# Zynamite®

## WHITEPAPER

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Award winning innovation for increased physical and mental energy

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SCIENCE BASED
NATURAL INGREDIENTS

FROST & SULLIVAN
BEST 2019 PRACTICES AWARD
EUROPEAN SPORTS NUTRITION AND HEALTH INGREDIENTS NEW PRODUCT INNOVATION AWARD

INDEX

## I. INTRODUCTION

Zynamite® gives sustained focus and increases mental and physical energy without any negative side effects like jitters, nausea, anxiety or increased blood pressure.

### WHAT DO TIRED PEOPLE NEED?

Stressed or fatigued people lack enthusiasm and mostly feel exhausted and desperate. What they desire is a sustained boost of energy that improves physical performance, concentration, attention, alertness and mood.

### THE PROBLEM WITH CAFFEINE

Because of the mental energy and focus provided by caffeine, billions of cups of coffee are consumed daily to assist people to cope. However, caffeine is addictive and most people consume too much of it and suffer from its side effects and withdrawal symptoms[1].

### IDEAL FOR SPORTS PERFORMERS

Zynamite® is doping free and ideal for sports professionals or weekend warriors who are aiming to increase their physical and mental energy performance.

## Zynamite®

**What is Zynamite®?**

Zynamite® is Nektium's patent-pending proprietary *Mangifera indica* extract standardized to ≥ 60% mangiferin.

*Mangifera indica*, the common mango tree, is cultivated extensively in the tropical and subtropical regions of the world. Infusions and decoctions of mango leaves are used in traditional health systems and have been known for centuries for their health benefits[2,3].

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**How does Zynamite® work?**

Zynamite® is a COMT inhibitor that activates brain waves and increases Long-Term Potentiation in a remarkably similar pattern to caffeine[4,5]. While caffeine antagonizes adenosine receptors, Zynamite® acts non-selectively on multiple CNS targets to stimulate brain activity without causing side-effects.

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**Zynamite® is protected**

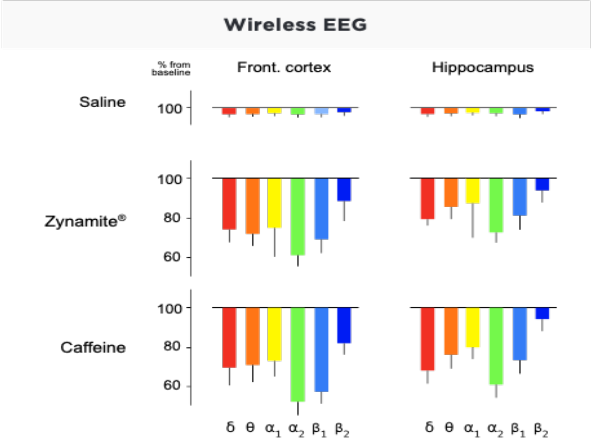
Zynamite® is protected by 3 pending patents:

1. Compositions for Enhancing Brain Activity
2. Compositions for Reducing Craving, Enhancing Mood & Decreasing Stress
3. Compositions for Improving Sports Performance

# II. PRECLINICAL STUDIES ON ZYNAMITE®

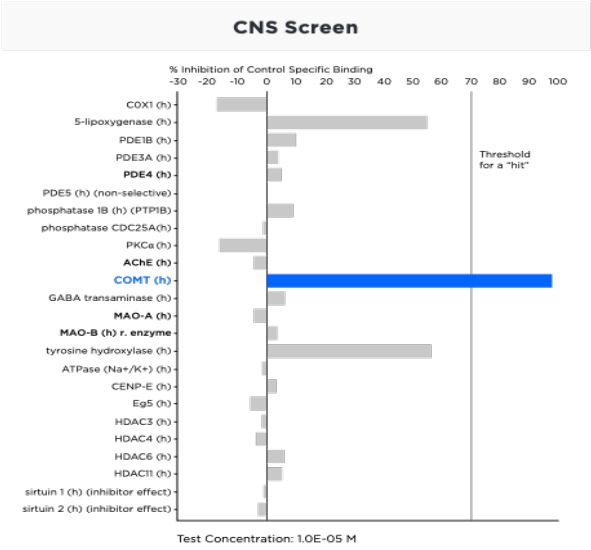
## WIRELESS EEG

The Central Nervous System (CNS) activities of Zynamite® were investigated using cutting-edge neurophysiological studies including *in vivo* functional electroencephalogram (EEG) in four brain regions, for six brain wave frequency ranges. In collaboration with Professor Wilfried Dimpfel, Justus-Liebig University, Giessen, Germany, the EEG of Zynamite® was compared to that of caffeine. Results demonstrated that the pattern of electrical activation for both Zynamite® and caffeine are remarkably similar in the brain frontal cortex and in the hippocampus[4,5]. The colored bars represent the six frequency bands studied.




## CNS SCREEN

Furthermore, detailed *in vitro* studies were performed, looking at 90 different CNS targets.



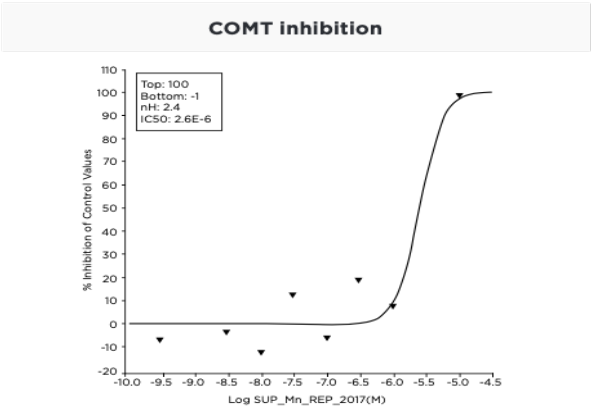

**Conclusion**

**Zynamite® crosses the blood brain barrier and has a strikingly similar brain activity activation on EEG to caffeine.**

**- Zynamite® combined with caffeine has a synergistic effect.**

**- Zynamite® and caffeine have two have different molecular mechanisms of action.**

**- Zynamite® is a COMT inhibitor. COMT modulates the levels of dopamine, serotonin and nor-epinephrine.**

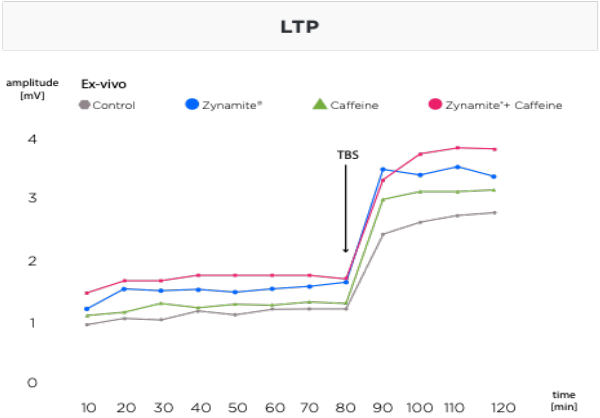


# II. PRECLINICAL STUDIES ON ZYNAMITE®

## LONG-TERM POTENTIATION

The effect of Zynamite® was tested in Long-Term Potentiation (LTP) in the rat hippocampus, which is the area of the brain responsible for memory. LTP enables the brain to form memories and helps athletes to automate coordination skills[6].

In a study comparing the effect of Zynamite®, caffeine and the combination of Zynamite® + caffeine on LTP, Zynamite® had a greater effect on LTP than caffeine, while the combination of Zynamite® + caffeine demonstrated a remarkable synergy in increasing LTP[4,5].




**Conclusion**

**- Zynamite® increased Long-Term Potentiation more than caffeine.**

**- Zynamite® can increase attention, learning and memory and can thus be considered as a nootropic that can be used to completely replace caffeine or dramatically reduce the dose of caffeine in a product.**

## TOXICOLOGY

To confirm the safety of ingestion of Zynamite®, Nektium commissioned a 90-day *in vivo* repeat dose oral gavage toxicity study of Zynamite®. Based on the observations made the No Observed Adverse Effect Level (NOAEL) was determined as follows.
NOAEL: 2000 mg/kg bw/day.

# III. CLINICAL STUDIES ON ZYNAMITE®

## CLINICAL STUDIES ON SPORTS PERFORMANCE

Sports performance is a major arena for caffeine replacement products because around 80% of sports performance products contain caffeine as an ergogenic aid, often in combination with nootropics.

In collaboration with Professor Dr. Jose López Calbet, University of Las Palmas, Spain, the effect of Zynamite® on performance and muscle fatigue was studied in three randomized, double-blind, placebo-controlled trials in caffeine-free formulations containing polyphenols, commonly used as antioxidants in sports products.

After acute (48 hours) and prolonged (15 days) supplementation with a low dose of 140mg Zynamite® + 50mg Luteolin intake and a high dose of 420mg Zynamite® + 150mg Luteolin intake, taken eight hourly, 12 physically active young men performed repeated bicycle ergometer Wingate sprint tests[7].

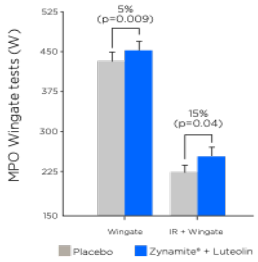
In a second study, the effect of 140mg Zynamite® intake, taken eight hourly for 48 hours was tested a) with 50mg Luteolin and b) with 600mg Quercetin. 30 young athletes (13 women) performed Wingate sprints[8].

In a third trial, muscle biopsies of cyclists during sprints were taken to study the physiological mechanism of action of Zynamite® at molecular level in muscle tissue.

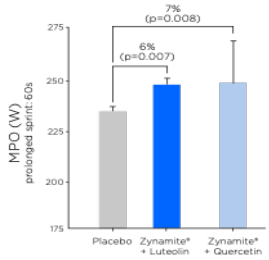
Peak power output (PPO), mean power output (MPO), oxygen uptake ($VO_2$), respiratory variables, cerebral vascular reactivity, muscle oxygenation and cerebral oxygenation were analysed after exhaustion and after exhaustion followed by bilateral isquemia-reperfusion (IR), a model for simulation of fatigue.

Both Zynamite® formulations enhanced exercise sprint performance, likely by improving brain oxygenation and allowing a higher muscle extraction of oxygen. These effects were observed following 48h and 15 days of supplementation without significant differences between the two doses tested[7].

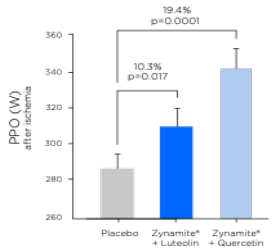
**Improved Performance (MPO)**
after 30sec sprint




**Improved Performance (MPO)**
after 60sec sprint




**Improved Performance (PPO)**
after ischemia



# III. CLINICAL STUDIES ON ZYNAMITE®

## MEAN POWER OUTPUT (MPO)

Compared to placebo, MPO was improved in athletes taking Zynamite® + Luteolin in the 30s Wingate test by 5% (p=0.009), while in the Wingate test following IR, the improvement was 15% (p=0.04).

Compared to placebo, MPO was improved in athletes taking Zynamite® formulations in the prolonged 60s sprint by 6% (p=0.007) for Zynamite® + Luteolin and 7% (p=0.008) for Zynamite® + Quercetin.

## PEAK POWER OUTPUT (PPO)

Compared to placebo, PPO was improved in athletes taking Zynamite® formulations in sprints performed at high exhaustion following IR, by 10.3% for Zynamite® + Luteolin and 19.4% for Zynamite® + Quercetin.

## OXYGEN UPTAKE ($VO_2$MAX) AND BRAIN OXYGENATION

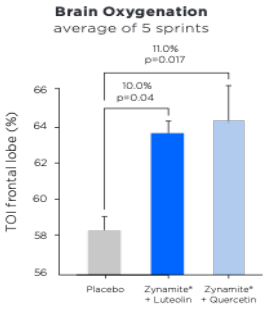
Zynamite® + Quercetin improved $VO_2$max by 6.1%, with a corresponding increase in brain oxygenation of 11% in women.

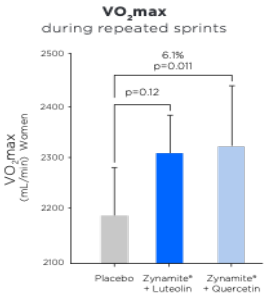
## MUSCLE OXYGENATION

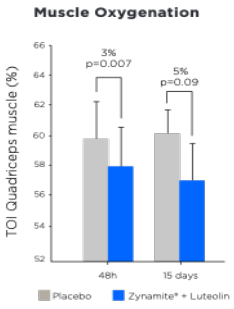
After the ingestion of 140mg of Zynamite® + Luteolin, the quadriceps muscle tissue oxygenation index (TOI) during sprint exercise was 3% lower (p= 0.007) after 48h and 5% lower (p= 0.09) after 15 days, indicating enhanced muscle $O_2$ extraction.

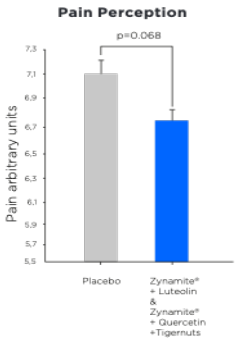
## PAIN PERCEPTION

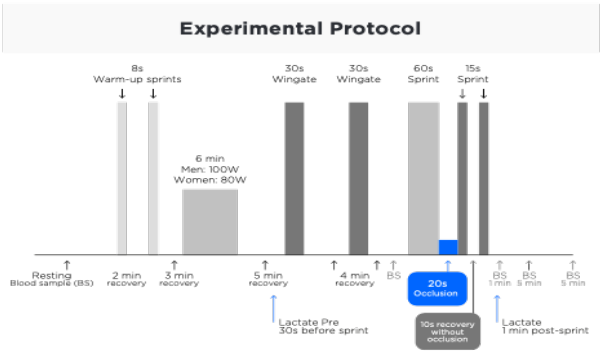
Pain perception was reduced in Zynamite® in formulations compared to placebo (p= 0.068).




**Conclusion**

**Nektium's sports performance studies demonstrate that Zynamite® has better ergogenic activity than caffeine, without cardiovascular or other side effects. Zynamite® is doping-free, tested against WADA list of doping agents.**

# III. CLINICAL STUDIES ON ZYNAMITE®

## CLINICAL STUDIES ON MENTAL ENERGY

Nootropics boost cognitive function and memory and improve reaction time, focus and performance with no negative rebound effects, like those experienced from caffeine. Popularity for nootropics has increased significantly in recent years.

The nootropic effect of 500mg Zynamite® was studied in two randomized, double blind, placebo-controlled cross-over pilot clinical trials. 16 participants took Zynamite® compared to placebo.

### MOOD AND STRESS

The study showed that Zynamite® significantly reduced fatigue after only 1.5 hours, analyzed with the Profile of Mood States questionnaire (POMS). Zynamite® reduced stress during the Calculation Performance Tests, evidenced by Galvanic skin response.

### HEART RATE VARIABILITY AND BLOOD PRESSURE

Zynamite® had no side effects and no change in heart-rate variability or blood pressure over the course of the study - variables typically affected by caffeinated products.

### EEG

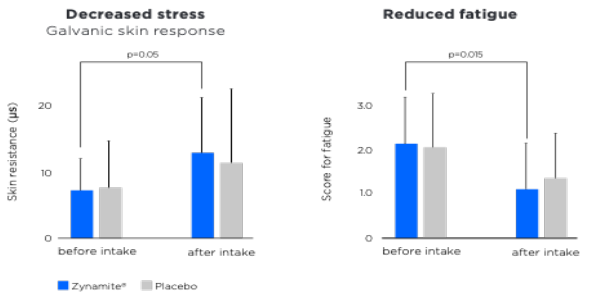
During performance of two cognitively demanding challenges, a Number Sequence Test (NST) and a Number Connection Test (NCT), Zynamite® had a significant activating effect on the brain compared to placebo as determined by frequency analysis of the changes in electrical activity across six brain wave frequency ranges (colour coded) in the EEG of the association cortex (change from time-averaged baseline assigned as 100% **p<0.05, ***p<0.001.

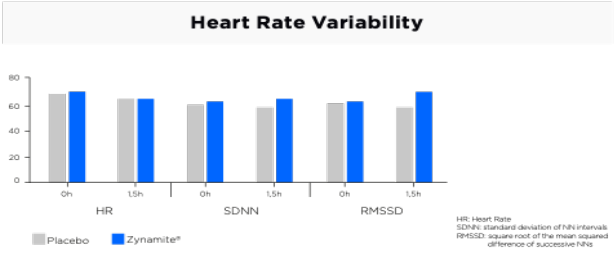
### PSYCHOMETRIC TESTS

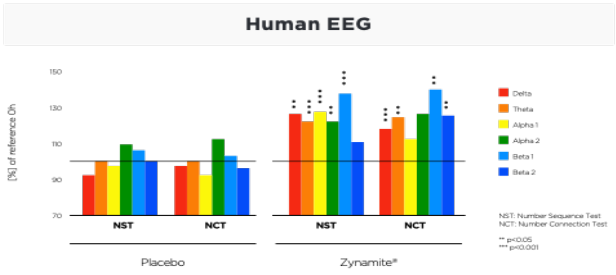
Reaction time was significantly faster for Zynamite® compared to placebo.

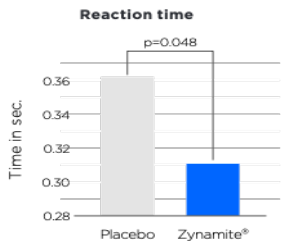
**Conclusion**

**The results of these clinical studies demonstrate that Zynamite® enhances attention, reduces mental fatigue and improves reaction time - results typically shown for caffeine. The advantage of Zynamite® is that this extract also reduced stress, and there were no side-effects, including no changes in heart rate or blood pressure.**



## IV. REGULATORY

Mango leaves have a well-established food and beverage use throughout the tropics of the world where mango trees are cultivated. They are also listed as food supplement in Italy, France and Belgium.

Specific countries that were notified for the marketing of mango leaf extract (60% mangiferin) under the brand name Zynamite® include: Italy, France, Belgium, Germany and Finland. Furthermore the authorities of Australia and New Zealand were notified as well.

## V. MANUFACTURING PROCESS

### DNA BARCODING: IDENTIFICATION OF SPECIES

The botanical raw material used for Zynamite® first undergoes macroscopic inspection to ensure it conforms with reference plant material. DNA barcoding by the Royal Botanical Garden, Madrid, is used to positively confirm its botanical identity. Additionally, UHPLC chromatographic profiles are used to confirm the presence of characteristic markers and to quantify the content of mangiferin.

### QUALITY ASSURANCE & CERTIFICATIONS

Zynamite® is the result of high quality botanical raw material combined with meticulous manufacturing procedures. Nektium's facilities and production processes strictly comply with cGMP (independently audited and certified annually) and rigorous quality control programs that ensure a high-quality product.

Nektium Pharma S.L. is authorized by the Spanish Health & Food Agency for the production of botanical and fruit extracts in conformance with RD 1712/1991 and Spanish Regulations.

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