November, 2018 ● Volume 4, Issue 2

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ISSN 2377-8350

# ADVANCES IN FOOD TECHNOLOGY AND NUTRITIONAL SCIENCES

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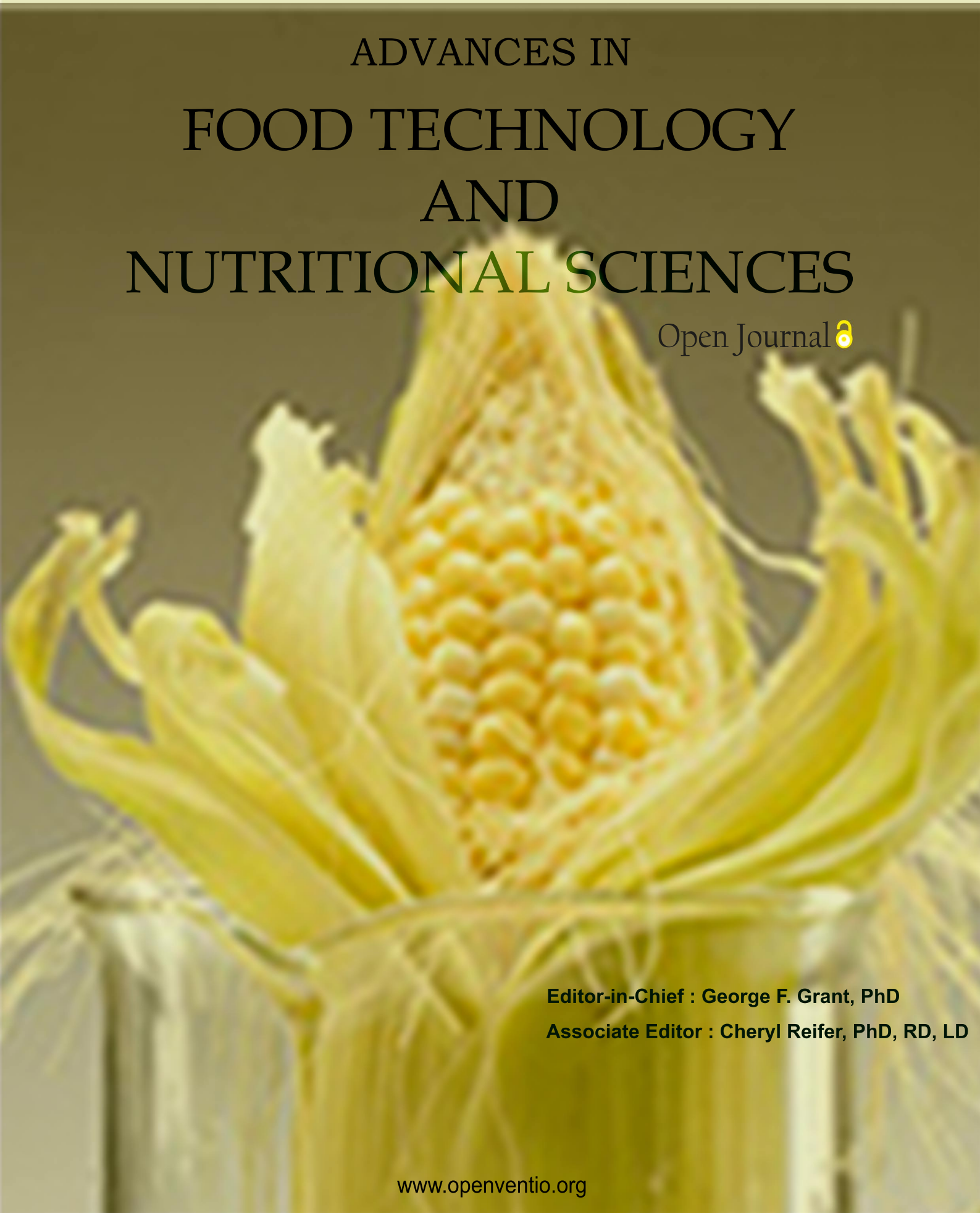



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ISSN 2377-8350

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## PREFACE

When Advances in Food Technology and Nutritional Sciences – Open Journal invited me to write an editorial, I decided to assign it to my 2018-Biochemical Nutrition graduate students.

My students have diverse educational and cultural backgrounds and have been exposed to a variety of tech-based learning. However, research and thesis writing frequently involves the development of new complex reading skills associated with comprehension and synthesis of a tremendous volume of information, along with in-depth critical analysis, evaluation and elegant academic writing style.

For this purpose, I followed the "*scaffolded*" approach where I gave my students the creative freedom to pursue their passion and to funnel their topic. In this issue, my students highlighted the current progress related to diverse hot spot research area in both human and animals.

In the era of growth promoting antibiotics ban, Alison Ferver discussed in the first editorial the chemical mechanisms of antimicrobial activity of phytogenics and their potential use as future alternatives. In the second editorial, Danielle Graham et al. described the necrotic enteritis (NE) prevalence and its dramatic effects on poultry health and wellbeing which in turn resulted in heavy economic loss, and finally discussed the beneficial role of xylanase to reduce NE incidence. Lauren Thomas et al. elegantly reported, in the third editorial, a mechanistic understanding of antioxidant impact on cognitive function in canine species.

As obesity is a major health problem in the USA as well as worldwide, the last two student groups focused on this metabolic disorder. Samuel Walker et al. presented intermittent fasting as an effective strategy for preventing obesity and its associated-complications particularly type 2 diabetes mellitus. In the last chapter, Reagan Cauble et al. fine-tuned the role of leptin and NLRP3 inflammasome in obesity pathogenesis.

My goal here is to promote curiosity and to help my students understand complex questions, and to constantly question information and explore more sources. My overall hope is to promote critical and independent thinking and to create research- and question-mindsets. Finally, I really enjoyed interacting with my students and would like to thank them for their dedication, perseverance, and hard work.

— Dr. Sami Dridi

ISSN 2377-8350

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*Editorial*

# Phytogenics as an Alternative to Antibiotics: Chemical Mechanism behind Antimicrobial Activity of Essential Oils

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***Article information***
**Received:** October 7th, 2018; **Accepted:** October 11th, 2018; **Published:** October 15th, 2018

***Cite this article***
Ferver A, Dridi S. Phytogenics as an alternative to antibiotics: Chemical mechanism behind antimicrobial activity of essential oils. *Adv Food Technol Nutr Sci Open J.* 2018; 4(2): e1-e3. doi: 10.17140/AFTNSOJ-4-e012

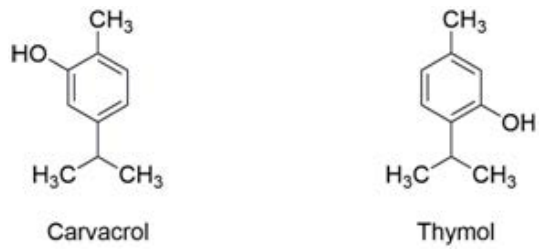
## INTRODUCTION

Since the 1950s, antibiotics have been the "silver bullet" for the treatment of diseases in both the medical and livestock industries. The use of subtherapeutic antibiotics in broilers not only prevents disease outbreaks but also increases meat yield and feed conversion.[1] The mode of action for the added growth promoter effects of antibiotics stems from their ability to control microbial populations in the gut, decreasing toxic microbial byproducts and limiting competition for nutrients in the gastrointestinal tract (GIT).[2,3] These growth promoting effects have made antibiotics a common feed additive in the poultry industry.[4] However, decades of exposing microorganisms to low doses of antibiotics has created a selection pressure for antibiotic-resistant bacteria.[5] In a 2017 study in Ghana, over sixty percent of *Staphylococci* isolates from poultry farms and farm workers were resistant to multiple antibiotics, including tetracycline, one of the most common antibiotics in the poultry industry.[6] The European Union banned the use of food animal growth-promoting antibiotics in 1986. In the USA, the guidelines for industry issued by the Center for Veterinary Medicines of the Food and Drug Administration (FDA, 2012) recommend use of antibiotics only for the prevention, control and treatment of infections in animals but not for the promotion of growth, increased performance, and improved feed efficiency. Alternatives to antibiotics are, therefore, needed in order to continue the efficiency and sustainability of the poultry production. A promising alternative is phytogenic essential oil. In this editorial, we will review how the structure of phytochemicals within essential oils contributes to the antimicrobial activity and growth promotion in broilers.

## ANTIMICROBIAL MECHANISM OF ESSENTIAL OILS

Derived from plants and herbs, essential oils contain antimicrobial phytochemicals that modulate microbial populations in the GIT to prevent disease and promote growth, even after vaccination or when challenged with high doses of microbes, including *Clostridium perfringens*.[7-9] Terpenoids act as non-specific bactericidal antimicrobials at high doses by altering the structure and function of the cytoplasmic membrane and disrupting membrane protein binding and ATP synthesis.[10] Terpenoids ability to interfere with the phospholipid bilayer structure and integrity is due to the positioning of the hydroxyl group and the hydrophobicity of the benzene ring and substituents.[11] Carvacrol and thymol are terpenoids in essential oils from herbs like thyme and oregano that have become increasingly more popular as feed additives in the poultry industry.[12] They are both substituted phenols but differ in the location of the hydroxyl group on the aromatic ring. As seen in Figure 1, carvacrol has a hydroxyl group bonded in the ortho position relative to the methyl group and thymol has the hydroxyl in the meta position.

**Figure 1.** *Chemical Structures of Terpenoids*




When comparing the antimicrobial activity of these terpenoids, carvacrol differs in its mode of action due to the dif-

ference in chemical structure of these compounds. In the case of thymol, interactions between the polar heads of bilayer membranes and the hydroxyl group, coupled with the hydrophobicity of the rest of the molecule, results in a disruption of membrane integrity, causing increased membrane permeability and fluidity.[13] This fluidity alters the proton motive force in the cell through the leaking of ions, such as $H^+$, causing cytoplasmic coagulation.

It also interferes with the holding of membrane proteins, which contributes to the leakage of ions and intracellular molecules such as ATP.[14] Carvacrol also increases membrane permeability. However, the positioning of the hydroxyl group near methyl rather than isopropyl, as in the case of thymol, enables the molecule to act as a proton exchanger and more easily form hydrogen bonds.[15,16] By bringing $H^+$ into the cytoplasm and facilitating the movement of $K^+$ out, the $H^+$ gradient needed for ATP synthesis is disrupted. When exposed to carvacrol, the ATP pool within the cell is depleted and there is an increase in intracellular ATP.[17] In the case of Gram negative bacteria, the hydrogen bonding capacity of carvacrol and its small size allows it to pass more readily through the outer membrane *via* porins.[11,17,18] This allows access to the cytoplasmic membrane and aids in the antimicrobial capacity of carvacrol. The significance of the free hydroxyl group and delocalized electron system is demonstrated by the lack of antimicrobial capacity of carvacryl acetate and menthol when compared to carvacrol. Carvacryl acetate shares the hydrophobic properties of carvacrol but lacks the hydroxyl group, replaced with a carboxylic acid. The inability to form hydrogen bonds reduces the molecules ability to disrupt the integrity of the cytoplasmic membrane. In menthol, the benzene ring is replaced with a 6-carbon single bonded ring, removing the delocalized electron system. This inhibits the molecules proton exchanging abilities.[19]

When analyzing the use of thymol and carvacrol as feed additives, their stability at varying pH is crucial to their effectiveness in the GIT. In the broiler GIT, the pH ranges from 2.5 to 8.[20] When compared to other essential oil components, carvacrol and thymol maintained antimicrobial activity against multiple organisms after exposure to pH values from 2 to 7.[21] The ability of essential oils to decrease microbial population in the GIT results in less competition for nutrient absorption, decreased microbe fermentation, and a more stable pH. In terms of growth promotion, these terpenoids have been shown to increase body weight and average daily gain in a manner comparable to antibiotic growth promoters.[22,23] The reduced fermentation and pH stability decreases the decarboxylation of limiting amino acids and provides optimal conditions for digestive enzyme activity, resulting in an increased digestibility of nitrogen and availability of nutrients, promoting overall growth.[24,25]

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-8350

ADVANCES IN
FOOD TECHNOLOGY AND NUTRITIONAL SCIENCES
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## Editorial

# Xylanase Supplementation in Wheat-based Diets and the Influence on Necrotic Enteritis in Broilers: A Translational Model for Human Malnutrition

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***Article information***

**Received:** October 7th, 2018; **Accepted:** October 11th, 2018; **Published:** October 16th, 2018

***Cite this article***

Beer L, et al. Xylanase supplementation in wheat-based diets and the influence on necrotic enteritis in broilers: A translational model for human malnutrition. *Adv Food Technol Nutr Sci Open J*. 2018; 4(2): e4-e5. doi: 10.17140/AFTNSOJ-4-e013

In the poultry industry, necrotic enteritis results in substantial production and economic losses each year. Outbreaks are more prevalent due to the removal of antibiotic growth promoters.[1] *Clostridium perfringens*, a commensal organism within the gastrointestinal tract of poultry, is the primary bacterial etiology responsible for necrotic enteritis.[2] In the absence of a host, *C. perfringens* spores can remain dormant in the environment for long durations, possibly between flocks.[3] *Eimeria* spp. colonization commonly predisposes broilers to the disease due to epithelial cell damage and increased mucus production, which provides an ideal environment for proliferation of *C. perfringens*.[4] Dietary ingredients, such as wheat can affect the integrity of the gastrointestinal tract and potentially induce necrotic enteritis.[2,5]

Wheat is a variable feed grain that is high in insoluble non-starch polysaccharides.[6] Non-starch polysaccharides fed in moderate amounts can slow passage rates due to the gizzard's ability to retain insoluble fiber.[7] High-levels of non-starch polysaccharides present in wheat diets can increase viscosity in the small intestine due to their lack of digestibility.[6] According to Branton et al broilers challenged with *C. perfringens* and fed wheat-based diets had higher necrotic enteritis lesion scores than the challenged and non-challenged corn-based diet controls.[5]

Research studies have shown that enzyme addition to broiler diets can mitigate the negative effects of necrotic enteritis and improve growth performance.[8] Moreover, xylanase supplementation to poultry diets is widely accepted as this enzyme functions to break down arabinoxylans located within plant cell walls, producing greater nutrient bioavailability and reducing negative non-starch polysaccharides.[6] Within wheat-based broiler diets, supplementation of xylanase has been shown to increase apparent metabolizable energy, improve ileal nutrient digestibility, decrease ileal digesta viscosity, reduce feed conversion ratio, and diminish levels of *C. perfringens*.[9,10,11] Additionally, xylanase supplementation to wheat-based diets may alleviate damage inflicted by necrotic enteritis upon the intestinal mucosal barrier partly through protective mechanisms which contribute to the reduction of apoptotic epithelial cells and intestinal permeability.[12] Taken together, these results indicate the positive impacts that the inclusion of enzymes such as xylanase appear to have upon the growth performance of broilers, leading to a potentially significant economical contribution.

The utilization of xylanase within animal feed for improved growth performance suggests a potential area of nutritional improvement through poultry production as an efficient protein source to feed the future. Furthermore, xylanase is a naturally-occurring enzyme that can have beneficial impacts on human health and digestion through the degradation of fiber, although humans are unable to synthesize xylanase and must rely on microorganisms. Additionally, xylanases might offer some benefit within the food industry, particularly for the acceleration of bakery products.[13] Therefore, the use of supplemental xylanase can be potentially beneficial, especially in malnourished countries, to support the breakdown of fiber and further utilization of previously inaccessible nutrients. Xylanase has been extensively used in the baking industry leading to an increase in bread volumes, greater absorption of water, and improved resistance to fermentation.[14,15] Additionally, the fiber-breaking enzymes are capable of hydrolyzing the non- digestible carbohydrates that bind and compromise fiber utilization. Therefore, xylanase can be a digestive aid to improve the nutritional value and digestion of fibrous foods.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-8350

ADVANCES IN
FOOD TECHNOLOGY AND NUTRITIONAL SCIENCES
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*Editorial*

# Mechanistic Understanding of Antioxidants Impact on Cognitive Function in Geriatric Canines

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***Article information***

**Received:** October 7th, 2018; **Accepted:** October 11th, 2018; **Published:** October 17th, 2018

***Cite this article***

Thomas LR, Booth HA, Beane KE, Bottoms KA, Dridi S. Mechanistic understanding of antioxidants impacts on cognitive function in geriatric canines. *Adv Food Technol Nutr Sci Open J*. 2018; 4(2): e6-e8. doi: 10.17140/AFTNSOJ-4-e014

## INTRODUCTION

Canine cognitive dysfunction syndrome (CDS) is a collection of symptoms, or behavioral changes, described specifically in dogs of advanced age unrelated to any other diagnosable illness. Symptoms may include an altered sleep-wake cycle, newly developed destructive behavior, inappropriate elimination, excessive vocalization, pacing or wandering, and altered social interaction with the owner.[1-4] In regards to aging, the brain is one of the most susceptible tissues in the body because of its high oxygen requirement, poor endogenous antioxidant capacity, and limited regenerative ability.[5,6] A number of pathologic changes have been identified in the aged canine brain, many of which have also been described in humans diagnosed with Alzheimer's disease (AD). As a result, the dog is often used as a high-relevant comparative animal model for studies on AD in humans.[7-9] The most commonly recognized changes in the canine brain include decreased total brain volume (or atrophy), enlargement of the lateral ventricles, choroid plexus, meningeal and vascular fibrosis, neuronal loss, decreased neuronal regenerative capacity, lipofuscin build-up, intracytoplasmic inclusion formation, and diffuse β-amyloid plaque formation–specifically in the frontal cortex and hippocampal regions.[5,7,10,11] Several studies have suggested a significant correlation between β-amyloid deposition and the severity of cognitive dysfunction in aged canines[4], similar to that which occurs in humans with Alzheimer's disease though the exact mechanisms between these changes and the development of cognitive dysfunction syndrome in canines is yet to be fully established.[5] However, it has been shown that oxidative damage to lipids and proteins due to reactive oxygen species increases in the brain with age.[12] As a result, diets fortified with antioxidants may help to prevent and/or mitigate some of these destructive changes, thus decreasing the incidence and/or severity of cognitive dysfunction syndrome.[1,4]

### Free Radicals, Reactive Oxygen Species and Antioxidants

Generally speaking, any molecule that contains at least one unpaired electron in the outer shell is intensely reactive and is called a "free radical" or, if it contains oxygen, a reactive oxygen species (ROS).[13] The body spontaneously creates reactive oxygen species such as the superoxide, hydroxyl, peroxyl (RO2 •), alkoxyl (RO• ), and hydroperoxyl (HO2 • ) free radicals as by-products of cellular respiration. In low concentrations, ROS aid in maturing cellular structures, immune system destruction of foreign pathogens, and cellular signaling.[14-16] When excess ROS remain un-neutralized by the body's natural defenses, they can cause oxidative stress on the surrounding tissues. This is because the free radicals undergo further reactions with surrounding molecules leading to the formation of peroxides, subsequent degradation into smaller molecular units, and then formation of dimer aggregates. This then detrimentally affects the functional efficiency and the productive ability of these cells. The free radical theory of aging was developed in the mid-20th century and suggests that aging is caused by the continued detrimental effects of free radicals over an organism's lifespan as well as a decrease in the ability to recover from cellular damage caused by free radicals and other reactive oxygen species (ROS).[17]

Antioxidants are substances found in the diet that have the ability to reduce the effect of ROS and potentially delay the effects of aging associated with cognitive dysfunction. In order to combat ROS within cells, the body protects itself by using various antioxidant mechanisms. Antioxidants and their mechanisms are classified as either enzymatic (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx)) or non-enzymatic (vitamin E, vitamin C, plant polyphenols, carotenoids, and glutathione).[18,19] For the purposes of this editorial, we chose to focus primarily on the functions of the naturally occurring, non-enzy-

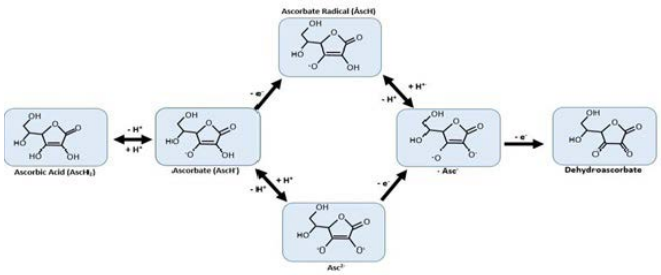
matic antioxidants, vitamin E and vitamin C, which are commonly incorporated into commercial canine diets specifically formulated to combat brain aging.[20, 21]

Vitamin E (α-tocopherol) works by impeding free radical chain reactions. It intercepts lipid peroxyl radicals (LOO•), and terminates lipid peroxidation chain reactions.[18] The resulting radical (α-tocopherol-O•) is considered stable under normal conditions, and helps prevent lipid peroxidation.

$$LOO^{\cdot} + \alpha\text{-tocopherol-OH} \rightarrow LOOH + \alpha\text{-tocopherol-O}^{\cdot}$$

Vitamin C (ascorbic acid 2) is a free radical scavenger. It generates vitamin E within cell membranes by combining with glutathione (GSH) or other compounds capable of donating reducing equivalents. Once vitamin C donates an electron to lipid radicals, the structure is converted to an ascorbate radical[18,19,22] which then prevents the lipid peroxidation chain reaction (Fig. 1).[18]

**Figure 1.** *Mechanism of Radical Scavaging Activity of Ascorbic Acid 2*




### Antioxidants and Canine Cognitive Function

Aged dogs have been used in studies to determine the effects of antioxidant supplementation on the reduction of oxidative stress in the brain and the consequent effects on cognitive function. Several recent studies have used aged beagles to determine if a combination of behavioral enrichment and antioxidant supplementation would begin to more closely resemble cognitive function of younger beagles given the same treatment.[4,23-26] The antioxidant-rich diet contained a broad spectrum of antioxidants (vitamins E and C as well as those occurring in fruits and vegetables such as spinach, tomato, grape and carrot) as well as two mitochondrial cofactors (carnitine and lipoic acid).[25] Over a nearly three year period, the aged dogs showed significant improvement in areas such as spatial attention and oddity discrimination.[4,27] Other areas such as visual discrimination and frontal function of the brain maintained performance in antioxidant enriched diets. However, in aged dogs with untreated diets there was a significant decline.[25] Dogs subjected to both antioxidant-enriched diets as well as behavioral enrichment showed superior improvements compared to either treatment alone.[24,25] It should be noted that the young dogs with antioxidant enriched diets did not show significant difference in cognitive function from the young dog control group.[28] This finding suggests that aged dogs in particular benefit from antioxidant supplementation. Dogs progression in cognitive deficits as they age is similar to that of humans, thus making them a useful model in age-related cognitive dysfunction research. The beneficial effect of an antioxidant-rich diet on aged dogs prove a possible therapeutic approach that may be translated to humans with cognitive dysfunction, such as Alzheimer's Disease.[30]

### Current Dietary Recommendations

As described above, studies have shown that a mixed diet of antioxidants is needed to reach maximum results.[29,30] Vitamin E, vitamin C, β-carotene, and trace minerals including selenium, copper, zinc, and manganese, are common antioxidant sources utilized in canine diets.[30] Additionally, antioxidants synergistically work with mitochondrial cofactors, such as alpha-lipoic acid and Acetyl-L-carnitine, to reduce the effect of ROS and oxidative stress on age-related cognitive dysfunction[4,30,31] and should be incorporated into the diet as well. Two mainstream diets enriched with antioxidants and labeled to help reduce signs of cognitive dysfunction syndrome in dogs include the Hill's Prescription Diet Canine b/d and the Purina Pro Plan Bright Mind. Both diets are enhanced with a mixture of vitamins E and C as well as carnitine and lipoic acid or selenium and vitamin A respectively.[20,21] Currently, there are no formally published daily dosage recommendations for any of the individual antioxidants in relation to canine CDS.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-8350

ADVANCES IN
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*Editorial*

# Intermittent Fasting: A Potential Effective Strategy for Preventing Obesity and Type II Diabetes Mellitus

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***Article information***

**Received:** October 7th, 2018; **Accepted:** October 11th, 2018; **Published:** October 22nd, 2018

***Cite this article***

Walker S, Tacinelli AM, Wu H, Pendergraft S, Horsfall K, Dridi S. Intermittent fasting: A potential effective strategy for preventing obesity and type II diabetes mellitus. *Adv Food Technol Nutr Sci Open J.* 2018; 4(2): e9-e12. doi: 10.17140/AFTNSOJ-4-e015

## PREVALENCE OF OBESITY & TYPE 2 dIABETES

The prevalence of obesity among adults has increased significantly in the past few decades. In the US alone, one in three adults is classified as obese.[1] Most commonly, obesity results from an imbalance of limited energy expenditure to compensate for excess energy intake. However, a number of factors have been identified as possible contributors towards the increasing obesity rates worldwide, therefore acting as a multifaceted problem to resolve.[2] Obesity is considered a primary contributor towards the development of type 2 diabetes mellitus (T2DM).[3] T2DM is characterized by the inability of pancreatic β-cells to produce a sufficient amount of insulin (insulin resistance) in response to necessary levels of glucose uptake. As a result of inhibited insulin secretion, glucose is not taken up into target tissues such as muscle and adipose tissue, leading to elevated blood glucose levels, or hyperglycemia.[4,5] Hyperglycemia can subsequently lead to vascular damage and other adverse effects.[6]

## IMPORTANCE OF INTERMITTENT FASTING RELATING TO OBESITY & T2DM

Intermittent fasting (IF), a form of calorie restriction, has gained popularity in recent years as a methodology for combating obesity and development or progression of type 2 diabetes. IF regimes can vary in fasting durations. Common variations of IF include alternate day fasting (ADF), in which one day consists of a 75% energy restriction followed by a day of *ad libitum* food consumption or 16/8 IF, which includes consuming 100% of energy needs in an 8 hour time period followed by a 16 hour fast.[7,8] Dysregulated insulin/glucose pathways, shown as glucose tolerance and insulin resistance, is the most frequently reported symptom of T2DM and has been discussed broadly in recent years. Studies implementing IF have shown normal and overweight human subjects have efficacy for weight loss.[9] In addition to being an effective method for weight loss, IF can also improve specific health indicators associated with chronic disease in the overweight and obese population, such as insulin resistance.[10] Research on IF's weight loss benefits is aimed at understanding its metabolic effects on many age-related diseases, including type 2 diabetes.[10] However, limited research exists on assessing fasting glucose and insulin levels in patients undergoing IF.

## MECHANISM OF IF ACTION

Changes in fasting blood glucose levels have been observed in humans undergoing ADF.[11,12] As much as a 6% decrease was observed between overweight patients' fasting glucose levels after 8 to 12 weeks of an ADF versus an *ad libitum* diet.[13] Adversely, a significant insulin reduction of approximately 20% was observed in intermittently fasted overweight and obese adults, respectively.[14] Similar effects of decreased blood glucose and insulin levels resulting from IF have also been observed in human studies. This suggests effects of IF treatment on the insulin transduction pathway, as well as pathways involving cytokine-induced food intake behavior, may be responsible for improving glucose tolerance. A study involving New Zealand obese mice undergoing a calorie-restricted IF diet showed improved blood insulin sensitivity in an oral glucose tolerance test, higher blood glucose clearance in insulin tolerance tests, and lower blood glucose and insulin compared to mice fed an *ad libitum* diet.[15]

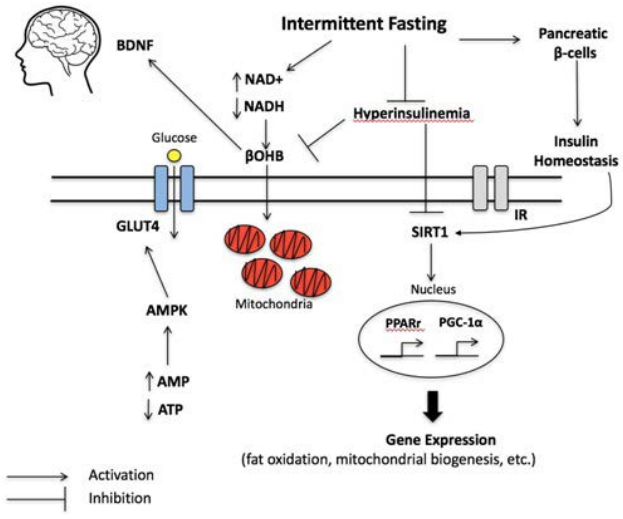
Improvements in the insulin transduction pathway in response to IF may be a consequence of increased expression of sirtuins (SIRTs). SIRT1 is a protein complex involved in cellular energy sensing *via* the ratio of nicotinamide adenine dinucleotide

(NAD+) and its reduced form nicotinamide adenine dinucleotide (NAD) + hydrogen (H) (NADH).[16] The ratio between NAD+ and NADH represent overall oxidative phosphorylation capacity within the cell. Higher levels of NAD+ in response to fasting and exercise are shown to increase SIRT1 activity.[17] Conversely, SIRT1 activity is reduced during periods of hyperinsulinemia.[18] β-hydroxybutyrate (βOHB), a ketone body, is elevated during fasting.[19] Downstream metabolism of βOHB for acetyl-CoA production requires less NAD+ consumption when compared to glucose, thus expression of SIRT1 perpetuates in parallel with the duration of the fast. In addition, βOHB and periods of intermittent fasting upregulate the expression of brain derived neurotrophic factor (BDNF).[20,21] BDNF, a protein in the hypothalamus, is shown to decrease in response to T2D.[22,23] Increased expression of BDNF is shown to have protective effects against the development and progression of T2D including: increased energy expenditure, decreased dietary intake, and decreased fasting blood glucose.[24] Interestingly, BDNF administration is shown to reduce food intake and correct hyperglycemia in leptin receptor deficient *db/db* mice.[25] Increased SIRT1 expression regulates energy expenditure through modulation of cellular respiration. Translation of mitochondrial biogenesis and lipid oxidation are both regulated by peroxisome proliferator-activated receptors (PPARs) and coactivator-1a (PGC-1a).[26] Both of these proteins are downregulated in response to hyperinsulinemia and insulin resistance.[27] Upregulating their expression through increased SIRT1 activity may serve as a novel approach in combating metabolic abnormalities observed in T2D such as intracellular fat depositions. (Figure 1)

As IF elicits similar effects as calorie restriction, it is worthwhile to test if the expression of adipocyte-specific glucose transporter 4 (GLUT4) is increased as shown in obese mice undergoing calorie-restriction.[28] It is believed that IF could induce the secretion of leptin in adipose tissue through up-regulating GLUT4 expression in T2D. The role of the GLUT4 transporter serves as a mediator for improved glucose disposal in response to altered nutrition status. GLUT4 transcription is shown to be tightly regulated in response to energy sensing within the cell. In response to prolonged exercise and calorie restriction, 5' AMP-activated protein kinase (AMPK) activity increases and promotes translocation of GLUT4 to the cell membrane surface. However, the potential of IF influencing this interaction has led to non-correlative results in both human and animal studies.[29]

Contrastingly, in 2014, Dorighello et al. Reported that wild type mice under IF regimen developed symptoms of diabetes including elevated blood glucose and insulin levels, glucose intolerance, and insulin resistance while reduced food intake was observed. Mechanistic understanding the effects of IF can be beneficial towards attenuating or preventing the increasing prevalence of chronic diseases such as obesity and T2D. However, due to the contradicting evidence in current literature, further research is still needed for understanding the mechanisms of IF on various biomarker responses and appetite control.

**Figure 1.** *Anti-diabetic Effects of Intermittent Fasting via SIRT1 Signaling*



## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2377-8350

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*Editorial*

# Leptin Activates NLRP3 Inflammasome-Associated with Type II Diabetes and Obesity

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***Article information***
**Received:** October 7th, 2018; **Accepted:** October 11th, 2018; **Published:** October 23rd, 2018

***Cite this article***
Cauble R, et al. Leptin activates NLRP3 inflammasome-associated with type II diabetes and obesity. *Adv Food Technol Nutr Sci Open J.* 2018; 4(2): e13-e16. doi: 10.17140/AFTNSOJ-4-e016

## INTRODUCTION

Obesity is a major health problem worldwide and is often associated with leptin resistance and inflammation.[1] In this editorial, we will briefly describe the leptin system and the (NOD)-like receptor protein 3 (NLRP3) inflammasome and discuss recent discoveries related to their interaction and role in the development of metabolic disease mainly obesity and Time-division multiplexing (TDM).

## LEPTIN

Leptin is a hormone mainly secreted by adipocytes and is known for its role in long-term energy regulation, food intake, and body weight. As a hormone, its primary responsibility is to report the amount of adipose tissue in the body to the hypothalamus.[2] Leptin concentrations in both blood serum and plasma are elevated in direct correlation with a high body mass index (BMI) and percent body fat. A constant elevation of leptin in the body, caused by sustained over eating habits, overloads the hypothalamus and results in leptin resistance; like we observe in obese subjects.[3]

This resistance is a major factor in causing the chronic inflammatory diseases seen frequently in obese individuals such as asthma, diabetes, and inflammatory bowel disease. In fact, during the active stages of rheumatoid arthritis (an additional condition related to chronic inflammation), leptin levels are elevated. On the other hand, malnourished individuals with decreased leptin levels suffered more infectious diseases, but had significantly lower rates of inflammation. These results are believed to be an indication of leptin's role in activating the body's inflammatory immune responses, resulting in these chronic conditions.[4]

Leptin also operates similarly to pro-inflammatory cytokines known as adipocytokines.[4] The hormone has been reported to control energy expenditure and metabolism, and modulate the innate and adaptive immune responses. The stimulation of natural killer cells, chemotaxis of neutrophils, and secretion of tumor necrosis factor (TNF)-α, IL-6 and IL-12 from macrophages[4,5] also involves leptin. These increase leptin concentrations in adipose cells and create a cycle of constant stimulation of reactants that encourage inflammation.[4]

Furthermore, leptin promotes Th17 cell responses[6] which are a subset of effector memory T-cells that induce tissue inflammation and destruction that are markers of immune inflammatory diseases[7] and decrease the number of T-regulatory cells.[8,9] Fat stores release leptin around various lymph nodes signaling to the rest of the immune system if the body has enough energy stored to initiate an immune response which causes continuous leptin circulation in obese or individuals with type II diabetes.[3]

## NLRP3 INFLAMMASOMES

The nucleotide binding domain and leucine-rich repeat containing receptor (NLR) family are proteins that form inflammasomes.[10,11] The NLRs are classified and named in accordance with their domain structure.[11] The nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is mainly expressed in macrophages and has a pivotal role in development and maintenance of autoimmunity and inflammation. Research has investigated the role of leptin on NLRP3 inflammasome and found that leptin is an activator and modulator of this inflammasome.[12]

Activation of the NLRP3 inflammasome (Figure 1) is thought to be a two-step process.[13] The initial step is a priming step. When exposed to pathogen-associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs), phosphorylation of toll-like receptors occurs and NF-ϰB is activated.[14] NF-ϰB causes an increase in transcription of inactivated forms of NLRP3, proIL-1β, and proIL-18.[15] A secondary stimulus causes activation of the inflammasome by oligomerizing inactive NLRP3, apoptosis-associated speck-like protein, and procaspase-1. This structure catalyzes the modification of procaspase-1 to caspase-1. This conversion contributes to the production of functional IL-1β and IL-18.[16] The activation of the inflammasome in the second step has been proposed using three different models; potassium efflux as induced by extracellular ATP, the generation of reactive oxygen species (ROS) *via* PAMP and DAMP, and crystalline structures causing lysosomal rupture and the release of its contents including cathepsin B.[17]

Leptin promotes IL-18 secretion by activating caspase-1. Caspase-1 in conjunction with NLRP3 inflammasomes regulates the production and secretion of IL-18 via proteolyticall digestion pro-IL-18.[8,18] More specifically, the IL-18 promotion via leptin is done so by enhancing reactive oxygen species (ROS) synthesis and K+ efflux. This relationship activates the NLRP3 inflammasome.[12]

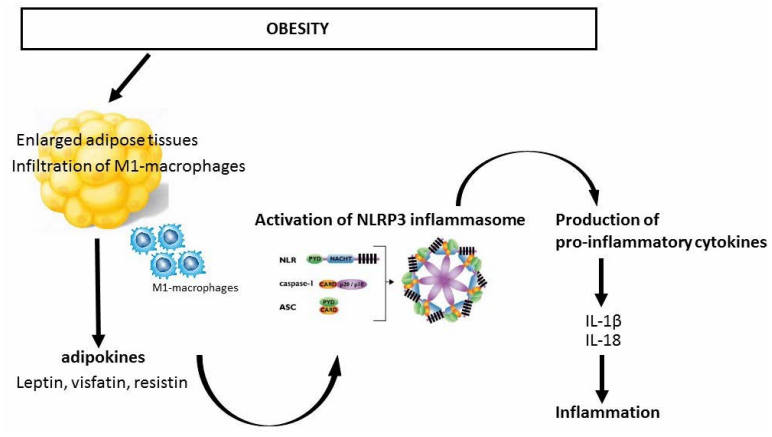
The role of NLRP3 inflammasome in metabolic syndrome and type II diabetes can be split into two subcategories which include mediated roles by sensing endogenous inflammasome activators and indirect roles by inflammasome associated alteration by manipulation of the gut microbiota.[19] There are multiple mechanisms that have been investigated that could potentially activate the NLRP3 inflammasome in high fat induced diets; one of which includes a pancreatic hormone that is co-secreted with insulin and triggers IL-1ß secretion by isolate macrophages.[20]

## OBESITY AND TYPE II DIABETES

Improvements Inflammation is a player in the pathogenesis of obesity. The chronic overfeeding associated with obesity causes macrophage saturation in the adipose tissue and results in pro-inflammatory cytokine production.[21] This endogenous signaling triggers the intracellular innate immune NLRP3 sensor, results in caspase-1 activation and the production of IL-1ß and IL-18.[21] These cytokines are directly related to the development of insulin resistance that we observe in type II diabetes.[16,22] Specifically, IL-1ß inhibits adipocyte differentiation[23,24] while the absence of IL-18 induces obesity and insulin resistance.[25,26] Conversely, the absence of the NLRP3 inflammasome has been shown inhibit the development of obesity-induced insulin resistance[27], which would suggest that the inflammasome is a contributor.

Different immune cells, including proinflammatory macrophages, have been shown to penetrate the adipose tissue (AT) and affect its homeostasis by increasing the production of cytokines such as IL-1β, IL-6 and TNF. Macrophages and other innate immune cells can promote inflammatory reactions through detection of pathogen- or danger –associated molecular patterns (PAMPs or DAMPs) using a variety of pattern-recognition receptors (PRRs). One type of PRRs identified are nucleotide-binding oligomerization domain-like receptors (NLRs), specifically looking at NLRP3.[28]

**Figure 1.** *Potential Interaction between Leptin and NLRP3 Inflammasome in Obesity Pathogenesis*
*As fat cells enlarge when body weight increases (progress from lean to overweight to obese), oxygen availability to cells declines which leads to infiltration of type I macrophages. This in turn activates NLRP3 inflammsome and production of mature proinflammatory cytokines (IL-1β and IL-18) leading to inflammation*



When PAMPs or DAMPs are activated the NLRP3 interacts with the adapter protein apoptosis-associated speck-like protein (ASC). Then, the caspase recruitment domain (CARD) of ASC binds to the CARD domain on procaspase-1, forming the NLRP3 inflammasome.[28] This causes procaspase-1 self-cleavage, creating the active caspase-1, which leads to the conversion of IL-1β and IL-18 immature forms to their active forms that are secreted. NLRP3 inflammasome-activated IL-1β has a vital role in the development of obesity-induced insulin resistance (IR) and type 2 diabetes mellitus (T2DM).

Research involving the relationship between obesity and NLRP3 are working towards finding therapies to decrease obesity along with decreasing the expression of NLRP3. Research has found decreased NLRP3 and IL-1β expressions in subcutaneous adipose tissue (SAT) from T2DM patients after a year of calorie restriction and exercise-mediated weight loss. Scientists have also found that there is a relationship between nutrient excess and inflammation from the initiation of the NLRP3 inflammasome by dietary free fatty acids (FFAs) which are DAMPs. In mice research, scientists have found that high fat diets (HFDs) increase NLRP3 expression in AT, but found that calorie-restricted diets will often decrease the expression of this gene.[28] Further research will be needed to find a solution for the human model, but in mice models, the ablation of NLRP3 protected the mice against HFD-induced obesity and IR as well as decreasing the blood glucose and insulin levels.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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