-targeted therapies are not sufficient to bring them into full remission," says the study's lead author, Nunzio Bottini, M.D., Ph.D., associate professor at La Jolla Institute and associate professor of medicine at UCSD. "Even if your inflammation is completely under control with the help of current therapies – and they are excellent – the damage to the skeletal structure is not necessarily arrested in the long term because synoviocytes continue to cause damage," he explains.

FLSs secrete proteases that digest cartilage, and they also promote osteoclasts differentiation, which in turn attack the bone and generate erosions. Blocking the action of these synovial fibroblasts will directly protect joints from cartilage destruction.<sup>14</sup>

In a study published in *Cell Biology Toxicology*, synovial tissues were collected from 15 RA patients who had undergone a total knee replacement therapy; the cells were treated with Andrographolide for 48 hours.<sup>15</sup> The study found that andrographolide induced cell death in these human RA-FLSs (rheumatoid arthritis fibroblast-like synoviocytes) via cytochrome-C release and caspase-3 activation. ***The author suggests that andrographolide could be a potential therapeutic in supporting against joint destruction in both osteoarthritis and RA.***

A condition called synovial hypoxia frequently occurs in patients with RA, contributing to tendon rupture and perpetual joint destruction. Fifty percent of RA patients also experience inflammation of the synovial tissue surrounding the tendons, which is associated with multiple ruptures and a poor prognosis for long-term joint function.

RA patients often have high levels hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), a chemical linked to inflammation in the synovial tissues.

In a study published in *Life Sciences*, synovial tissue was obtained from 50 RA patients during a knee joint arthroscopy.<sup>16</sup> The researchers found that Andrographolide significantly decreased the cartilage-degrading

enzymes MMPs, induced by hypoxia. Andrographolide inhibited the migration, prevented the invasion of RA-FLS and increase of MMPs in RA-FLSs via the inhibition of HIF-1 $\alpha$  signaling. Hypoxia causes RA-FLS migration and invasion. Andrographolide inhibited hypoxia-induced migration and RA-FLS invasion, thus suggesting the potential for Andrographolide in benefiting those with joint degeneration.

Figure 10: Joint Anatomy and Cartilage Degradation

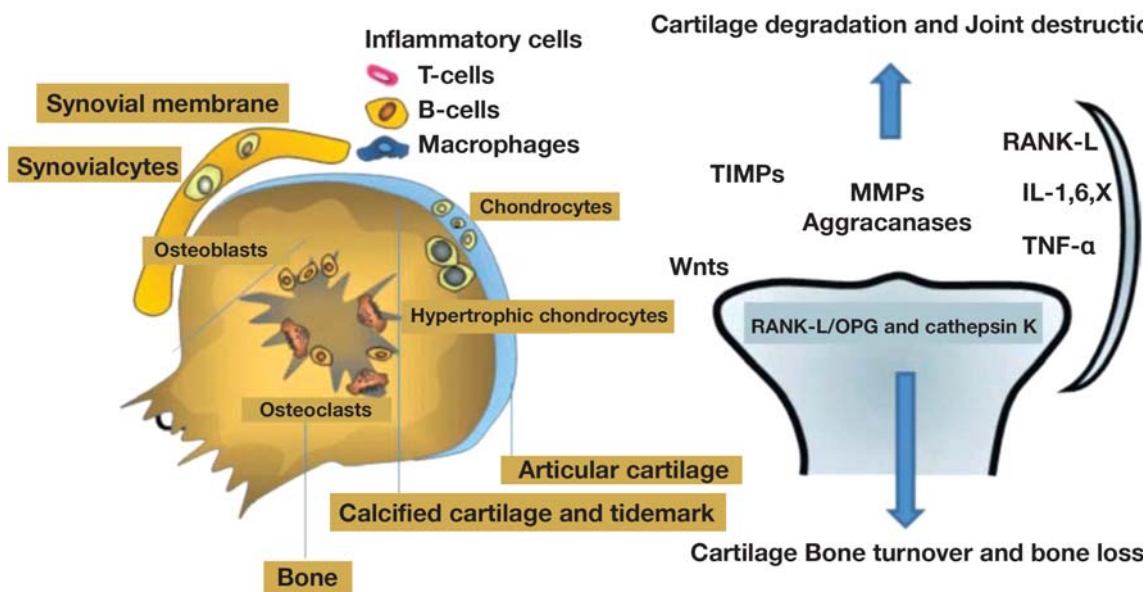
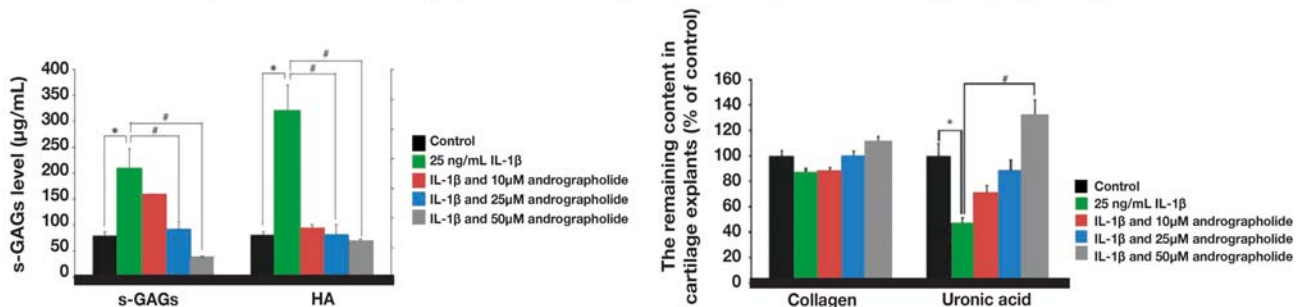


Figure 11: Effect of Andrographolide on Cartilage Explants. Adapted from S. Tangyuenyong et al. (7)





# ParActin® ~ Strengthens Muscular Health

Just like other bodily tissues muscles are susceptible to damage. Trauma, infections, certain medications or strenuous exercise can cause varying degrees of muscle injury. As the saying goes, “No pain, no gain.” But if you’re over the age of 40, no pain is a good thing. If you find yourself in the discomfort zone, your body may be trying to tell you something.

By the age of 40, the body has endured years of wear and tear, and is more susceptible to injury caused by repetitive stress. While you may feel strong and ready to take on any physical activity, your bones, muscles and joints could be more delicate than you realize. As we age, our musculoskeletal system (i.e., bones, joints, tendons, ligaments and muscles) changes by gradually losing muscle mass, connective tissues (i.e., tendons, ligaments, cartilage and other support structures), flexibility and the resilience that was present at a younger age.

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) mediated by ROS has been associated with muscle wasting and weakness. NF- $\kappa$ B is a key regulator of muscle atrophy and its inhibition prevents the loss of skeletal muscle mass in response to various catabolic stimuli including TNF- $\alpha$ . Oxidative stress plays an important role in the loss of skeletal muscle mass and function. Therefore,

increased antioxidant expression could be a protective measure against oxidative stress and skeletal muscle atrophy.

In a mouse study published in *Journal of Applied Physiology*, the lack of Nrf2 resulted in 68% increase in reactive oxygen species (ROS), 48% greater rate of fatigue and 35% reduction in force. Research showed that regular moderate exercise help prevents oxidative stress-induced muscle wasting via the increase in Nrf2 activation, which resulted in increases in antioxidants and enhanced muscle contractile activity.

Previous research had shown that **ParActin®** is an effective NF- $\kappa$ B inhibitor and an Nrf2 activator, and may have benefits in preventing oxidative stress-induced muscle wasting. In a pivotal study published in *Skeletal Muscle*, mdx mice (i.e., mice studied for muscle degeneration and regeneration) were given **ParActin®** or placebo for three months.<sup>17</sup> **ParActin®** was shown to significantly reduce the activity of NF- $\kappa$ B in skeletal muscle in the treated group, thereby promoting muscle health and recovery, making it ideal for those engaged in regular fitness routines, hard labor or athletic participation. Four significant positive effects were observed in this study, as follows:

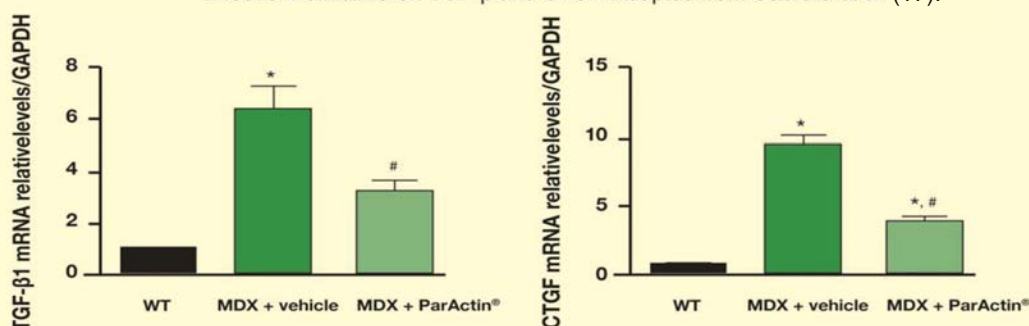
## 1: ParActin® Reduced Fibrosis & Pro-Fibrotic Factor

Transforming growth factor type beta (TGF- $\beta$ 1) has been shown to inhibit skeletal muscle regenerative processes and induce muscle fibrosis (scarred tissues). Fibrosis is the result that begins with tissue injury and inflammation. When tissue is damaged, profibrotic cytokines such as TGF- $\beta$  are released, which signals connective tissue (fibronectin, type-I and type-III collagen) to commence wound repair. While this fibrotic tissue provides early support for damaged skeletal muscle, skeletal muscle fibrosis impairs muscle function, negatively affects muscle regeneration after injury and increases muscle

susceptibility to re-injury; therefore, it is considered a major cause of muscle weakness, stiffness, abnormal joint function, and nerve pain. Recurring injury and loss of muscle strength after muscle injuries has been attributed to TGF- $\beta$ 1-induced fibrosis within the muscle.

The administration of **ParActin®** significantly decreased TGF- $\beta$ 1 and CTGF, two pro-fibrotic factors that contribute to fibrosis. As a result, fibronectin, collagen I and collagen III levels were reduced, thereby confirming **ParActin's®** ability to improve muscle function recovery.

Effect of ParActin® on TGF- $\beta$  and CTGF. Adapted from Cabrera *et al.* (17).



## 2: **ParActin®** Reduced Muscle Damage

Strenuous exercise and overtraining can lead to structural damage to muscle cells, triggering white blood cell activity to increase after muscle soreness, thus leading to the inflammatory response. Muscle fiber necrosis has been noted especially in marathon runners whose muscle fibers revealed remarkable damage (usually associated with break in, or absence of, muscle surface fiber membrane) and resulting in irreversible damage to muscle fibers.

In the mdx mouse study, the administration of **ParActin®** significantly reduced muscle fiber necrosis and cumulative muscle damage compared with control mdx mice.

The *Tibialis anterior* muscles in the andrographolide-treated mdx mice showed a striking reduction in the damaged areas of muscle, and a more complete and healthy muscle fiber membrane structure compared with untreated mdx mice.

**Table 1 Cumulative muscle damage in exercised mdx mice treated or not with andrographolide**

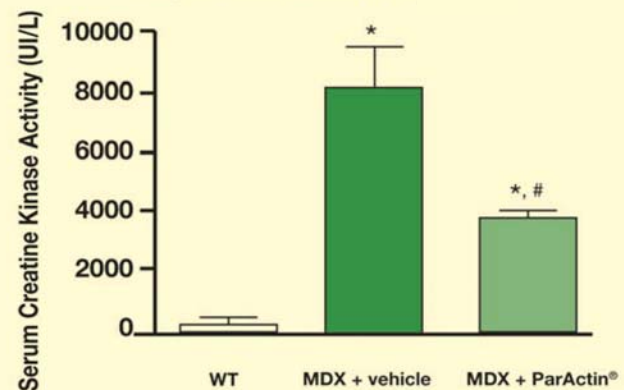
	Necrosis	Regeneration	Cumulative damage
mdx + vehicle	7.63 ± 0.85	42.14 ± 4.03	49.77 ± 4.61
mdx + andrographolide	4.14 ± 0.51 <sup>b</sup>	30.23 ± 2.86 <sup>a</sup>	34.37 ± 2.97 <sup>a</sup>

## 3: **ParActin®** Lowered Serum Creatine Kinase

Creatine kinase (CK) is a type of enzyme found within muscles, including the heart and brain. Serum CK indicates the overall health of the muscles within the body and a serum CK test showing elevated levels indicates muscle strain that may have been caused by simply heavy exercise, muscle inflammation and other skeletal muscle damage.

Serum CK levels were significantly lowered in the **ParActin®** – treated mdx mice suggesting less muscle damage during exercise.

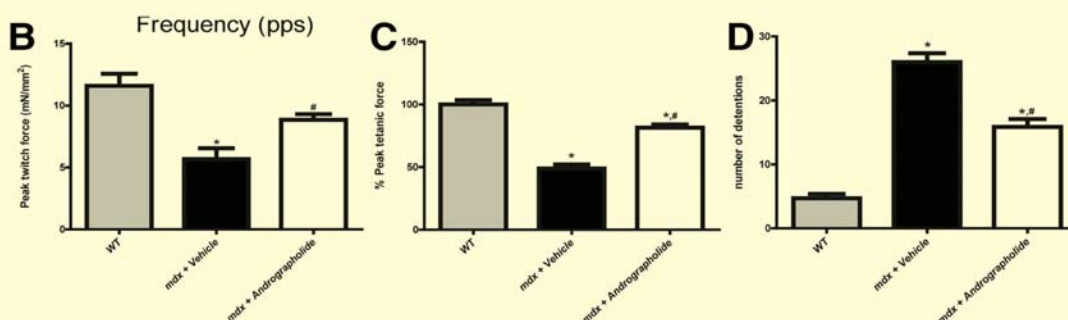
Effect of Andrographolide on Creatine Kinase.  
Adapted from Cabrera *et al.* (17).



## 4: **ParActin®** Improved Skeletal Muscle Strength And Exercise Performance

**ParActin®** administrated mdx mice showed a significant increase in the generation of isometric force, an increase

twitch force by 54.2% and increase in tetanic force by 50.3% in the *Tibialis anterior* muscle (in front of the shin); and a significant decrease in the number of fall back in the treadmill running protocol, with a recovery score of 45.5%.





**ParActin®** reduced fibrosis and pro-fibrotic factor. Transforming growth factor type beta (TGF-β1) and connective tissue growth factor (CTGF) have been shown to inhibit skeletal muscle regenerative processes. They replace scarred connective tissue that is composed of fibronectin, as well as type-I and type-III collagen.

While this fibrotic tissue provides early support for damaged skeletal muscle, these new fibers do not arrange in the same direction the original fibers were oriented. This results in scarring (fibrosis) in the injured muscle that often causes stiffness, abnormal joint function, nerve pain and restricts the regenerative process. Recurring injury and loss of muscle strength after muscle injuries may be attributable to TGF-β1–induced fibrosis within the muscle.

**ParActin®** administration significantly decreased fibronectin, collagen I and collagen III levels in the mdx mice. In addition, the **ParActin®** treatment group saw reduced TGF-β1 and CTGF, two pro-fibrotic factors that contribute to fibrosis and prevent proper muscle regeneration process. By blocking

TGF-β1 and thus reducing scar tissue, **ParActin®** can facilitate improved muscle function recovery. (see Figure 14)

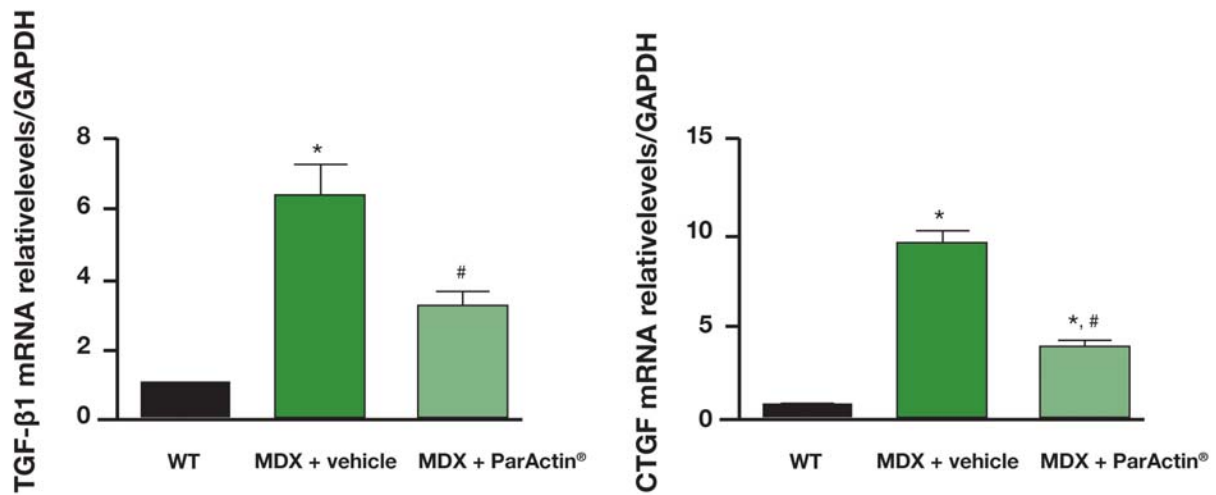
**ParActin®** reduced muscle damage and lowered serum creatine kinase. Strenuous exercise and overtraining can lead to structural damage to muscle cells, triggering white blood cell activity to increase after muscle soreness, thus leading to the inflammatory response. This has been noted especially in marathon runners whose muscle fibers revealed remarkable damage after both training and marathon competition.

The muscle damage causes calcium to leak out of the muscle, further leading to the activation of enzymes that break down cellular proteins in the muscle. These proteins then cause an inflammatory response by the immune system, which then leads to swelling (water retention at the site of injury) and pain.

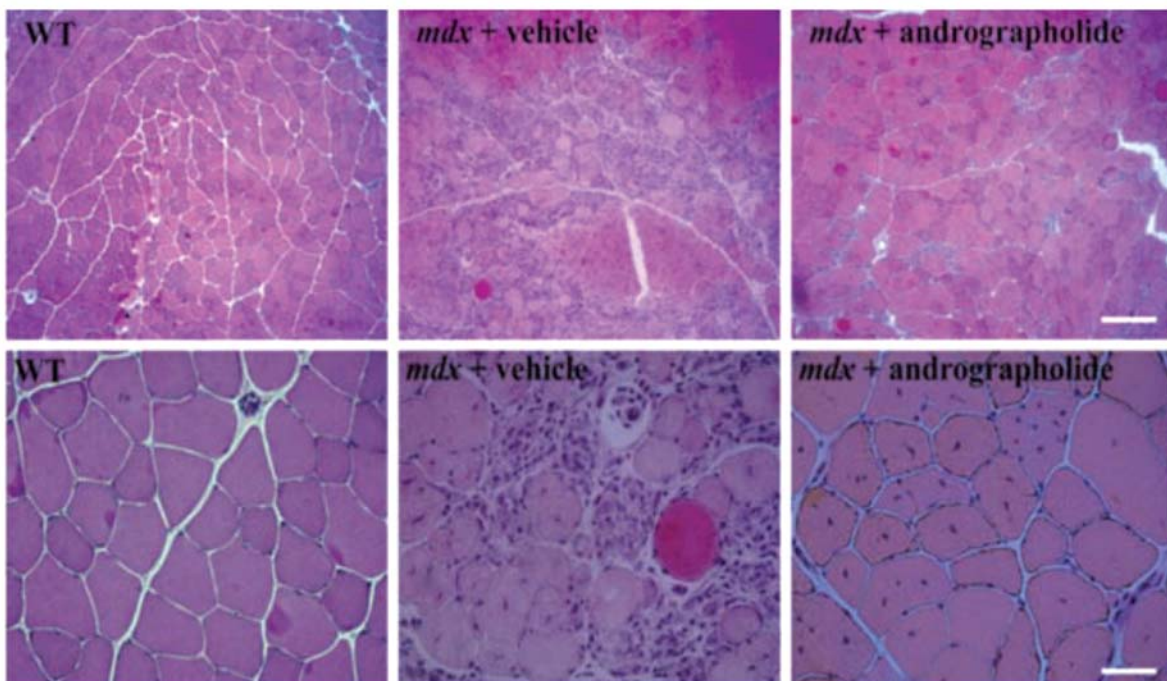
In the mdx mouse study, the administration of **ParActin®** reduced necrosis and cumulative muscle damage compared with control mdx mice. (see Figure 15)



**Figure 14:** Effect of ParActin® on TGF- $\beta$  and CTGF. Adapted from Cabrera *et al.* (17).



**Figure 15:** Effect of Andrographolide on Muscles. Adapted from Cabrera *et al.* (17).





Creatine kinase (CK) is a type of enzyme found within your muscles, including the heart and brain. Serum CK indicates the overall health of the muscles within the body and if a serum CK test shows elevated levels, it indicates muscle strain that may have been caused by simply heavy exercise or something as serious as a heart attack.

Muscle inflammation and other skeletal muscle damage are associated with an elevated CK level. Depending upon muscle damage severity, some may have CK levels that are as much as 100 times normal levels. Serum CK levels were significantly decreased in **ParActin**<sup>®</sup>-treated mdx mice compared with control mdx mice, with an approximately 50% recovery score. (see Figure 16)

**ParActin**<sup>®</sup> improved skeletal muscle strength and exercise performance. **ParActin**<sup>®</sup>-administrated mdx mice showed improved skeletal muscle strength and enhanced exercise performance. **ParActin**<sup>®</sup>-administrated mdx mice showed a significant increase in the generation of isometric force (see Figure 17); an increase twitch and tetanic force in the *Tibialis anterior* (TA) muscle (in front of the

shin); and a significant decrease in the number of fall back in the treadmill running protocol, with a recovery score of 45.5%. (see Figure 18)

The author concludes that the supplement group exhibited less severe muscular dystrophy, performed better in an exercise endurance test and had improved muscle strength compared to control mdx mice.

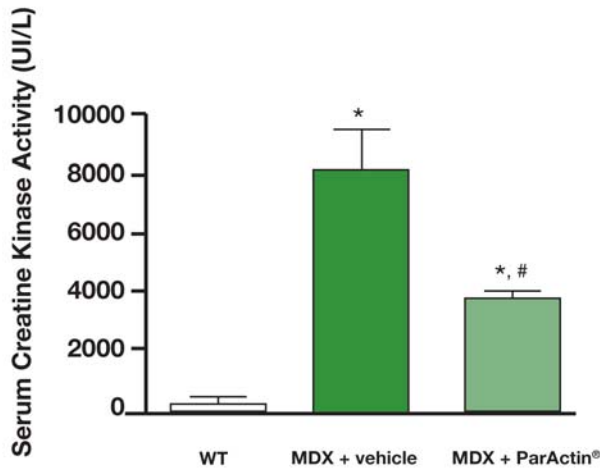
As you can see, mobility, movement and exercise can be bolstered by improved bone, joint and muscle status. And these improvements can lead to overall better health, lowered weight – and bolstered immunity.

Researchers in one study asserted, “Moderate physical activity or moderate-regulated training may enhance the immune function mainly in less fit subjects or sedentary population.”<sup>18</sup>

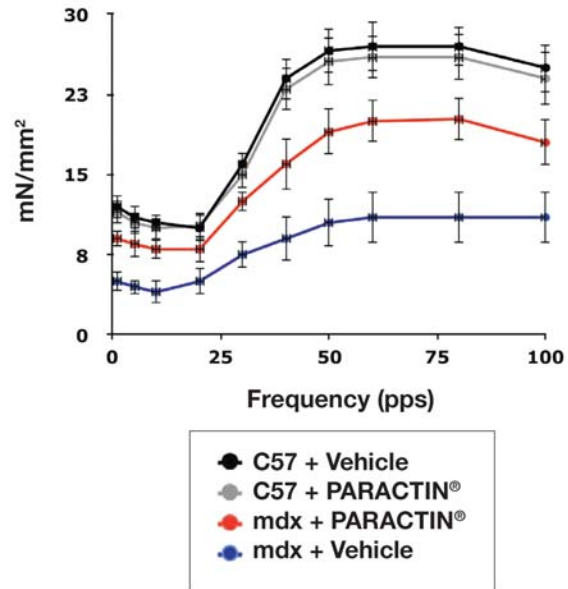
And **ParActin**<sup>®</sup>, unlike curcumin, also has a direct effect on immune function, giving it yet another source of strength to be the top contender.



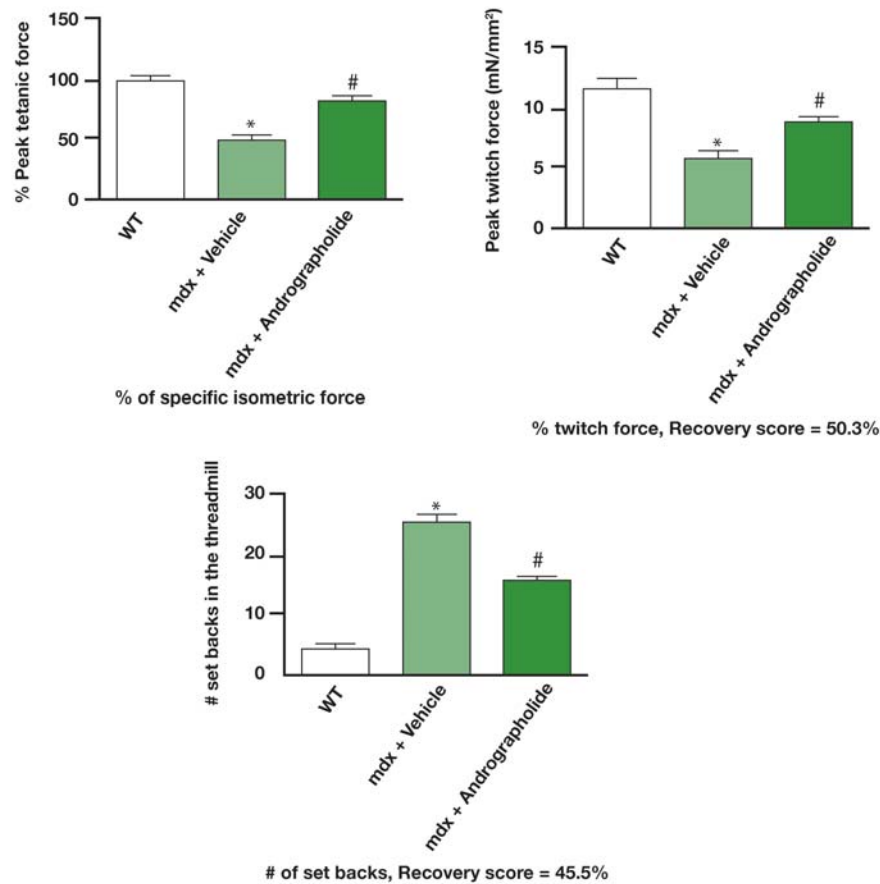
**Figure 16:** Effect of Andrographolide on Creatine Kinase. Adapted from Cabrera *et al.* (17).



**Figure 17:** Effect of ParActin® on Muscles. Adapted from Cabrera *et al.* (17).



**Figure 18:** ParActin® Improves Functional Capacity. Adapted from Cabrera *et al.* (17).





## **ParActin® ~ Superior Immune Support**

Another related way in which **ParActin®** vanquishes its competition is through its clinically shown ability to promote desirable immune function.

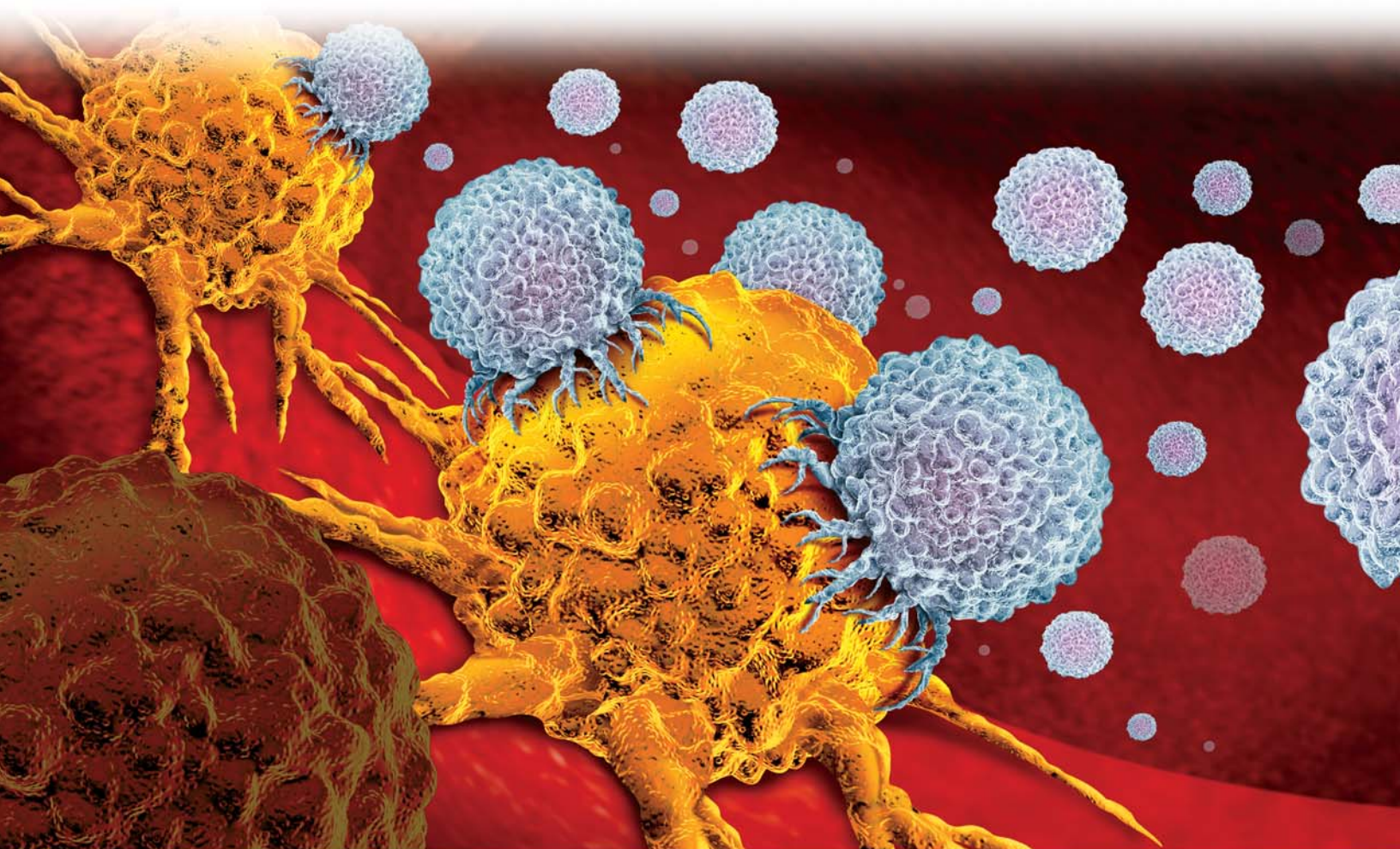
Stressors – environmental, mental/emotional and physical – all conspire to hamper the immune system's effective functioning, creating an imbalance that may result in colds, flu and exacerbated allergies. Cold and flu can reach epidemic proportions during the winter months. There are more than 95 million flu cases in the United States annually, according to the Centers for Disease Control and Prevention, and more than 62 million cases of the common cold.

When the immune system is balanced and healthy, it launches a series of events to engage in battle with an invading virus. Interferon gamma plays an important role in the first line of defense against viral infections; they are part of the non-specific immune system and are induced at

an early stage in viral infections such as in influenza—before the specific immune system has had time to respond. Interferon-gamma is produced by certain activated T-cells and NK cells and is made in response to viral antigens or when stimulated by lymphocytes. Interferons are responsible for reacting to conditions like colds, fever, shivers, migraines and gastrointestinal disorders. Interferon gamma interacts with other interleukin molecules such as interleukin-2 and others to form a complex, lymphokine regulatory network.

Think of it this way, when your immune system is unbalanced, it's like being a ship that's listing to one side or stuck in the doldrums. **ParActin®** can help right the ship and move it forward for smooth sailing.

In a randomized, double-blind placebo-controlled study, 109 healthy students were given either 25 mg per day of





**ParActin**<sup>®</sup> or placebo for three months.<sup>19</sup> During the first month, there was no significant change between the groups, evaluated for the presence or absence of common colds. However, during months two and three, there was significantly less incidence of common cold in the **ParActin**<sup>®</sup> group (30%) compared to the placebo group (62%).

In another randomized, double-blind placebo-controlled study of 158 adults already with common cold symptoms, 200 mg of **ParActin**<sup>®</sup> per day for five days were shown to significantly decrease the intensity of symptoms compared to the placebo group.<sup>20</sup>

According to Dr. Hancke, HPI's Chief Scientific Officer, at a low dosage (50 mg), **ParActin**<sup>®</sup> stimulates natural defense mechanisms by activating NF-kB, thereby increases the production of cytokines such as interferon gamma and interleukin-2 to help boost the immune response in winter. Once an individual begins to feel under the

weather, 300 mg of **ParActin**<sup>®</sup> inhibits NF-kB, thereby reducing the production of pro-inflammatory cytokines such as interferon gamma and interleukin-2 to help produce a better sense of wellness. The immune and inflammation balancing properties of **ParActin**<sup>®</sup> may assist the body to help fight a viral antigen while reducing the overload of cytokines.<sup>21</sup>

Further, **ParActin**<sup>®</sup> protects immune function via its adaptogenic abilities. The aim of one study was to pharmacologically evaluate the beneficial effect of andrographolide on stress-induced thermoregulatory and other physiological responses in mice for 11 consecutive days. Observations revealed that, like *A. paniculata* extracts, pure andrographolide also possess adaptogenic properties. The study authors also noted that their observations showed that andrographolide is functionally a diazepam-like desensitizer of biological mechanisms, and processes involved in stress trigger thermoregulatory and other physiological responses.<sup>22</sup>

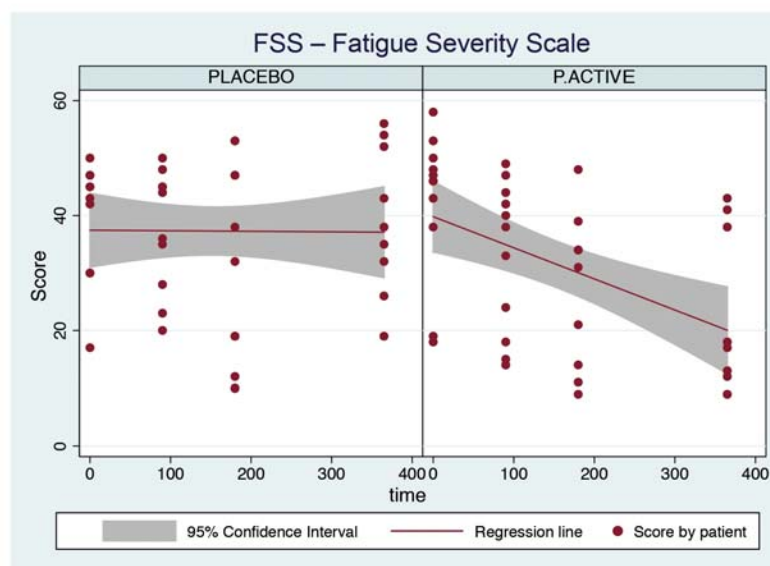




## ParActin® ~ Reduces Fatigue – Increases Serotonin

Multiple sclerosis (MS) is considered one of the most common non-traumatic causes of disability in the world. Muscle spasms, sensory and motor complications, cognitive disorders, anxiety, depression, and fatigue are common symptoms of MS. Fatigue is one of the most common symptoms of MS patients and it substantially decreases the quality of life. Research had shown that patients with MS have significantly lower serotonin content compared to healthy individuals (206 ng/109 vs. normal range of 600-700 ng/109) in a soon to be published study.

In a randomized, double-blind, placebo-controlled trial published in *BMC Neurology*, 22 patients with relapsing-remitting multiple sclerosis (RRMS) were enrolled in a 12-month study. Researchers saw that those in the andrographis group showed a significant reduction in their FSS (Fatigue Severity Scale) score compared to the placebo group, equivalent to a 44% reduction at 12 months.



FSS	T=0	T=12	% Change
Active Mean (n=11)	39.0	20.6	-47%
Placebo Mean (n=10)	34.2	33.2	-2.92%
P-Value	0.2908	0.0141	

No statistically significant differences were observed for relapse rate, EDSS (Expanded Disability Status Scale) or inflammatory parameters, however, there is a trend in reducing new lesions among the andrographis group.

### # of Patients with new T2 at the end of study

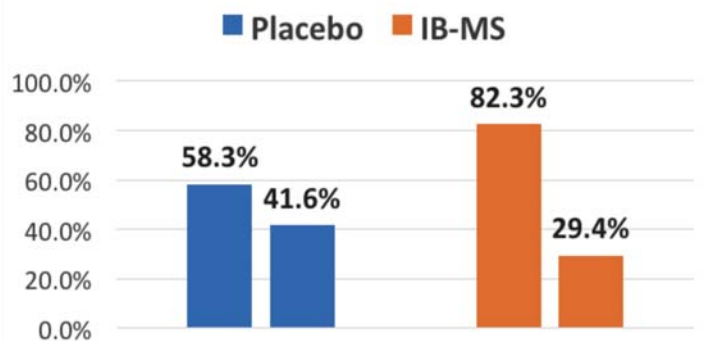
IB-MS (n=5)	0	0%
Placebo (n=8)	4	50%

### # of Patients with new Gadolinium at the end of study

IB-MS (n=5)	0	0.00%
Placebo (n=8)	5	62.5%

A new, soon to be published, 24-month study on progressive MS also shows benefit from consuming andrographis compared to placebo. Disability progression was significantly halted in the andrographolide group – 82.3% of the patients were disabled in the beginning of the study, and after 24 months only 29.4% of the patients were worsening compared to 41.6% in the placebo group.

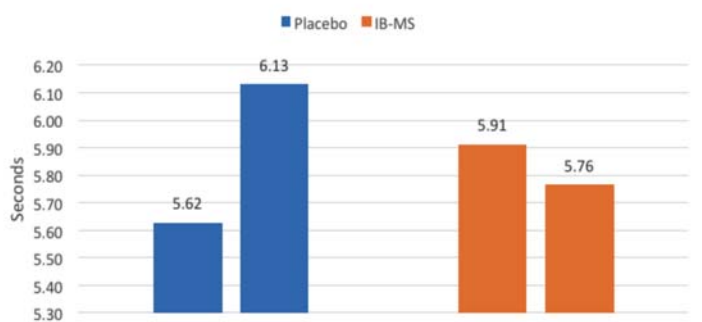
## Disability Progression



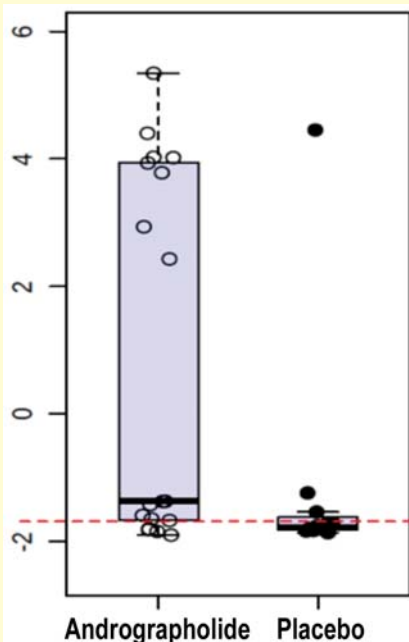
	Placebo=12	IB-MS=17
Disability Progression at T=0 Stable/Progressing	41.7%/58.3%	17.6%/82.3%
Disability Progression at T=24 Stable/Progressing	58.3%/41.6%	70.6%/29.4%

This is accompanied by reduction in EDSS score (disability improved) for the andrographolide group vs the increase in score in the placebo group (disability worsen).

## EDSS (Mean)



EDSS Score	T=0	T=24
IB-MS	5.91	5.76
Placebo	5.63	6.13



Additionally, the fatigue score in the andrographolide group was significantly reduced. This is confirmed by the significant increase in serotonin levels. When healthy levels of serotonin are sustained, participants feel better, and this is why all the quality of life health questionnaire scores showed significant improvement.



## **ParActin® ~ GRAS**

After an exhaustive review of scientific literature, it was deemed obvious that the herb *Andrographis paniculata* and its extracts, **ParActin®** specifically, including isolated andrographolide, prepared for human consumption are very safe for use.

*Andrographis* is always noted as a safe remedy in the texts that go back more than a thousand years. As with nearly anything humans consume, there are some individuals

who will experience an unwanted reaction. Warning labels on foods alert the consumer to peanuts, shellfish, soy, corn, wheat, etc. Compared to these common foods, *andrographis* and extracts like **ParActin®** are far safer by orders of magnitude. Another very important reason that *andrographis* products, and specifically, andrographolide, the main constituent of interest, are very safe for human use is the fact that purified andrographolide is available as an injection product. This speaks for itself.

## **ParActin® ~ Clean, Sustainable Features**

We know that consumers are ever-more conscious about clean labels, purity, simplicity, authenticity and sustainability. They care that what they put into their bodies and what they provide their loved ones does no harm.

**ParActin®** fulfills these high demands.

As a botanical, **ParActin®** has nothing undesirable in it that typically comes from bovine or other animal sources (eggshells and seafood shells). As more and more Americans are discovering they have food sensitivities and/or allergies, **ParActin®** is a clean ingredient. It is also non-GMO, cultivated without pesticides (wild-crafted) and also available in an organic version.

**ParActin®** is attractive for any consumer from vegans to omnivores; there is no limit to potential consumers.

**ParActin®** is:

- **BSE-Free (non-bovine)**
- **Shellfish-free**
- **Eggshell-free**
- **Non-GMO**
- **Vegan**
- **Wild-crafted**
- **Non-irradiated, TSE-free**
- **Certified Kosher and Halal**
- **Available in organic and conventional**
- **GRAS**

## **ParActin® ~ Summation**

***In the battle for inflammatory-regulation supremacy, it is clear that ParActin® can beat curcumin. It costs less. It doesn't have to be processed further for bioavailability.***

***And it does so much more for human health.***



# FAQs About ParActin®

## What claims can be made for ParActin®?

Multiple human clinical studies allow for the following claims:\*

- **Supports Healthy Inflammatory Response**
- **Supports Healthy Joint Function**
- **Strengthens Joints and Eases Joint Flare-ups**
- **Improves Flexibility and Mobility**
- **Maintains Bone Mass and Strength**
- **Supports Muscle Health**
- **Supports Healthy Immune Response**
- **Supports Healthy Cartilage**

## What are the dosage amounts for ParActin®?

Typical dosage recommendations, based on traditional use and on the available scientific evidence in humans, are 300 mg daily, which may be taken in 150 mg doses twice daily. Those seeking optimum support may take as much as 600 mg daily.

## Is ParActin® patented?

Yes. **ParActin®** has U.S. Patent #8,084,495 B2, Composition and Use: "Composition of Labdane Diterpenes Extracted From *Andrographis paniculata*, Useful For The Treatment Of Autoimmune Diseases, And Alzheimer's Disease By Activation of PPAR-Gamma Receptors."

## Where is ParActin® grown and processed?

*Andrographis paniculata* is widely cultivated in India, China and Southeastern Asia. **ParActin®** is sustainably harvested and is processed in a GMP-certified and ISO 9001-2008 certified Quality Management Systems facility.

## Is ParActin® GRAS (Generally Recognized As Safe?)

It is not GRAS for food products, but it is allowed for use in dietary supplements.

*Andrographis paniculata*

## What are ParActin's® mechanisms of action on joints?

- **Inhibits NF- $\kappa$ B binding to DNA**
- **Inhibits IKK**
- **Inhibits COX-2 and reduces PGE2**
- **Inhibits NFAT—bone erosion**
- **Stimulates osteoblasts and calcium deposition**
- **Decreases Rheumatoid Factor—TNF- $\alpha$**
- **Reduces IgA and IgM: cartilage damage**
- **Reduces C-Reactive Protein**
- **Promotes regulatory T cell (Treg), CD4+CD25+**
- **Reduces AP-1 and STAT3 in synovial tissue**





## Glossary of Terms

**AP-1:** Activator protein 1 is involved in cellular proliferation, transformation and death.

**ARE:** (antioxidant response element) a region of DNA within the nucleus of the cell.

**CAT:** (catalase) is a common enzyme that breaks down hydrogen peroxide to water and oxygen.

**CD4 + CD25:** Two types of regulatory T-cells that control the burst of superantigen-induced cytokine production.

**COX-2:** Cyclooxygenase-2 is an enzyme responsible for the formation of prostaglandins, prostacyclins and throm-boxanes, which are involved in the inflammatory response.

**C-reactive protein:** An acute phase reactant, meaning that its levels will rise in response to inflammation.

**IgM and IgA:** Immunoglobins M and A are two types of antibodies in the blood that primarily protect individuals from infections inside the body's tissue, organs and blood.

**IKK $\beta$ :** An IRF5 kinase that instigates inflammation.

**IL-2:** Interleukin-2 is a type of cytokine-signaling molecule in the immune system and a protein that regulates the activities of white blood cells that are responsible for immunity.

**IL-6:** Interleukin-6 acts as both a pro-inflammatory cytokine and an anti-inflammatory cytokine.

**Keap1:** (Kelch ECH associating protein 1), prevents Nrf2 from migrating to the nucleus through adhesion.

**NFAT:** Nuclear factor of activated T-cells is a general name applied to a family of transcription factors shown to be important for immune response.

**NF- $\kappa$ B:** Nuclear factor-kappa B is a protein complex that controls transcription of DNA, cytokine production and cell survival.

**Nrf-2:** (nuclear factor erythroid 2-related factor 2) regulates cellular defense mechanisms against environmental stressors, and helps resolve inflammation.

**PGE2:** Prostaglandin E2 is a prostaglandin that ultimately induces fever. It also suppresses T-cell receptor signaling and may play a role in the resolution of inflammation.

**PPAR- $\gamma$ :** Peroxisome proliferator-activated receptor gamma is a nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids.

**ROS:** (reactive oxygen species) is a type of free radical.

**SOD:** (superoxide dismutase) an enzyme that helps transform the free radical superoxide to ordinary molecular oxygen or hydrogen peroxide.

**STAT3:** Signal transducer and activator of transcription 3 is a protein-coding gene that has been found to play a fundamental role in converting normal cells to cancerous cells.

**Synovial membrane:** The soft tissue found between the articular capsule (joint capsule) and the joint cavity of synovial joints.

**TNF- $\alpha$ :** Tumor necrosis factor alpha is a cell-signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction.



HP Ingredients Corporation (HPI) is a fast-growing research-based botanical company that offers unique, innovative, science-based, clinically proven, patented, safe and natural ingredients to the nutraceutical industry. HPI's ingredients address today's most common chronic health conditions; they help support optimal testosterone, energy, heart, blood sugar, cholesterol, weight management, brain and memory health.

HPI was founded in 2001 by Annie Eng with the goal of bringing nature and science together. Today, HP Ingredients is an innovative nutraceutical company dedicated to

providing cutting-edge, science-based nutraceuticals that addresses cholesterol, blood glucose control, weight management, joint health, andropause and healthy aging. HPI believes in ongoing research and development for its premier ingredients.

Working with top scientists from around the world, HPI is dedicated to ongoing research on its proprietary ingredients in a qualitative manner similar to pharmaceutical products. The company believes in supporting its products with proven science, bringing well-researched, patented plant extracts to the nutraceutical industry.

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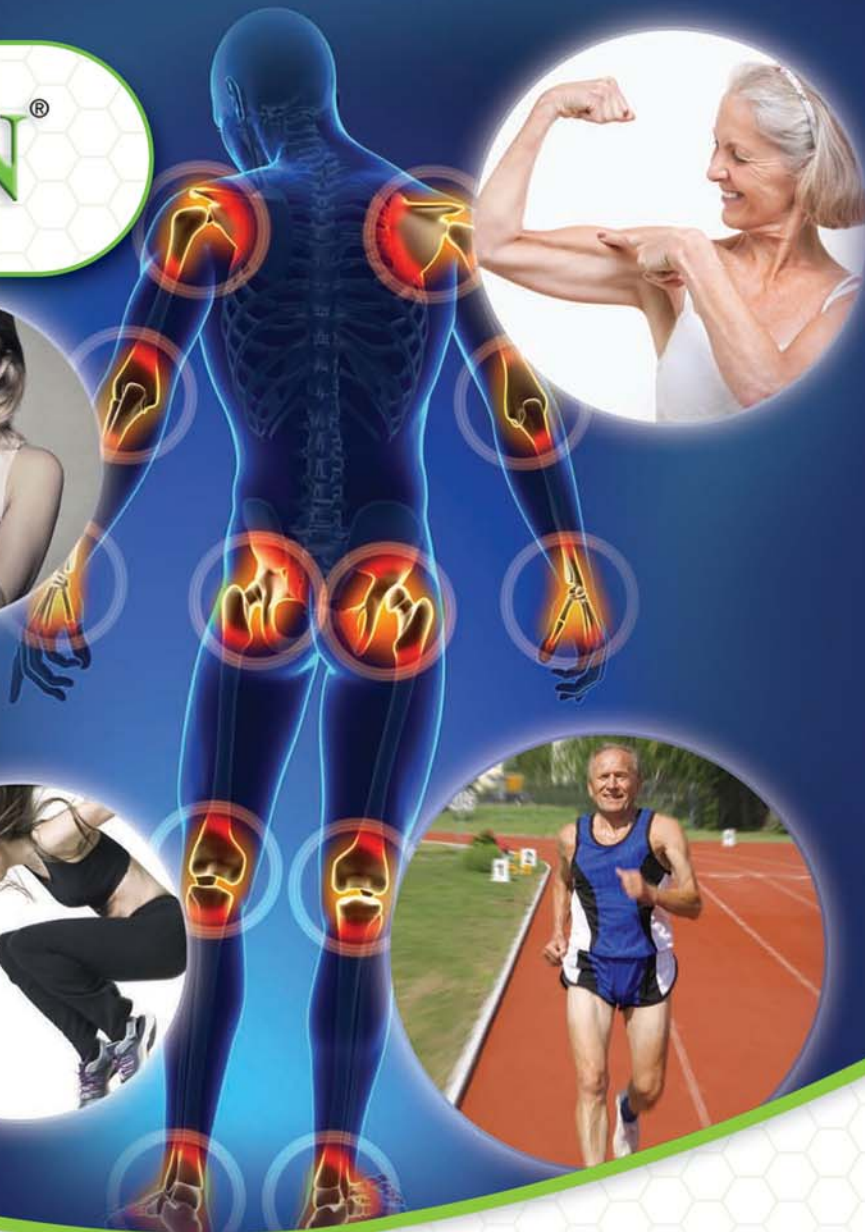
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