

## THE RELATIONSHIPS BETWEEN MICROBIOTA AND EXERCISE

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Review paper

### Abstract

The gut microbiota consists of trillions of microorganisms of different species that produces several signaling molecules of a hormonal nature which are released into the blood stream and act at distal sites. Gut microorganisms significantly affect host nutrition, metabolic function, immune system, and redox levels, and may be modulated by several environmental conditions, including physical activity. Athletes have varying gut microbiota compositions that appear to reflect the activity level of the host in comparison to sedentary people. The present review provides an overview of how gut microbiota may have a key role in controlling the oxidative stress and inflammatory responses as well as improving metabolism and energy expenditure during intense exercise.

**Key words:** microbiota, nutrition, sport, athletes, exercise, polyphenols.

### Introduction

The gut microbiota (MB) is an ecosystem consisting of bacteria, archaea, viruses, protists and fungal communities living in the human gut. Over the last 10-15 years, understanding of the composition and functions of the human gut MB has increased exponentially. To a large extent, this has been due to new "omic" technologies that have facilitated large-scale analysis of the genetic and metabolic profile of this microbial community, revealing it to be comparable in influence to a new organ in the body and offering the possibility of a new route for therapeutic intervention. It could also be considered as an immune system: a collection of cells that work in unison with the host, which can promote health but sometimes also cause the disease.

The commensal human gut MB has become the focus of interest from several disciplines, primarily because of its contribution to health and risk of disease throughout life. The changing composition of the MB is linked with changes in human behavior. Many of the elements of a modern lifestyle, particularly in early life, influence the composition of the MB. Disturbances of the MB at various ages may confer disease risk (Kim & Jazwinski, 2018). The MB may also be a risk or protective factor in relation to immunoallergic and metabolic disorders. Thus, a signaling network among the MB, host immunity and host metabolism has become evident, with diet influencing each component of this triad (Clarke et al, 2014).

The microbiota-host relationships could stimulate the energy metabolism, hydration, oxidative stress, and inflammation in the gastrointestinal tract. Moreover, food as prebiotics, probiotics, or other functional foods could modify the MB composition and improve both overall health (i.e., improving the situations of the intestinal epithelium and the immune system reply) and performance (i.e., improving energy availability from diet and

controlling the inflammation levels in athletes) (Mach & Fuster-Botella, 2017).

### Current understanding of the gut microbiota

Human beings, comparable to other higher organisms, live in symbiosis with their coevolved MB. The human digestive tract is inhabited by numerous microorganisms. The total estimated number of gut microorganisms is somewhere between  $10^{13}$  and  $10^{14}$ , hovering around the total estimated number of human body cells ( $3\sim 4\times 10^{13}$ ). Bacteria outnumber all other domains of gut microbes, and the total number of species found in the gut MB is valued to be about 500 ~1,000. (Sender et al, 2016). The majority of the human microorganisms reside in the gastrointestinal tract, where, besides cooperating to the digestion, they perform numerous other functions that are essential for the human host. These functions include the production of vitamins, education of the immune system, communication with the intestinal cells, and modulation of the host's behavior (Rajilić-Stojanović & de Vos, 2014).

In the period of the gastrointestinal MB research, lasted from the early seventies till the molecular revolution in the beginning of this century, it was recognized that the MB in the gastrointestinal tract is dominated by bacterial species (Rajilić-Stojanović & de Vos, 2014). The most populous bacterial phyla, constituting more than 90% of the gut MB, are *Bacteroidetes* and *Firmicutes*. The remainder consists of many species in other phyla in lower abundance, such as *Actinobacteria* and *Verrucomicrobia*. These microorganisms inhabit the human gut and form a complex community interacting with each other and with the host, some of which may provide significant metabolites and functions for healthy aging. The gut MB promotes digestion and food absorption for host energy production, whereas in the colon, complex

carbohydrates are digested and subsequently fermented into short chain fatty acids (SCFAs) such as n-butyrate, propionate, and acetate. Propionate and acetate are carried in the bloodstream to a variety of different organs where they are used as substrates for energy metabolism, particularly by the hepatocyte cells, which use propionate for gluconeogenesis (Allen et al, 2017).

The gut MB also plays an important role in the function and induction of the host immune system, protection from pathogens, and stimulation and maturation of epithelial cell (Figure 1).

Dietary composition effects the composition of gut MB: diets with a low quantity of fiber and rich in refined carbohydrates and fat produce a decrease in community diversity with alterations in structure and activity of the microorganisms. Apart from diet, exercise is considered as one of the main environmental motives possibly influencing gut MB composition in humans and animals (Donati Zeppa et al. 2019).

Numerous environmental factors shape the gut MB; even if a dominant role is played by diet, physical exercise is also emerging as an important modulator. Understanding the action of exercise on gut MB composition and structure is still in its infancy and the meaning of MB on exercise adaptation remains unknown, but a few researches have shown the impact exercise has on the gut MB configuration (Mach & Fuster-Botella, 2017). Endurance athletes present a high prevalence of upper respiratory tract infections and gastrointestinal troubles, containing amplified permeability of the gastrointestinal epithelial wall, also called "leaky gut", interference of mucous thickness and higher rates of bacterial translocation.

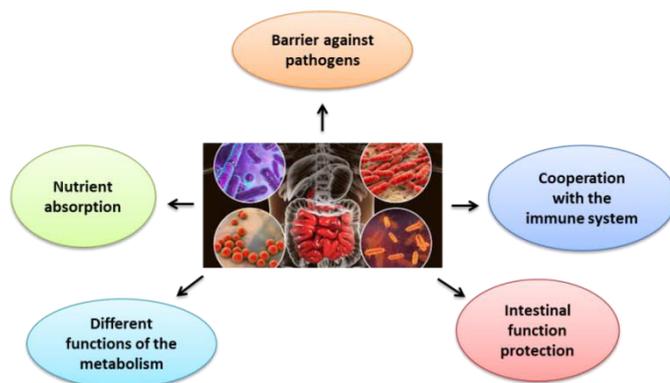


Figure 1. Possible protective effects of microbiota

### The relationships between microbiota and exercise.

Although little is known about how the gut MB may contribute to an individual's exercise performance, accumulating literature shows that exercise alone induces modifications in the gut MB composition (Clark & Mach, 2016). The gut bacterial population is modulated by gender, genetics, age, and

ethnicity, i.e., non-modifiable factors, and by modifiable factors such as host health, physical activity, diet, and eventual antibiotic therapies. Physical exercise is linked with the positive modulation of gut MB biodiversity; the potential mechanisms by which exercise might alter the gut microbiome have been investigated in animal and human studies (Donati Zeppa et al. 2019).

The modifications of gut MB induced by physical exercise are due to the gut transit time, the modification of the bile acids profile, the production of SCFAs via AMPK activation, the modulation of the Toll-Like Receptors signaling pathway, immunoglobulin A (IgA), the number of B and CD4+ T cells, and finally, to the weight loss (Donati Zeppa et al. 2019). Furthermore, regular exercise reduces the heat shock proteins' response to heat stress, preventing the breakdown of tight junction proteins between intestine epithelial cells. Thus, the exercise represents a hormetic stressor to the gut that stimulates beneficial adaptations and improves the long-term resilience of the gut barrier (Donati Zeppa et al. 2019).

The abundance of taxa involved in energy and carbohydrate metabolism, such as *Prevotella* and *Methanobrevibacter smithii*, were found to be significantly higher in professional than amateur cyclists, and were correlated with the frequency of training (Petersen et al., 2017). These results provide a framework for common constituents of the gut community in individuals who follow an exercise-rich lifestyle. These data also suggest how certain organisms such as *M. smithii* may beneficially influence the metabolic efficiency of the gut community in professional cyclists due to synergistic metabolic cross-feeding events (Petersen et al., 2017).

Physical activity based on long-distance running led to significant increase in the *Coriobacteriaceae* family. Notably, this bacterial family, along with others, is involved in the conversion of scarcely absorbed dietary polyphenols to bioavailable and bioactive derivatives (Braune & Blaut, 2016).

A recent observational study comparing the fecal bacterial profile of male elite rugby players with non-athlete healthy subjects showed that athletes had lower levels of *Bacteroidetes* and greater amounts of *Firmicutes* than controls. Since extremes of exercise often accompany extremes of diet, Clarke et al. addressed the issue by studying professional athletes from an international rugby union squad. Compositional analysis of the MB was explored and each participant completed a detailed food frequency questionnaire. Athletes and controls differed significantly with respect to plasma creatine kinase (a marker of extreme exercise), and inflammatory and metabolic markers. More importantly, athletes had a higher diversity of gut micro-organisms, which in turn positively correlated with protein consumption and creatine kinase. The authors concluded that your results provide evidence for a beneficial impact of exercise on gut

MB diversity but also indicate that the relationship is complex and is related to accompanying dietary extremes (Clarke et al, 2014).

The physiological and biochemical demands of intense exercise elicit both muscle-based and systemic responses. The main adaptations to endurance exercise include the correction of electrolyte imbalance, a decrease in glycogen storage and the increase of oxidative stress, intestinal permeability, muscle damage, and systemic inflammatory response. Adaptations to exercise might be influenced by the gut MB, which plays an important role in the production, storage, and expenditure of energy obtained from the diet as well as in inflammation, redox reactions, and hydration status (Mach & Fuster-Botella, 2017). Literature supports the hypothesis that intestinal MB might be able to provide a measureable, effective marker of an athlete's immune function and that microbial composition analysis might also be sensitive enough to detect exercise-induced stress and metabolic disorders (Mach & Fuster-Botella, 2017). Again, it is important to highlight that human gut MB composition remains relatively stable over time, exhibiting resilience to perturbations, or returning totally or partially to the previous composition after stimulus cessation. The resilience to perturbations implies that positive changes in exercise and dietary habits aimed at inducing positive effects on the MB need to be maintained for a long period to be effective (Donati Zeppa et al., 2019).

The current evidence supports the role of exercise as a significant behavioral factor that can affect qualitative and quantitative changes in the gut microbial composition with benefit to the host. Exercise appears to be able to enrich MB diversity, increase the *Bacteroidetes-Firmicutes* ratio, and stimulate the proliferation of bacteria which can modulate mucosal immunity, recover barrier functions, and stimulate bacteria capable of producing molecules that protect against gastrointestinal syndromes. Recent studies provide further evidence for a role of exercise in shaping the MB, with elite runners having a greater abundance of *Veillonella* that appears to confer a metabolic advantage for endurance exercise by converting exercise-induced lactate to propionate. Pre-clinical studies with *Veillonella* show a 13% increase in endurance performance. It is likely that the diverse, metabolically favorable intestinal MB evident in the elite athlete is the cumulative manifestation of many years of high nutrient intake and high degrees of physical activity and training throughout youth, adolescence and during adult participation in professional sports (Jäger et al., 2019).

After analyzing the gut MB composition of the participants of the American Gut Project, it was concluded that increasing moderate exercise frequency from never to daily causes greater diversity among the *Firmicutes* phylum, which contribute to a healthier gut environment.

Additionally, gut MB can improve some of the other exercise-induced disturbances in the gastrointestinal tract like oxidative stress, and hydration levels (Mach & Fuster-Botella, 2017).

### Microbiota and Exercise-Induced Stress

Athletes are subjected to multi-stress conditions of regular, intensive, and/or prolonged exercise routines. High-intensity activity not supported by an adequate training level, or overtraining syndrome, may be a stressor for the organism and may also have a negative result on gut MB. This is in agreement with the hormetic properties of reactive oxidative species (ROS) (D'Angelo & Rosa, 2020) generated by exercise and by specific commensal gut MB. Oxidative stress is a condition, which has been observed during ageing, under certain pathological conditions (D'Angelo et al, 2012; D'Angelo et al, 2013), and a number of studies have revealed that it is also related to contractile activity (D'Angelo & Rosa, 2020a).

Numerous species of human commensal gut bacteria are capable of generating low levels of ROS, which may contribute to sharpening the beneficial effects promoted by normal MB. Modulation of ROS-mediated signaling may occur during quantitative or qualitative changes in the composition of gut MB following rapid dietary changes, antibiotic therapy, or probiotic intake: These modulations may consequently modify and/or reduce the generally positive influence of microbiota-derived ROS. Changing from a "beneficial" to a "detrimental" response will depend on many variables, which also include the duration and intensity of muscle effort and the overall antioxidant status of the organism (Clark & Mach, 2017).

The basic principle in training theory is to push athletes to increase their training volume and intensity to the limits to maximize their performance. High-intensity exercise, especially if not proportional to training level, has a profound impact on oxidative stress, muscle damage, systemic inflammation, and immune responses. Excessive exercise and inadequate recovery cause physical and psychological stress, that are interrelated and lead to performance decline, fatigue, insomnia, anxiousness, inflammation, and immunosuppression (Clark & Mach, 2016).

From the gut MB perspective, an excessive exercise induces a stress that increases intestinal permeability, which might lead bacteria and their toxic products to enter into the bloodstream and activate systemic inflammation. Exercise alters the turnover of molecules involved in metabolic patterns and stimulates the release of neuroendocrine hormones interacting with the gut directly or indirectly through the immune system. Alongside the adaptation of gut MB to exercise training, intestinal microbiota's influence on exercise performance should be considered (Clark & Mach, 2016).

## The effect of diet on microbiota

Nutritional support (D'Angelo & Tafuri, 2020; D'Angelo & Cusano, 2020, D'Angelo et al, 2019), has the potential to partially mitigate the exercise-induced changes without interfering with the signaling activities necessary for training adaptations (Motti et al, 2018; Meccariello et al, 2020).

Nutrition has a very special influence on the microbiome; food components that are indigestible to human enzymes (e.g., fibers) provide substrates for microbial metabolism in the gut. Because bacteria are specialized in the fermentation of various substrates, complex diets can lead to a number of metabolic products, especially vitamins and SCFAs, which are vital to human health (Zopf et al, 2018).

Diet is an established modulator of gut MB composition, with significant change reported within 24 h of a dietary modification. Various food components, dietary patterns, and nutrients all have the potential to alter considerably the growth of different gut microbial populations. Protein intake appears to be a strong modulator of the microbiota, with whey protein showing some potential benefits. Carbohydrates are well known for their profound effect on the gut MB, with increased intake of dietary fiber associated with microbial richness and/or diversity. Increased fat intake may promote higher concentrations of bile-tolerant bacteria. (Jäger et al., 2019)

In researching the human gut microbiota, it is difficult to examine exercise and diet separately as this relationship is compounded by changes in dietary intakes that often are associated with physical activity (Figure 2). Furthermore, comparing the microbiota of non-athletes to athletes and ascribing any observed differences to exercise alone is not advisable. Athletes generally consume a diet that differs from the general population that has implications for the composition of the gut MB (Jäger et al., 2019).

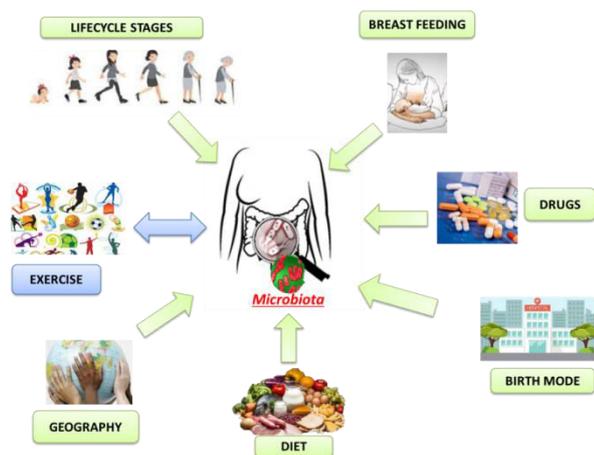


Figure 2. Microbiota conditioning factors.

The composition of the diet and food-associated microbes in athletes can condition the composition of gut microorganisms able to increase energy metabolism, oxidative stress, and systemic inflammation status, and the microbial species that synthesize toxic metabolites from protein degradation. The recurrent incidence of the above situations in athletes represents the basis for today's popularity of antioxidant-containing sport nutrition supplements. A key category among antioxidants are polyphenols (D'Angelo, 2020), a wide group of natural plant-derived compounds, commonly included in supplements intended for sport use (i.e., berry extracts, etc.) and are also known to interact with microbiota. Particularly, polyphenols are phytochemicals, which can act as pro-oxidant (D'Angelo et al, 2019a; Martino et al, 2018; D'Angelo et al, 2017; D'Angelo et al, 2012a; Boccellino et al, 2020) or as anti-oxidant (Zappia et al, 2010; D'Angelo & Sammartino 2015) effects. In fact, polyphenols' biological activity is not limited to their antioxidant capacity (del Monaco et al, 2015; Vuoso et al, 2020); indeed, they exert other effects, which may be beneficial in supporting sports practice (D'Angelo 2020a). For example, pomegranate polyphenols are renowned for their anti-inflammatory and anti-infective activity (D'Angelo & Rosa, 2020a). Once taken orally, polyphenols have been shown to interact with MB at different levels. The 'prebiotic-like' effects of polyphenols have been observed using both *in vitro* and *in vivo* models, and polyphenols-rich foods were shown to modulate gut microbiota, stimulating the growth of beneficial bacteria such as *Lactobacilli* and *Bifidobacteria*.

In consideration of the positive interactions between gut microbiota and polyphenols, Marchesi *et al.* presented the concept of the "three P's" for gut health: The three P's stand for prebiotics, probiotics, and polyphenols. Hence polyphenols were promoted at the same biological level as prebiotics (Marchesi et al., 2016). Unfortunately, the reduced oral bioavailability is a severe limit to the potential beneficial actions of these phytochemicals. On the whole, it can be concluded that the reciprocally positive interactions between polyphenols and MB might converge toward the promotion of beneficial conditions supporting athletes in sport practice. Instead, probiotics are live non-pathogenic microorganisms, which, when administered in adequate amounts, confer microbial balance, particularly in the gastrointestinal tract. They have received a renewed interest in the past years in athletes, since they can contribute to general health and, indirectly, sustain and/or improve performance. Interestingly probiotics are known to promote a development of mood state and disorders and it is conceivable that the probiotic-mediated improvement of mood status may indirectly and positively impact on athlete's conditions. Some authors reported beneficial actions of gut MB health on mood disorders which impact on performance, such as anxiety and depression (Bravo et al., 2012).

## Conclusion

In conclusion, intensity, timing, and type of exercise can influence the composition of gut MB. It has been demonstrated that physical activity performed at low levels, but continuously, can increase MB diversity, improving the metabolic profile and immunological responses of the subjects, while acute strenuous exercise may cause deleterious effects on the athletes' microbiota and his general health. Gut MB composition can influence training adaptation and athletic performance: indeed, it is involved in the metabolism and delivery of nutrients, hormones, and vitamins important to sustain exercise. On the whole, good gut MB conditions positively affect athletes' health with favorable consequences on their training adaptation and performances.

Some supplements intended for sport use contain probiotics, proteins, polyphenols, and other molecules which are known to interact with microbiota at multiple levels, for example in promoting the selection and growth of healthy specific microorganisms, and limiting the bacterial species that produce toxic metabolites.

To this end, the design of methods, including adequate and rational supplementation, capable of implementing the richness and metabolic capacity of the microbiota could be a useful strategy to improve athletes' health, training response, adaptations, and ultimately, performance; the interactions between exercise, gut microbiota, and sport nutritional supplements are still largely unknown, and should be a research focus in the near future.

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## References

- Allen, J.M., Mailing, L.J., Niemi, G.M., Moore, R., Cook, M.D., White, B.A., Holscher, H.D., & Woods, J.A. (2018). Exercise Alters Gut Microbiota Composition and Function in Lean and Obese Humans. *Medicine and science in sports and exercise*, 50(4), 747–757.
- Boccellino, M., Quagliuolo, L., & D'Angelo, S. (2020). Annurca Apple Polyphenols' Effects in Combination with Cisplatin on A549 Cells. *Current Nutrition & Food Science*, 16(1).
- Braune, A., & Blaut, M. (2016). Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut microbes*, 7(3), 216–234.
- Bravo, J.A., Julio-Pieper, M., Forsythe, P., Kunze, W., Dinan, T.G., Bienenstock, J., Cryan, J.F. (2012). Communication between gastrointestinal bacteria and the nervous system. *Current Opinion in Pharmacology*, 12, 667–672.
- Clarke, S.F., Murphy, E.F., O'Sullivan, O., Lucey, A.J., Humphreys, M., Hogan, A., Hayes, P., O'Reilly, M., Jeffery, I.B., Wood-Martin, R., Kerins, D.M., Quigley, E., Ross, R.P., O'Toole, P.W., Molloy, M.G., Falvey, E., Shanahan, F., & Cotter, P.D. (2014). Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*, 63(12), 1913–1920.
- Clark, A., & Mach, N. (2016). Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. *Journal of the International Society of Sports Nutrition*, 13, 43.
- Clark, A., & Mach, N. (2017). The Crosstalk between the Gut Microbiota and Mitochondria during Exercise. *Frontiers in physiology*, 8, 319.
- D'Angelo S. (2020). Current Evidence on the Effect of Dietary Polyphenols Intake on Brain Health. *Current Nutrition & Food Science*, 17.
- D'Angelo S. (2020). aPolyphenols: Potential beneficial effects of these phytochemicals in athletes. *Current Sports Medicine Reports*, 19(7); 260-265.
- D'Angelo, S. & Cusano, P. (2020). Adherence to the Mediterranean diet in athletes. *Sport Science*, 13 (Suppl 1), 58-63.
- D'Angelo, S., La Porta, R., Napolitano, M., Galletti, P., Quagliuolo, L., & Boccellino, M.R. (2012)a. Effect of Annurca apple polyphenols on human HaCaT keratinocytes proliferation. *Journal of Medicinal Food*, 15(11), 1024-1031.
- D'Angelo, S., Lembo, S., Flora, F., De Bonis, M.L., Balato, A., Ayala, F., Balato, N., Galletti, P., & Zappia, V. (2012). Abnormal isoaspartyl residues in erythrocyte membranes from psoriatic patients. *Archives of Dermatological Research*, 304(6), 475-479.
- D'Angelo, S., Martino E., & Cacciapuoti, G. (2019)a. Effects of Annurca Apple (*Malus pumila* cv Annurca) Polyphenols on Breast Cancer Cells. *Current Nutrition & Food Science*, 15(7), 745-751.
- D'Angelo, S., Martino, E., Ilisso, C.P., Bagarolo, M.L., Porcelli, M. & Cacciapuoti, G. (2017). Pro-oxidant and pro-apoptotic activity of polyphenol extract from Annurca apple and its underlying mechanisms in human breast cancer cells. *International Journal of Oncology*, 51,939-948.
- D'Angelo, S. & Rosa, R. (2020). Oxidative stress and sport performance. *Sport Science*, 13 (Suppl 1), 18-22.
- D'Angelo, S. & Rosa, R. (2020)a. The impact of supplementation with Pomegranate fruit (*Punica Granatum* L.) on sport performance. *Sport Science*, 13 (Suppl 1), 29-37.
- D'Angelo S, & Sammartino D. (2015). Protective effect of Annurca apple extract against oxidative damage in human erythrocytes. *Current Nutrition & Food Science*, 11 (4), 248-256.
- D'Angelo, S., Scafuro, M., & Meccariello, R. (2019). BPA and Nutraceuticals, Simultaneous Effects on Endocrine Functions. *Endocrine, Metabolic & Immune Disorders - Drug Targets*, 19(5), 594-604.

- D'Angelo, S., Trojsi, F., Salvatore, A., Daniele, L., Raimo, M., Galletti, P., & Monsurrò, M.R. (2013). Accumulation of altered aspartyl residues in erythrocyte membrane proteins from patients with sporadic amyotrophic lateral sclerosis. *Neurochemistry International*, 63 (6), 626-34.
- D'Angelo, S. & Tafuri, D. (2020). Nutraceutical: their role in improving sports performance. *Sport Science*, 13 (Suppl 1), 7-12.
- del Monaco, G., Officioso, A., D'Angelo, S., La Cara, F., Ionata, E., Marcolongo, L., Squillaci, G., Maurelli, L., & Morana, A. (2015). Characterization of extra virgin olive oils produced with typical Italian varieties by their phenolic profile. *Food Chemistry*, 184, 220-228.
- Donati Zeppa, S., Agostini, D., Gervasi, M., Annibalini, G., Amatori, S., Ferrini, F., Sisti, D., Piccoli, G., Barbieri, E., Sestili, P., & Stocchi, V. (2019). Mutual Interactions among Exercise, Sport Supplements and Microbiota. *Nutrients*, 12(1), 17.
- Jäger, R., Mohr, A.E., Carpenter, K.C., Kerksick, C.M., Purpura, M., Moussa, A., Townsend, J.R., Lamprecht, M., West, N.P., Black, K., Gleeson, M., Pyne, D.B., Wells, S.D., Arent, S.M., Smith-Ryan, A.E., Kreider, R.B., Campbell, B.I., Bannock, L., Scheiman, J., Wissent, C.J., Antonio, J. (2019). International Society of Sports Nutrition Position Stand: Probiotics. *Journal of the International Society of Sports Nutrition*, 16(1), 62.
- Kim, S., & Jazwinski, S.M. (2018). The Gut Microbiota and Healthy Aging: A Mini-Review. *Gerontology*, 64(6), 513-520.
- Mach, N., & Fuster-Botella, D. (2017). Endurance exercise and gut microbiota: A review. *Journal of sport and health science*, 6(2), 179-197.
- Marchesi, J.R., Adams, D.H., Fava, F., Hermes, G.D., Hirschfield, G.M., Hold, G., Quraishi, M.N., Kinross, J., Smidt, H., Tuohy, K.M., Thomas, L.V., Zoetendal, E.G., & Hart, A. (2016). The gut microbiota and host health: a new clinical frontier. *Gut*, 65(2), 330-339.
- Martino, E., Vuoso, D.C., D'Angelo, S., Mele, L., D'Onofrio, N., Porcelli, M., & Cacciapuoti, G. (2019). Annurca apple polyphenol extract selectively kills MDA-MB-231 cells through ROS generation, sustained JNK activation and cell growth and survival inhibition. *Scientific Reports*, 10 (1), 13045.
- Meccariello, R., Santoro, A., D'Angelo, S., Morrone, R., Fasano, S., Viggiano, A., & Pierantoni, R. (2020). The Epigenetics of the Endocannabinoid System. *International Journal of Molecular Sciences*, 21(3), 1113.
- Motti, M.L., D'Angelo, S., & Meccariello, R. (2018). MicroRNAs, Cancer and Diet: Facts and New Exciting Perspectives. *Current Molecular Pharmacology*, 11, 90-96.
- Petersen, L.M., Bautista, E.J., Nguyen, H., Hanson, B.M., Chen, L., Lek, S.H., Sodergren, E., & Weinstock, G.M. (2017). Community characteristics of the gut microbiomes of competitive cyclists. *Microbiome*, 5(1), 98.
- Rajilić-Stojanović, M., & de Vos, W.M. (2014). The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS microbiology reviews*, 38(5), 996-1047.
- Sender, R., Fuchs, S., & Milo, R. (2016). Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS biology*, 14(8), e1002533.
- Vuoso, D.C., Porcelli, M., Cacciapuoti, G., & D'Angelo, S. (2020). Biological activity of MelAnnurca flesh apple biophenols. *Current Nutrition & Food Science*. 16, (1).
- Zappia, V., Galletti, P., Manna, C., D'Angelo, S., Napoli, D., De Bonis, M.L., & Capasso, G. (2010). Effects of Hydroxytyrosol on Cyclosporine Nephrotoxicity. In: Victor R. Preedy and Ronald Ross Watson, editors, *Olives and Olive Oil in Health and Disease Prevention*. Oxford: Academic Press, (pp. 1245-1252).
- Zopf, Y., Reljic, D., & Dieterich, W. (2018). Dietary Effects on Microbiota-New Trends with Gluten-Free or Paleo Diet. *Medical sciences (Basel, Switzerland)*, 6(4), 92.

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