HOW POLYPHENOLS CONTRIBUTE TO OPTIMAL HEALTH AND IMMUNE RESPONSE

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June 16, 2020

There is no question scientific testing shows that a diet full of natural foods is our best defense against pathogens. Contained within these plants are phytochemicals. One class of phytochemicals are polyphenols. They are a large group of heterogeneous compounds characterized by hydroxylated phenyl moieties, and are found mostly in plants, including fruits, vegetables, nuts, seeds, and cereals, as well as natural nutraceuticals such as MLG-50™ fulvic mineral powder, or beverages such as tea, coffee and wine [1].

Polyphenols have become an intense focus of research due to their potential benefits to health, particularly in relation to the prevention of cancer [2, 3] and cardiovascular diseases [4, 5].

Their suggested beneficial effects are anticarcinogenic [6, 7], antiatherogenic [8, 9], antiulcer [10], antithrombotic [11, 12], anti-inflammatory [13, 14], antiallergenic [15, 16], anticoagulant [17], immune modulating [18], antimicrobial [19, 20], vasodilatory [21], and analgesic activities [22].

To achieve these health benefits, polyphenols require in situ processing by the gut microbiota to be transformed into a potentially more bioactive, low-molecular-weight metabolite [23]. Faria et al. (2014) reviewed that total polyphenol absorption in the small intestine is relatively low (5%–10%) in comparison to other macro- or micronutrients. The remaining 90%–95% of polyphenols transit to the large intestinal lumen and accumulate in the millimolar range. From the lumen, together with conjugates excreted from bile, they are exposed to the enzymatic activities of the gut microbiota [24]. The microbiota that colonize the distal regions of the colon represent the highest concentration of microorganisms found in human body, as well as the most diverse [25]. It is known that the human gut has an ecosystem of around 10^{13}–10^{14} bacterial cells, an estimate 10 times that of human somatic cells [26]. In addition, the aggregate microbial genome (i.e., microbiome) is predicted to contain more than three million genes, or 150 times more than human genes [27].

The reciprocal relationship between polyphenols and gut microbiota may contribute to host health benefits. The need to clarify the molecular mechanisms underlying the observed prebiotic enrichment of beneficial bacteria and antimicrobial activities against gut pathogenic bacteria is apparent [23, 29-33].

Commensals residing in the gut may improve health by protecting against gastrointestinal disorders and pathogens, processing nutrients, reducing serum cholesterol, strengthening intestinal epithelial tight cell junctions, producing antibodies, increasing mucus secretion and modulating intestinal immune response through cytokine stimulus [34, 35].

Furthermore, the gut microbiota bio-transforms polyphenols into metabolites that may have greater biological activity than their precursor structures [23]. In short, the gut microbiota is essential for the maintenance of intestinal homeostasis and overall optimal human health [28].

Gut Health, Inflammation and Immunity

Gut microbiota (GM) plays several crucial roles in host physiology and influences several relevant functions. In more than one respect, it can be said that " you feed your microbiota and it feeds you"[36].

GM diversity is affected by diet. Our GM influences metabolic and immune functions of the host's physiology. Consequently, an imbalance of GM, or dysbiosis, may be the cause or at least may lead to the progression of various pathologies such as infectious diseases, gastrointestinal cancers, inflammatory bowel disease, and even obesity and diabetes. Therefore, GM is an appropriate target for nutritional interventions to improve health.

For this reason, phytochemicals, such as polyphenols (e.g. fulvic acids) that can influence GM have recently been studied as adjuvants for the treatment of obesity, inflammatory diseases and overall immune health.

Phytochemicals include prebiotics and probiotics, as well as several chemical compounds such as polyphenols and derivatives, carotenoids, and thiosulfates. The largest group of these comprises polyphenols, which can be subclassified into four main groups:

1. flavonoids (including eight subgroups)
2. phenolic acids (such as curcumin)
3. stilbenoids (such as resveratrol)
4. and lignans

Once nutrients and nutraceuticals (e.g. polyphenols) have been incorporated into the body, the gut environment is essential in maintaining homeostasis; in this sense, like GM, the surface of the intestinal mucous membrane plays a fundamental role in the preservation of homeostasis. Consequently, the correct functioning of its permeability is of great importance [36].

Several pathologies, as well as susceptibility to metabolic diseases, have been linked to alterations in the permeability of the intestinal barrier. Humans possess two interacting genomes: their own complete set of DNA and that of the microbiome genome (e.g. the entire genome of each of the multitude of microbes that colonize our small and large intestine) the majority of which resides in the gut, in the layer of mucin glycoproteins (mucus) produced by the cells called goblet cells [37].

The microbiome provides products such as vitamins and nutrients to human cells, thereby establishing a beneficial ecosystem for host physiology and preventing the proliferation of pathogens [38]. Thus, a symbiotic relationship is established between both genomes, through the expression of pattern recognition receptors (PRRs) that sense the presence of intestinal microbiota, through the microbe-associated molecular patterns (MAMPs).

This communication between the two genomes results in the accuracy of the mucosal barrier function, by regulating the production of its components: mucus, antimicrobial peptides, IgA and IL-22, facilitating homeostasis, and immune health [38-40]. Therefore, GM and the human host influence each other by exchanging their metabolic active molecules [41], working together, as a hologenome, to maintain mutual health [42].

Polyphenols and Cytokine Modulation

Cytokines are important mediator proteins, essential in networking communication for the immune system. Cytokines can be produced by lymphocytes (lymphokines), or monocytes (monokines) with pro-inflammatory and anti-inflammatory effects. Cytokines with chemotactic activities are termed chemokines. The equilibrium between pro-inflammatory cytokines (IL-1β, IL-2, TNFα, Il-6, IL-8, IFN-γ . . .) and anti-inflammatory cytokines (IL-10, IL-4, TGFβ) are thought to be an important parameter in immune response homeostasis and inflammation underlining many disease states [43].

In vivo and *in vitro* studies demonstrate that polyphenols affect macrophages by inhibiting multiple key regulators of inflammatory response such as the inhibition of TNFα, IL-1β, and IL-6 [44]. Flavonoids, as well, have an important anti-inflammatory effect by influencing cytokines' secretion. Several flavonoids are found to inhibit the expression of various pro-inflammatory cytokines and chemokines like TNFα, IL-1β, IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1) in multiple cell types such as LPS-activated mouse primary macrophages, activated human mast cell line, activated human astrocytes, human synovial cells, and human peripheral blood mononuclear cells [45-50]. Modulation of inflammatory cytokines is one of many common mechanisms by which polyphenols in general exert their immunomodulatory effects.

Polyphenols, Inflammation, and Modulation of the NFκB Signaling Pathway

NF-κB or nuclear factor kappa-light-chain-enhancer of activated B cells is a complex protein that plays a key role in deoxyribonucleic acid (DNA) transcription, cytokine production and cell survival. It controls immune, inflammation, stress, proliferation and apoptotic responses of a cell to multiple stimuli [51].

The expression of a large number of genes involved in inflammation is controlled by NF-κB and the inhibition of NF-κB can be of a great benefit in controlling inflammatory conditions [52]. Several polyphenols modulate NF-κB activation and reduce inflammation[53, 54]. For example, genistein or quercetin repress LPS-induced activation of NF-κB in monocytes and reduces the inflammation by inhibiting NF-κB activation upon adenosine monophosphate activated protein kinase stimulation in LPS-stimulated macrophages [55, 56]. Flavonoids can modulate NF-κB activation cascade at early phases by affecting IKK activation and regulation of oxidant levels or at late phases by affecting binding of NF-κB to DNA in T-cells [57]. Hydroxytyrosol, and resveratrol inhibit NF-κB activation, and the expression of VCAM-1 in LPS-stimulated human umbilical vein endothelial cells [58].

In summary, polyphenols can modulate NF-κB activation cascade at different steps such as by affecting IKK activation and regulating of the oxidant levels or by affecting binding of NF-κB to DNA leading to an important anti-inflammatory effect responsible for their potential value in treating chronic inflammatory conditions (Figure 1).

Polyphenols, Oxidative Stress, and Inflammation

Higher production of reactive oxygen species (ROS) is associated with oxidative stress and protein oxidation [59]. Subsequently inflammatory molecules and different inflammatory signals (i.e., peroxiredoxin2) are triggered by protein oxidations [60]. Furthermore, overproduction of ROS can prompt tissue injury that initiates the inflammatory process [61-65].

Therefore, the classical antioxidant actions of polyphenols undoubtedly contribute to their anti-inflammatory roles by interrupting the ROS-inflammation cycle (Figure 2). Polyphenols are known for their antioxidant activities; they scavenge a wide-ranging selection of ROS. Polyphenols can scavenge radicals and chelate metal ions, for example quercetin chelates iron ion [66]. They also inhibit multiple enzymes responsible of ROS generation [67]. In fact, free metal ions, as well as highly reactive hydroxyl radical release, is increased by the formation of ROS.

To the opposite, polyphenols are able to chelate metal ions like Fe^{2+}, Cu^{2+}, and free radicals which lead to a reduction of highly oxidizing free radicals in the body [68]. Transition metal ions, like Fe^{+2}, Cu^{2+}, Co^{2+}, Ti^{3+}, or Cr^{5+}, results in OH• formation from H_2O_2 [69, 70]. Curcumin is able to chelate transition metal (Cu^{2+} and Fe^{2+}) ions. Alike, EGCG and quercetin chelate Fe^{2+} (iron ion) [66]. Polyphenols like apocynin, resveratrol, and curcumin can inhibit NOX (NADPH oxidase) causing a reduction in the generation of O_2• during infections consecutively in endothelial cells in THP1-monocytes [71-73].

Additionally, polyphenols can attenuate the mitochondrial ATP synthesis by blocking the mitochondrial respiratory chain and ATPase. As a result, ROS production is diminished. Curcumin [74], EGCG [75], phenolic acids [76], capsaicin [77], quercetins [78], anthocyanins [78], and resveratrol analogs [79] inhibit xanthine oxidase. Thus, they reduce ROS production.

Polyphenols affect the activity of cyclooxygenase, lipoxygenase, and NOS (nitric oxide synthase) as per found in macrophages [80]. These enzymes are known to metabolize arachidonic acid and their inhibition moderates the production of key mediators of inflammation (prostaglandins, leukotrienes, and NO . . .) [80].

Polyphenols exert the anti-inflammatory action by different mechanisms: radical scavenging, metal chelating, NOX inhibition, tempering the mitochondrial respiratory chain, inhibition of certain enzymes involved in ROS production, like xanthine oxidase and upregulation of endogenous antioxidant enzymes.

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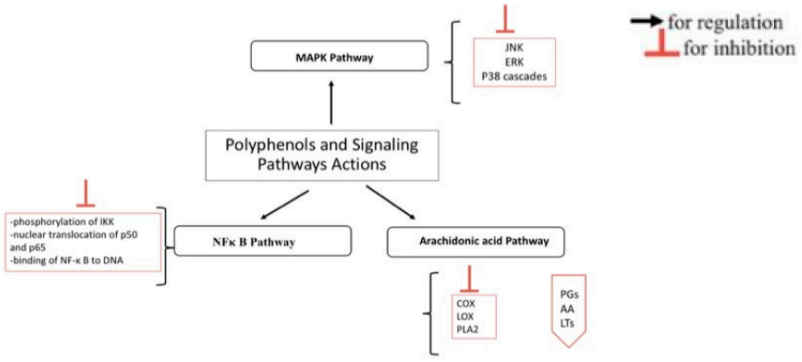

Figure 1. Potential points of action of polyphenols within inflammatory cascade. NF-κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; IKK: IkB-kinase; ERK: extracellular signal-related kinases; JNK: c-Jun amino-terminal kinases; p38 (or p38-MAPK): p38-mitogen-activated protein kinase; COX: cyclooxygenase; LOX: lipoxygenase; AA: arachidonic acid; PLA2: phospholipase A2; PGs: prostaglandins; LTs: leukotriens. For references see the text.

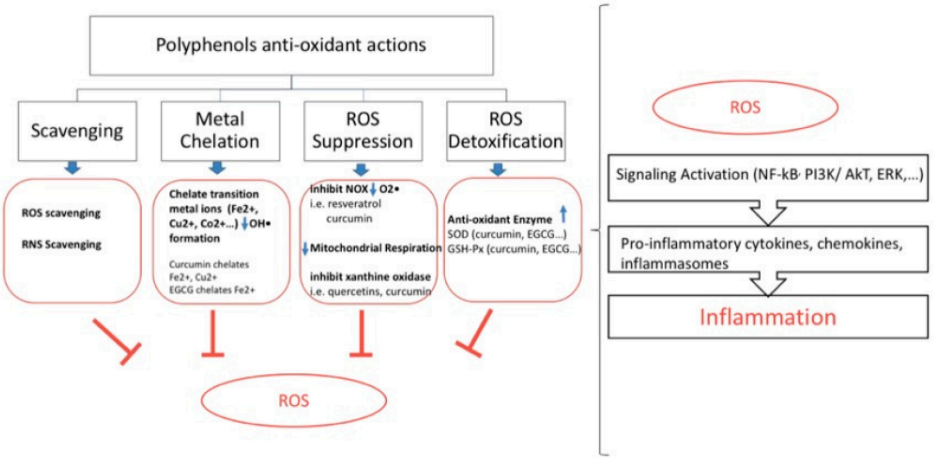

Figure 2. Key polyphenolic anti-oxidant actions in relation to anti-inflammation. Polyphenols scavenge radicals, chelate metal ions, inhibit ROS production and promote ROS detoxification. On the right panel ROS contribution to inflammation. ROS: reactive oxygen species; RNS: reactive nitrogen species; NOX: NADPH oxidase; SOD: superoxide dismutase; GSH-PX: glutathione peroxidase; ERK: extra-cellular signal regulated kinases; PI3K/AkT: phosphatidylinositide 3-kinases/protein kinase B; EGCG: epigallactocatechine gallate.

Conclusion

In conclusion, the vast number of published studies proved the immunomodulatory role of polyphenols *in vivo* and *in vitro*. Different underlying regulatory mechanisms are now well elucidated. These data highlighted here help demonstrate the promising role of polyphenols in prevention and therapy of diseases with underlining inflammatory conditions, including cancer, neurodegenerative diseases, obesity, type II diabetes, and cardiovascular diseases. It is generally believed that polyphenol activity is principally located in the gut where their immune-protective and anti-inflammatory activities are initiated and subsequently ensuring systemic anti-inflammatory effects. Since different polyphenols can have multiple intracellular targets, additional data is needed to determine the consequences of the interaction or the synergistic effects between multiple polyphenolic compounds or polyphenols and commonly used medications. Moreover, further *in vivo* and meta-analysis studies in humans are necessary to fully reveal the mechanisms of action of polyphenols in several physiological conditions in order to produce important insights into their prophylactic and therapeutic uses.

References

1. Puupponen-Pimiä, R., et al., *Development of functional ingredients for gut health.* Trends in Food Science & Technology, 2002. **13**(1): p. 3-11.
2. Chen, D., et al., *EGCG, green tea polyphenols and their synthetic analogs and prodrugs for human cancer prevention and treatment.* Adv Clin Chem, 2011. **53**: p. 155-77 https://www.ncbi.nlm.nih.gov/pubmed/21404918.
3. Weng, C.J. and G.C. Yen, *Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives.* Cancer Treat Rev, 2012. **38**(1): p. 76-87 https://www.ncbi.nlm.nih.gov/pubmed/21481535.
4. Kuriyama, S., et al., *Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study.* JAMA, 2006. **296**(10): p. 1255-65 https://www.ncbi.nlm.nih.gov/pubmed/16968850.
5. Mursu, J., et al., *Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study.* Br J Nutr, 2008. **100**(4): p. 890-5 https://www.ncbi.nlm.nih.gov/pubmed/18377681.
6. Jeong, W.Y., et al., *Determination of polyphenols in three Capsicum annuum L. (bell pepper) varieties using high-performance liquid chromatography-tandem mass spectrometry: their contribution to overall antioxidant and anticancer activity.* J Sep Sci, 2011. **34**(21): p. 2967-74 https://www.ncbi.nlm.nih.gov/pubmed/21898818.
7. Ogunleye, A.A., F. Xue, and K.B. Michels, *Green tea consumption and breast cancer risk or recurrence: a meta-analysis.* Breast Cancer Res Treat, 2010. **119**(2): p. 477-84 https://www.ncbi.nlm.nih.gov/pubmed/19437116.
8. Liu, L., et al., *The antiatherogenic potential of oat phenolic compounds.* Atherosclerosis, 2004. **175**(1): p. 39-49 https://www.ncbi.nlm.nih.gov/pubmed/15186945.
9. Mulvihill, E.E. and M.W. Huff, *Antiatherogenic properties of flavonoids: Implications for cardiovascular health.* Canadian Journal of Cardiology, 2010. **26**: p. 17A-21A.
10. Zakaria, Z.A., et al., *In vivo antiulcer activity of the aqueous extract of Bauhinia purpurea leaf.* J Ethnopharmacol, 2011. **137**(2): p. 1047-54 https://www.ncbi.nlm.nih.gov/pubmed/21802502.
11. Han, N., et al., *Antithrombotic activity of fractions and components obtained from raspberry leaves (Rubus chingii).* Food Chem, 2012. **132**(1): p. 181-5 https://www.ncbi.nlm.nih.gov/pubmed/26434278.

12. Tao, W.W., et al., *Antithrombotic phenolic compounds from Glycyrrhiza uralensis.* Fitoterapia, 2012. **83**(2): p. 422-5 https://www.ncbi.nlm.nih.gov/pubmed/22197642.
13. Beara, I.N., et al., *Comparative analysis of phenolic profile, antioxidant, anti-inflammatory and cytotoxic activity of two closely-related Plantain species: Plantago altissima L. and Plantago lanceolata L.* LWT - Food Science and Technology, 2012. **47**(1): p. 64-70.
14. Zimmer, A.R., et al., *Antioxidant and anti-inflammatory properties of Capsicum baccatum: from traditional use to scientific approach.* J Ethnopharmacol, 2012. **139**(1): p. 228-33 https://www.ncbi.nlm.nih.gov/pubmed/22100562.
15. Chung, S.-Y. and E.T. Champagne, *Reducing the allergenic capacity of peanut extracts and liquid peanut butter by phenolic compounds.* Food Chemistry, 2009. **115**(4): p. 1345-1349.
16. Schmitz-Eiberger, M.A. and M.M. Blanke, *Bioactive components in forced sweet cherry fruit (Prunus avium L.), antioxidative capacity and allergenic potential as dependent on cultivation under cover.* LWT - Food Science and Technology, 2012. **46**(2): p. 388-392.
17. Bijak, M., et al., *Anticoagulant effect of polyphenols-rich extracts from black chokeberry and grape seeds.* Fitoterapia, 2011. **82**(6): p. 811-7 https://www.ncbi.nlm.nih.gov/pubmed/21596108.
18. Schutz, K., et al., *Immune-modulating efficacy of a polyphenol-rich beverage on symptoms associated with the common cold: a double-blind, randomised, placebo-controlled, multi-centric clinical study.* Br J Nutr, 2010. **104**(8): p. 1156-64 https://www.ncbi.nlm.nih.gov/pubmed/20487584.
19. Silva, J.C., et al., *Antimicrobial activity, phenolic profile and role in the inflammation of propolis.* Food Chem Toxicol, 2012. **50**(5): p. 1790-5 https://www.ncbi.nlm.nih.gov/pubmed/22425940.
20. Xia, D., et al., *Phenolic compounds from the edible seeds extract of Chinese Mei (Prunus mume Sieb. et Zucc) and their antimicrobial activity.* LWT - Food Science and Technology, 2011. **44**(1): p. 347-349.
21. Mudnic, I., et al., *Antioxidative and vasodilatory effects of phenolic acids in wine.* Food Chemistry, 2010. **119**(3): p. 1205-1210.
22. dos Santos, M.D., et al., *Evaluation of the anti-inflammatory, analgesic and antipyretic activities of the natural polyphenol chlorogenic acid.* Biol Pharm Bull, 2006. **29**(11): p. 2236-40 https://www.ncbi.nlm.nih.gov/pubmed/17077520.
23. Selma, M.V., J.C. Espin, and F.A. Tomas-Barberan, *Interaction between phenolics and gut microbiota: role in human health.* J Agric Food Chem, 2009. **57**(15): p. 6485-501 https://www.ncbi.nlm.nih.gov/pubmed/19580283.
24. Faria, A., et al., *Interplay between anthocyanins and gut microbiota.* J Agric Food Chem, 2014. **62**(29): p. 6898-902 https://www.ncbi.nlm.nih.gov/pubmed/24915058.
25. Guinane, C.M. and P.D. Cotter, *Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ.* Therap Adv Gastroenterol, 2013. **6**(4): p. 295-308 https://www.ncbi.nlm.nih.gov/pubmed/23814609.
26. Cani, P.D. and N.M. Delzenne, *The role of the gut microbiota in energy metabolism and metabolic disease.* Curr Pharm Des, 2009. **15**(13): p. 1546-58 https://www.ncbi.nlm.nih.gov/pubmed/19442172.
27. Qin, J., et al., *A human gut microbial gene catalogue established by metagenomic sequencing.* Nature, 2010. **464**(7285): p. 59-65 https://www.ncbi.nlm.nih.gov/pubmed/20203603.
28. Arboleya, S., et al., *Establishment and development of intestinal microbiota in preterm neonates.* FEMS Microbiol Ecol, 2012. **79**(3): p. 763-72 https://www.ncbi.nlm.nih.gov/pubmed/22126419.
29. Tzounis, X., et al., *Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study.* Am J Clin Nutr, 2011. **93**(1): p. 62-72 https://www.ncbi.nlm.nih.gov/pubmed/21068351.
30. Queipo-Ortuno, M.I., et al., *Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers.* Am J Clin Nutr, 2012. **95**(6): p. 1323-34 https://www.ncbi.nlm.nih.gov/pubmed/22552027.
31. Rastmanesh, R., *High polyphenol, low probiotic diet for weight loss because of intestinal microbiota interaction.* Chem Biol Interact, 2011. **189**(1-2): p. 1-8 https://www.ncbi.nlm.nih.gov/pubmed/20955691.

32. Hervert-Hernández, D. and I. Goñi, *Dietary Polyphenols and Human Gut Microbiota: a Review.* Food Reviews International, 2011. **27**(2): p. 154-169.
33. Laparra, J.M. and Y. Sanz, *Interactions of gut microbiota with functional food components and nutraceuticals.* Pharmacol Res, 2010. **61**(3): p. 219-25 https://www.ncbi.nlm.nih.gov/pubmed/19914380.
34. Gotteland, M., et al., *Modulation of Helicobacter pylori colonization with cranberry juice and Lactobacillus johnsonii La1 in children.* Nutrition, 2008. **24**(5): p. 421-6 https://www.ncbi.nlm.nih.gov/pubmed/18343637.
35. Vitali, B., et al., *Impact of a synbiotic food on the gut microbial ecology and metabolic profiles.* BMC Microbiol, 2010. **10**: p. 4 https://www.ncbi.nlm.nih.gov/pubmed/20055983.
36. Spiljar, M., D. Merkler, and M. Trajkovski, *The Immune System Bridges the Gut Microbiota with Systemic Energy Homeostasis: Focus on TLRs, Mucosal Barrier, and SCFAs.* Front Immunol, 2017. **8**: p. 1353 https://www.ncbi.nlm.nih.gov/pubmed/29163467.
37. Zeng, T., et al., *Garlic oil alleviated ethanol-induced fat accumulation via modulation of SREBP-1, PPAR-alpha, and CYP2E1.* Food Chem Toxicol, 2012. **50**(3-4): p. 485-91 https://www.ncbi.nlm.nih.gov/pubmed/22138249.
38. Brown, E.M., M. Sadarangani, and B.B. Finlay, *The role of the immune system in governing host-microbe interactions in the intestine.* Nat Immunol, 2013. **14**(7): p. 660-7 https://www.ncbi.nlm.nih.gov/pubmed/23778793.
39. Carvalho, F.A., et al., *Toll-like receptor-gut microbiota interactions: perturb at your own risk!* Annu Rev Physiol, 2012. **74**: p. 177-98 https://www.ncbi.nlm.nih.gov/pubmed/22035346.
40. Takeuchi, O. and S. Akira, *Pattern recognition receptors and inflammation.* Cell, 2010. **140**(6): p. 805-20 https://www.ncbi.nlm.nih.gov/pubmed/20303872.
41. Hooper, L.V., T. Midtvedt, and J.I. Gordon, *How host-microbial interactions shape the nutrient environment of the mammalian intestine.* Annu Rev Nutr, 2002. **22**: p. 283-307 https://www.ncbi.nlm.nih.gov/pubmed/12055347.
42. Zhao, L. and J. Shen, *Whole-body systems approaches for gut microbiota-targeted, preventive healthcare.* J Biotechnol, 2010. **149**(3): p. 183-90 https://www.ncbi.nlm.nih.gov/pubmed/20176062.
43. Boshtam, M., et al., *Aptamers Against Pro- and Anti-Inflammatory Cytokines: A Review.* Inflammation, 2017. **40**(1): p. 340-349 https://www.ncbi.nlm.nih.gov/pubmed/27878687.
44. Gonzalez, R., et al., *Effects of flavonoids and other polyphenols on inflammation.* Crit Rev Food Sci Nutr, 2011. **51**(4): p. 331-62 https://www.ncbi.nlm.nih.gov/pubmed/21432698.
45. Comalada, M., et al., *Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure-activity relationship.* Biochem Pharmacol, 2006. **72**(8): p. 1010-21 https://www.ncbi.nlm.nih.gov/pubmed/16934226.
46. Blonska, M., Z.P. Czuba, and W. Krol, *Effect of flavone derivatives on interleukin-1beta (IL-1beta) mRNA expression and IL-1beta protein synthesis in stimulated RAW 264.7 macrophages.* Scand J Immunol, 2003. **57**(2): p. 162-6 https://www.ncbi.nlm.nih.gov/pubmed/12588662.
47. Sharma, V., et al., *Modulation of interleukin-1beta mediated inflammatory response in human astrocytes by flavonoids: implications in neuroprotection.* Brain Res Bull, 2007. **73**(1-3): p. 55-63 https://www.ncbi.nlm.nih.gov/pubmed/17499637.
48. Sato, M., et al., *Quercetin, a bioflavonoid, inhibits the induction of interleukin 8 and monocyte chemoattractant protein-1 expression by tumor necrosis factor-alpha in cultured human synovial cells.* J Rheumatol, 1997. **24**(9): p. 1680-4 https://www.ncbi.nlm.nih.gov/pubmed/9292787.
49. Min, Y.D., et al., *Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line.* Inflamm Res, 2007. **56**(5): p. 210-5 https://www.ncbi.nlm.nih.gov/pubmed/17588137.
50. Lyu, S.Y. and W.B. Park, *Production of cytokine and NO by RAW 264.7 macrophages and PBMC in vitro incubation with flavonoids.* Arch Pharm Res, 2005. **28**(5): p. 573-81 https://www.ncbi.nlm.nih.gov/pubmed/15974445.

51. Bitler, C.M., et al., *Hydrolyzed olive vegetation water in mice has anti-inflammatory activity.* J Nutr, 2005. **135**(6): p. 1475-9 https://www.ncbi.nlm.nih.gov/pubmed/15930455.
52. Karin, M., Y. Yamamoto, and Q.M. Wang, *The IKK NF-kappa B system: a treasure trove for drug development.* Nat Rev Drug Discov, 2004. **3**(1): p. 17-26 https://www.ncbi.nlm.nih.gov/pubmed/14708018.
53. Rahman, I., S.K. Biswas, and P.A. Kirkham, *Regulation of inflammation and redox signaling by dietary polyphenols.* Biochem Pharmacol, 2006. **72**(11): p. 1439-52 https://www.ncbi.nlm.nih.gov/pubmed/16920072.
54. Rahman, I., J. Marwick, and P. Kirkham, *Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NF-kappaB and pro-inflammatory gene expression.* Biochem Pharmacol, 2004. **68**(6): p. 1255-67 https://www.ncbi.nlm.nih.gov/pubmed/15313424.
55. Garcia-Lafuente, A., et al., *Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease.* Inflamm Res, 2009. **58**(9): p. 537-52 https://www.ncbi.nlm.nih.gov/pubmed/19381780.
56. Ji, G., et al., *Genistein suppresses LPS-induced inflammatory response through inhibiting NF-kappaB following AMP kinase activation in RAW 264.7 macrophages.* PLoS One, 2012. **7**(12): p. e53101 https://www.ncbi.nlm.nih.gov/pubmed/23300870.
57. Mackenzie, G.G., et al., *Epicatechin, catechin, and dimeric procyanidins inhibit PMA-induced NF-kappaB activation at multiple steps in Jurkat T cells.* FASEB J, 2004. **18**(1): p. 167-9 https://www.ncbi.nlm.nih.gov/pubmed/14630700.
58. Carluccio, M.A., et al., *Olive oil and red wine antioxidant polyphenols inhibit endothelial activation: antiatherogenic properties of Mediterranean diet phytochemicals.* Arterioscler Thromb Vasc Biol, 2003. **23**(4): p. 622-9 https://www.ncbi.nlm.nih.gov/pubmed/12615669.
59. Berlett, B.S. and E.R. Stadtman, *Protein oxidation in aging, disease, and oxidative stress.* J Biol Chem, 1997. **272**(33): p. 20313-6 https://www.ncbi.nlm.nih.gov/pubmed/9252331.
60. Salzano, S., et al., *Linkage of inflammation and oxidative stress via release of glutathionylated peroxiredoxin-2, which acts as a danger signal.* Proc Natl Acad Sci U S A, 2014. **111**(33): p. 12157-62 https://www.ncbi.nlm.nih.gov/pubmed/25097261.
61. Willcox, J.K., S.L. Ash, and G.L. Catignani, *Antioxidants and prevention of chronic disease.* Crit Rev Food Sci Nutr, 2004. **44**(4): p. 275-95 https://www.ncbi.nlm.nih.gov/pubmed/15462130.
62. Bryan, N., et al., *Reactive oxygen species (ROS)--a family of fate deciding molecules pivotal in constructive inflammation and wound healing.* Eur Cell Mater, 2012. **24**: p. 249-65 https://www.ncbi.nlm.nih.gov/pubmed/23007910.
63. Naik, E. and V.M. Dixit, *Mitochondrial reactive oxygen species drive proinflammatory cytokine production.* J Exp Med, 2011. **208**(3): p. 417-20 https://www.ncbi.nlm.nih.gov/pubmed/21357740.
64. Clark, R.A. and A.J. Valente, *Nuclear factor kappa B activation by NADPH oxidases.* Mech Ageing Dev, 2004. **125**(10-11): p. 799-810 https://www.ncbi.nlm.nih.gov/pubmed/15541774.
65. Geiszt, M. and T.L. Leto, *The Nox family of NAD(P)H oxidases: host defense and beyond.* J Biol Chem, 2004. **279**(50): p. 51715-8 https://www.ncbi.nlm.nih.gov/pubmed/15364933.
66. Heim, K.E., A.R. Tagliaferro, and D.J. Bobilya, *Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships.* The Journal of Nutritional Biochemistry, 2002. **13**(10): p. 572-584.
67. Mishra, A., et al., *Bauhinia variegata leaf extracts exhibit considerable antibacterial, antioxidant, and anticancer activities.* Biomed Res Int, 2013. **2013**: p. 915436 https://www.ncbi.nlm.nih.gov/pubmed/24093108.
68. Mishra, A., S. Kumar, and A.K. Pandey, *Scientific validation of the medicinal efficacy of Tinospora cordifolia.* ScientificWorldJournal, 2013. **2013**: p. 292934 https://www.ncbi.nlm.nih.gov/pubmed/24453828.
69. Marnett, L.J., J.N. Riggins, and J.D. West, *Endogenous generation of reactive oxidants and electrophiles and their reactions with DNA and protein.* J Clin Invest, 2003. **111**(5): p. 583-93 https://www.ncbi.nlm.nih.gov/pubmed/12618510.

70. Prousek, J., *Fenton chemistry in biology and medicine.* Pure and Applied Chemistry, 2007. **79**(12): p. 2325-2338.
71. Deby-Dupont, G., et al., *Resveratrol and curcumin reduce the respiratory burst of Chlamydia-primed THP-1 cells.* Biochem Biophys Res Commun, 2005. **333**(1): p. 21-7 https://www.ncbi.nlm.nih.gov/pubmed/15939398.
72. Chow, S.E., et al., *Resveratrol attenuates oxLDL-stimulated NADPH oxidase activity and protects endothelial cells from oxidative functional damages.* J Appl Physiol (1985), 2007. **102**(4): p. 1520-7 https://www.ncbi.nlm.nih.gov/pubmed/17194732.
73. Petronio, M.S., et al., *Apocynin: chemical and biophysical properties of a NADPH oxidase inhibitor.* Molecules, 2013. **18**(3): p. 2821-39 https://www.ncbi.nlm.nih.gov/pubmed/23455672.
74. Shen, L. and H.F. Ji, *Insights into the inhibition of xanthine oxidase by curcumin.* Bioorg Med Chem Lett, 2009. **19**(21): p. 5990-3 https://www.ncbi.nlm.nih.gov/pubmed/19800788.
75. Aucamp, J., et al., *Inhibition of xanthine oxidase by catechins from tea (Camellia sinensis).* Anticancer Res, 1997. **17**(6D): p. 4381-5 https://www.ncbi.nlm.nih.gov/pubmed/9494537.
76. Schmidt, A.P., et al., *Anti-nociceptive properties of the xanthine oxidase inhibitor allopurinol in mice: role of A1 adenosine receptors.* Br J Pharmacol, 2009. **156**(1): p. 163-72 https://www.ncbi.nlm.nih.gov/pubmed/19133997.
77. Nguyen, M.T. and N.T. Nguyen, *Xanthine oxidase inhibitors from Vietnamese Blumea balsamifera L.* Phytother Res, 2012. **26**(8): p. 1178-81 https://www.ncbi.nlm.nih.gov/pubmed/22821854.
78. Braunlich, M., et al., *Extracts, anthocyanins and procyanidins from Aronia melanocarpa as radical scavengers and enzyme inhibitors.* Nutrients, 2013. **5**(3): p. 663-78 https://www.ncbi.nlm.nih.gov/pubmed/23459328.
79. Huang, X.F., et al., *Synthesis of resveratrol analogues, and evaluation of their cytotoxic and xanthine oxidase inhibitory activities.* Chem Biodivers, 2008. **5**(4): p. 636-42 https://www.ncbi.nlm.nih.gov/pubmed/18421756.
80. Cheon, B.S., et al., *Effects of prenylated flavonoids and biflavonoids on lipopolysaccharide-induced nitric oxide production from the mouse macrophage cell line RAW 264.7.* Planta Med, 2000. **66**(7): p. 596-600 https://www.ncbi.nlm.nih.gov/pubmed/11105561.
81. Sarkar, A. and A. Bhaduri, *Black tea is a powerful chemopreventor of reactive oxygen and nitrogen species: comparison with its individual catechin constituents and green tea.* Biochem Biophys Res Commun, 2001. **284**(1): p. 173-8 https://www.ncbi.nlm.nih.gov/pubmed/11374887.
82. Sporn, M.B. and K.T. Liby, *NRF2 and cancer: the good, the bad and the importance of context.* Nat Rev Cancer, 2012. **12**(8): p. 564-71 https://www.ncbi.nlm.nih.gov/pubmed/22810811.
83. Chu, A.J., *Antagonism by bioactive polyphenols against inflammation: a systematic view.* Inflamm Allergy Drug Targets, 2014. **13**(1): p. 34-64 https://www.ncbi.nlm.nih.gov/pubmed/24251781.