

# Representative Research Behind B-Epic ImmunoCode

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**B-Epic ImmunoCode** includes three amazing proprietary, science-backed nutrient blends, combined with health-supporting Vitamins B12, C and D, and the essential mineral Zinc. These ingredients work together in a powerful, synergistic way to educate, activate, energize, guide and regulate effective immune system function, while supporting overall healthy structure and function of your body at the same time.

□ **Transfer Factor Blend consists of highly beneficial bovine colostrum extracts (including transfer factor, proline-rich polypeptides, lactoferrin, growth factors), fucosyl lactose (the dominant human-milk oligosaccharide), galactooligosaccharides (another human-milk oligosaccharide), and fucoidan. This blend is like a state-of-the-art instruction manual, plus graduate education, plus front-line tutoring for your immune system.**

□ **Transfer factor** is a scientifically-recognized intricate means of immune communication at the cellular level. Produced by the immune system, it is naturally designed to transfer highly concentrated, easily usable immune intelligence from one immune system to another, as from human mother to baby through her colostrum or “first milk.”<sup>1</sup> In 1949, Dr. H. Sherwood Lawrence demonstrated that transfer factors, when obtained from an immune-competent donor, could transfer that immune competence to immune-naïve recipients.<sup>2</sup> Transfer factors are essential components of immune health in even the most primitive of species, and have been found to be universally effective, regardless of differences between donor and recipient. This means TF is an effective means of “transferring immune system advantages from one species to another.”<sup>3</sup> The tiny size of these molecules make them nonallergenic;<sup>4</sup> and more than 50 years of scientific research has provided a wealth of evidence regarding transfer factor’s safety and benefits toward immune effectiveness.<sup>5,6,7</sup> TF is the essence of the immunologic message<sup>8</sup> and **relays “how to function” memory from the competent immune system to the naïve or compromised immune system.** The result is, 1) the ability to more rapidly recognize and respond to a wide range of health threats;<sup>9</sup> 2) effective immune system regulation, which helps to avoid inappropriate responses resulting in overreaction to non-harmful stimuli, or misdirected action toward one’s own tissues;<sup>10,11</sup> 3) antigen specific components of TF influence the activity of macrophages and cytotoxic T-lymphocytes, thus helping the immune system to function more effectively in recognizing certain microorganisms and antigens.<sup>12</sup> 4) activation of Natural Killer or “NK” cells, the first-line-of-defense immune-cell warriors whose function is to seek and destroy harmful microbes and abnormal cells;<sup>13,14</sup> [Though once believed to do this without prior stimulation, a 2004 research study conducted at Rockefeller University demonstrated that NK cells require activation to function effectively.<sup>15</sup>] and 5) supports effective immune response function in a variety of pathologies.<sup>16,17,18,19,20,21</sup>

□ **Proline-rich polypeptides (PRPs)** are another class of small colostrum-derived proteins that have ability to modulate certain immune processes.<sup>22,23</sup> Like TF, they are not species specific.<sup>24</sup> Scientific studies have shown PRPs: 1) demonstrate immunomodulatory effects on both innate and adaptive immune responses;<sup>25</sup> 2) enhance the maturation and function of thymus gland T-cells, important role-players in immune health;<sup>26,27</sup> 3) inhibit initiation of immune system overreaction or misdirection;<sup>28,29</sup> 5) modulate the production of cytokines [regulatory messaging proteins of the immune system];<sup>30,31</sup> and 6) are of value in the maintenance of healthy physiological processes in which oxidative stress contributes to age-related health challenges.<sup>32,33</sup>

□ **Lactoferrin (LF)** belongs to the family of iron-binding proteins. The LF found in the colostrum (first milk) of mammals offers many significant cross-species benefits.<sup>34</sup> Twenty-five years of research have shown LF to have a wide spectrum of immune-function enhancing properties.<sup>35,36,37</sup> When taken orally, lactoferrin: 1) enhances both local and systemic immune response;<sup>38</sup> 2) demonstrates an array of immunomodulating abilities, including enhancement of NK cell activity; 3) deprives microbes of iron essential for growth through its iron-binding ability;<sup>39</sup> 4) enhances gut health by stimulating the growth of gut-associated lymphatic follicles;<sup>40</sup> 5) promotes growth of “good” bacteria in the gut;<sup>41</sup> 6) protects against the toxicity of reactive oxygen radicals;<sup>42,43</sup> and 7) promotes bone growth.<sup>44</sup>

□ **Growth Factors**, derived from colostrum, support multiple regenerative effects that extend to: 1) all structural body cells; 2) the gut; 3) muscle and cartilage repair; and 4) promotion of wound healing.<sup>45,46,47</sup>

□ **La Madre (Human Milk Oligosaccharides, HMOs)** Among bioactive constituents of milk, human milk oligosaccharides (HMOs) are particularly significant. These are non-digestible carbohydrates forming the third largest solid component in human milk. HMOs in the human breast milk are a complex mixture of more than 200 non-digestible and nonnutritional carbohydrates.<sup>48</sup> The valuable effects of HMOs include shaping intestinal microbiota, imparting antimicrobial effects, developing intestinal barrier, and modulating immune response.<sup>49</sup> HMOs also function as antiadhesive antimicrobials that serve as soluble decoy receptors, prevent pathogen attachment to infant mucosal surfaces thereby lowering the risk for viral, bacterial and protozoan parasite infections.<sup>50</sup>

The HMOs found in human milk, are virtually absent in cow milk.<sup>51</sup> Obviously we cannot obtain HMOs from human mothers milk. Here is where advanced enzymology and biotechnology come into play. By mimicking the mammary gland processes, we can now obtain HMOs for the benefit not only of infants but adults can also now receive the benefits of HMOs.<sup>52,53</sup>

□ **2-Fucosyllactose (2'FL)** is the most abundant oligosaccharide in human milk.<sup>54</sup> Nevertheless not all mothers provide 2'FL to their infants. For example, 23% of all Chinese mothers do not produce 2'FL. And, among the remaining 77%, 2'-FL concentrations were found to be lower than those of Western populations but higher than those of African populations.<sup>55</sup> Among the many HMOs, 2'-Fucosyllactose (2'FL) is one of

the most effective HMOs in strengthening the intestinal barrier.<sup>56</sup>

□ **Galactooligosaccharides (GOS)** Along with other oligosaccharides found in human milk, galactooligosaccharides (GOS) act as adhesion inhibitors or decoys that tie up pathogens so they cannot attach to the gut wall and establish infections.<sup>57</sup> GOS can reduce the colonization of *E. coli* O157 by enhancing the gut barrier function. GOS can also relieve inflammation caused by pathogens. At the same time, GOS promotes the growth of beneficial probiotics such as *Akkermansia*, *Ruminococcaceae* and *Bacteroides*, and improves short chain fatty acid (SCFA) levels in the intestine.<sup>58</sup> Galactooligosaccharides (GOS) are a major prebiotic, which specifically increase Bifidobacteriaceae abundance especially in the case of the dysbiosis that occurs in diabetes.<sup>59</sup> Dysbiosis leads to leaky gut and leaky gut can cause neurological and psychiatric disorders.<sup>60, 61</sup>



**Fucoidan** is a family of fucose-containing oligosaccharides produced by brown algae. Fucoidan has been referred to as the “Milk of the Sea” in part because its healing properties are comparable to human milk. Used as a food staple for millennia, its safety has been demonstrated through both usage and scientific research.<sup>62, 63</sup> The immune-enhancing, health-promoting benefits of this plant-derived nutrient are drawing growing interest from both scientific and medical communities. Examples of reported benefits include: 1) support of both innate and adaptive immune function,<sup>64</sup> including enhancement of NK cells and Th1 activity,<sup>65</sup> and enhanced maturation and activity of dendritic cells (important immune cells for recognition of potentially harmful microbes);<sup>66</sup> 2) inhibition of growth of some potential pathogens;<sup>67,68</sup> 3) support of appropriate immune function response to abnormal cell growth.<sup>69,70,71</sup> 4) support of healthy vascular function;<sup>72,73,74</sup> 5) support of healthy inflammatory responses;<sup>75</sup> 6) support of healthy wound healing;<sup>76</sup> 7) potential radio-protective effects;<sup>77</sup> and chemo-protective effects;<sup>78</sup> 7) support in pain control;<sup>79</sup> 8) liver-protective effects;<sup>80</sup> 9) enhanced metabolism;<sup>81</sup> 10) inhibition of fat cell maturation, and enhancement of breakdown of fat.<sup>82,83,84</sup> and 11) may support beneficial modulation of endocrine hormones.<sup>85,86</sup>

Norovirus infections belong to the most common causes of human gastroenteritis (infectious diarrhea) worldwide, and epidemic outbreaks are responsible for hundreds of thousands deaths annually. Norovirus does bind to Human milk Oligosaccharides (HMOs) which provides some protection against infection but it was recently found that fucoidan ties up Norovirus even better than HMOs.<sup>87</sup>

## □ Vitamins and Minerals

□ **Vitamin B12, Methylcobalamin**<sup>88</sup> Vitamin B12 or cobalamin plays essential roles in folate metabolism and in the synthesis of the citric acid cycle intermediate, succinyl-CoA. Vitamin B12 deficiency is commonly associated with chronic stomach inflammation, which may contribute to an autoimmune vitamin B12 malabsorption syndrome called pernicious anemia and to a food-bound vitamin B12 malabsorption syndrome. Impairment of vitamin B12 absorption can cause megaloblastic anemia and neurologic disorders in deficient subjects. Normal function of the digestive system required for food-bound vitamin B12 absorption is commonly impaired in individuals over 60 years of age, placing them at risk for vitamin B12 deficiency. Vitamin B12 and folate are important for homocysteine metabolism. Elevated homocysteine levels in blood are a risk factor for cardiovascular disease (CVD). Although B vitamin supplementation has been proven effective to control homocysteine levels, current data from intervention trials have not shown that lowering homocysteine levels decreases CVD risk. The preservation of DNA integrity is dependent on folate and vitamin B12 availability. Poor vitamin B12 status has been linked to increased risk of breast cancer in some, but not all, observational studies. There is a need to evaluate whether supplemental vitamin B12, along with folic acid, could help reduce breast cancer incidence. Low maternal vitamin B12 status has been associated with an increased risk of neural tube defects (NTD), but it is not known whether vitamin B12 supplementation could help reduce the risk of NTD. Vitamin B12 is essential for the preservation of the myelin sheath around neurons and for the synthesis of neurotransmitters. While hyperhomocysteinemia may increase the risk of cognitive impairment, it is not clear whether vitamin B12 deficiency contributes to the risk of dementia in the elderly. Although B-vitamin supplementation lowers homocysteine levels in older subjects, the long-term benefit is not yet known. Both depression and osteoporosis have been linked to diminished vitamin B12 status and high homocysteine levels. Products of animal origin constitute the primary source of vitamin B12. Older individuals and vegans are advised to use vitamin B12 fortified foods and supplements to meet their needs. The long-term use of certain medications, such as inhibitors of stomach acid secretion, can adversely affect vitamin B12 absorption.

□ **Ascorbic Acid (Vitamin C)**, first demonstrated to strengthen immunity in 1942, plays multiple important roles in health.<sup>89</sup> In his book *Reishi, Ancient Herb for Modern Times*, Kenneth Jones reports; “Vitamin C reduces the high molecular weight of polysaccharides. As Vitamin C breaks up these sugars, their viscosity or stickiness drops and their bioavailability increases. Once the polysaccharides are reduced ... they are rendered more accessible to the immune system cell called the ‘macrophage.’ When this immune cell becomes activated, an array of other defenders is signaled to go into action to protect the body against disease.”<sup>90</sup> Examples of other benefits include: 1) maintenance of oral mucosal integrity; 2) erythropoietic (red blood cell) activity; 3) supports health of endothelial cells (lining of blood and lymphatic vessels, heart, eye, and body cavities);<sup>91, 92</sup> 4) iron absorption;<sup>93</sup> 5) leukocyte function;<sup>94</sup> 6) support of natural killer cell activity and T and B cell function;<sup>95</sup> 7) statistically significant increase in the serum levels of IgA, IgM and C-3 complement;<sup>96</sup> and 8) significant synergistic enhancement of immune benefits offered by maitake mushroom fraction-D.<sup>97</sup>

□ **Vitamin D**, once thought of primarily as the preventative for rickets and important for bone health, is now known to influence many fundamental physiological processes. These range from maintaining the health of our genes to multiple aspects of effective immune system function.<sup>98</sup> It's becoming ever clearer that appropriate Vitamin D levels significantly impact both quality and duration of life.<sup>99,100</sup> Dr. Michael Holick wrote, in the *New England Journal of Medicine*, “Of great interest is the role it (vitamin D) can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease.” He further noted that Vitamin D levels may also be a predictor of for many such diseases.<sup>101</sup> Ongoing research demonstrates a near doubling of the prevalence of vitamin D insufficiency in the US population over the last 10 years. It also reveals the adverse impact this insufficiency has on skeletal, infectious/inflammatory, and metabolic health in humans.<sup>102</sup> Among its many health-supporting roles, Vitamin D: 1) is essential for efficient absorption and utilization of calcium by the body, for maintenance of healthy blood calcium levels, and for healthy bone structure;<sup>103</sup> 2) supports healthy and controlled cell differentiation, critical to healthy cell structure and function;<sup>104,105</sup> 3) is essential for growth and effective

wound healing;<sup>106</sup> 4) supports immune system regulation;<sup>107,108,109</sup> 5) supports both innate immune responses (non-specific and not requiring prior exposure)<sup>110</sup> and adaptive immune responses (specific, according to stimulus);<sup>111,112,113</sup> 6) supports healthy inflammatory responses;<sup>114,115</sup> 7) supports healthy platelet function;<sup>116</sup> and 8) plays an important role in maintaining integrity of intestinal mucosal lining.<sup>117</sup>

□ **Zinc** was first recognized to be essential for human health over forty years ago.<sup>118</sup> As one of the most important trace elements, it plays a vital role in more than 300 enzymatic and biological processes,<sup>119</sup> and is considered a major element in assuring the correct functioning of an organism from the earliest embryonic stages to the last periods of life.<sup>120</sup> It is an essential element for growth and nervous system function,<sup>121</sup> and the relevance of zinc for immune efficiency has been well established.<sup>122</sup> Its supplementation has been demonstrated to increase the efficiency of the immune system in a number of study populations, ranging from those considered “healthy” to those with severe immune dysfunction.<sup>123, 124</sup> Within the immune system, zinc is crucial for development and function of neutrophils, NK cells, macrophages, T cells and B cells. It is a critical cofactor of Thymulin, a thymic hormone involved in T-cell maturation.<sup>125</sup> Zinc also plays an role in important oxidative modulating/antioxidant and balance of inflammatory processes,<sup>126</sup> thus reducing free-radical-induced cellular injury.<sup>127</sup>

□ **Innate Immune Blend is a proprietary blend of beta-glucans from yeast, and mushroom extracts selected for their exceptional biological potency. Mushrooms have been used to support healthy immune function for centuries by the Chinese, and in the late 1960s Western scientists joined those from the East in researching the mechanisms of mushrooms’ apparent benefits. This resulted in growing scientific evidence demonstrating their wide-ranging beneficial effects for human health.**



**Yeast Beta-glucans** play a key role in the health-enhancing benefits of the mushrooms noted above, but **Saccharomyces cerevisiae**, beta glucans derived from bakers yeast, is another highly respected and scientifically proven supporter of immune system effectiveness and overall health.<sup>128,129,130,131,132</sup> The fact that orally consumed Beta glucan is ingested and processed by macrophages places its full nutrient potential at the disposal of the immune system.<sup>133,134</sup> This could be one direct way Beta-glucans provide fuel for the immune system.<sup>135</sup> Examples of recognized beta-glucans benefits include: 1) enhanced initiation and amplification of both innate

and adaptive host defense;<sup>136,137</sup> 2) immunomodulatory effects,<sup>138</sup> with possible synergistic benefits in combination with vitamin C;<sup>139</sup> 3) activation of natural killer or NK-Cells, plus in turn, the T-Cells, and B-Cells - including selected cytokines and complement;<sup>140,141,142</sup> 4) enhanced immune defense against potentially harmful microbes;<sup>143,144,145,146,147</sup> 5) support of maintenance of healthy cell structure;<sup>148</sup> 6) enhancement of immune response to abnormal cells;<sup>149,150,151,152</sup> 7) notable antioxidant effects;<sup>153,154</sup> 8) adjunctive synergistic effect in some chemo and radiotherapy, with positive role in restoration of function in hematopoiesis (production of blood cells);<sup>155,156</sup> 7) protective effect against some potentially harmful genotoxic (toxic to gene) substances;<sup>157</sup> 9) support of healthy cholesterol levels;<sup>158,159</sup> 10) support of improvement in weight, metabolic and anthropometric body mass index, lipid profile (increased HDL cholesterol), basal glucose, and HbA1C;<sup>160,161</sup> 11) support of wound healing,<sup>162</sup> and 12) may enhance immune response to some immunizations.<sup>163</sup>



**Agaricus** (*Agaricus blazei* Murill) is highly valued for its richness in beta-glucans, and its health-enhancing benefits have been proclaimed for millennia. Having been validated through evidence-based science, some of the underlying reasons for its benefits include: 1) strong immunomodulating properties;<sup>164, 165</sup> 2) increased production of key immune cells (helper T-cells [CD4+] and cytotoxic T-cells [CD8+]);<sup>166, 167</sup> 3) production of leukocyte-enhancing, and NK-Cell activating effects;<sup>168</sup> 4) liver-health supportive effects;<sup>169, 170</sup> 5) significant production of cytokines (regulatory messengers of the immune system);<sup>171</sup> 6) effective antioxidant activity;<sup>172</sup> and 7) adjuvant benefits when used with some conventional therapies.<sup>173</sup>



**Chaga** (*Inonotus obliquus* L.) is one of nature’s oldest medicinal herbs. Among noted benefits, it: 1) evidences immune stimulating<sup>174</sup> and immune function enhancing properties.<sup>175,176</sup> 2) supports healthy inflammatory responses;<sup>177</sup> 3) demonstrates antioxidant effects;<sup>178</sup> and 4) inhibits oxidative damage in human lymphocytes.<sup>179</sup>



**Turkey tails** (*Trametes versicolor* L.) is the most widely researched of the immune-enhancing mushrooms. Studies of the physiological effects of this mushroom demonstrate that among other things it: 1) acts as an immunomodulator of NK cells<sup>180</sup> and an activator;<sup>181,182</sup> 2) increases thymus weight and evidences restorative effects;<sup>183</sup> and 3) supports healthy physiologic responses during chemotherapy and radiotherapy,<sup>184</sup> including support of white blood cell count.<sup>185</sup>



**Indian bread** (*Poria Cocos* Schw.) is a respected mushroom for which studies have shown: 1) support of effective immune function in recognition and response to abnormal cell development;<sup>186,187,188,189</sup> 2) support of healthy immune function in face of tumors through anti-angiogenic (preventing development of new blood supply) activity;<sup>190</sup> 3) demonstrates anti-inflammatory benefits;<sup>191,192</sup> and 3) multiple antioxidant benefits including neuronal protection that may help protect against Alzheimers' disease.<sup>193,194</sup>



**Maitake** (*Grifola frondosa* Dicks.) mushroom contains grifolan, an important beta-glucan polysaccharide that has been shown to: 1) activate macrophages<sup>195</sup> (a type of cell considered among the "heavy artillery" of the immune system), dendritic cells (another type of immune cells), and T cells;<sup>196</sup> 2) enhance NK cell activity;<sup>197,198</sup> 3) enhance thymus gland weight;<sup>199</sup> and 4) strengthen immune recognition and response to potentially harmful microbes.<sup>200</sup>



**Shiitake** (*Lentinus edodes* Berk.) contains a polysaccharide compound called lentinan that has been shown to: 1) demonstrate immunomodulatory properties;<sup>201</sup> 2) stimulate both innate and adaptive immune response function;<sup>202,203</sup> 3) offer liver-protective benefits;<sup>204,205</sup> and 4) demonstrate support of maintenance of healthy cell structure.<sup>206</sup> Lignins, another component of the Shiitake mushroom, have demonstrated strong support of healthy immune recognition and response to potentially harmful microbes.<sup>207</sup>



**Reishi** (*Ganoderma lucidum* Curtis) mushrooms possess immunomodulating abilities<sup>208</sup> and support healthy immune system function by: 1) strengthening cell-mediated immunity;<sup>209</sup> 2) supporting antibody formation;<sup>210</sup> 3) supporting immune cell recovery;<sup>211</sup> 4) supports activation and maturation of dendritic cells (important cells in adaptive immunity).<sup>212</sup> The Reishi also offers antioxidant benefits.<sup>213</sup>

□ **Antioxidant-Metabolic Blend** is a proprietary blend of plant extracts and natural acids incorporated into B-Epic ImmunoCode because of their remarkable ability to maximize the potential benefit of many nutraceuticals. Whether accomplished by improved absorption, increased bioavailability, enhanced circulation or greater antioxidant power, these ingredients offer exceptional support for effective immune function and vibrant overall health.



**Alpha Lipoic acid** is a natural antioxidant. Among other benefits, it: 1) helps the body more effectively rid itself of harmful environmental substances;<sup>214</sup> 2) synergistically decreases oxidative stress, when combined with nutraceuticals such as curcumin;<sup>215</sup> 3) enhances energy to the mitochondria (the powerhouse of the cells);<sup>216</sup> and 4) supports cardiovascular<sup>217</sup> and neurological<sup>218</sup> health.



**Curcumin** is the yellow component of the spice turmeric. Studies show curcumin: 1) exhibits varied immunomodulatory actions;<sup>219</sup> 2) has potent regulating effects on inflammatory processes;<sup>220</sup> 3) is a strong antioxidant that enhances cellular resistance to oxidative damage;<sup>221</sup> 4) promotes increased glutathione levels,<sup>222</sup> which improves the body's natural antioxidant shield and increases the efficiency of multiple detoxification processes; 5) has liver-protective benefits;<sup>223</sup> 6) specifically protects the gastrointestinal tract.<sup>224,225</sup> and 7) supports emotional health, with benefit being enhanced by taking curcumin and piperine (also contained in BEpic A.I.M. as Bioperine™) at the same time.<sup>226</sup>

Tumeric roots and powder.



**Pomegranate extract** is rich with phytonutrients known to provide multiple health benefits, including: 1) strong antioxidant properties;<sup>227,228</sup> 2) appropriate immune response;<sup>229,230</sup> 3) support of cardiovascular health;<sup>231,232</sup> One of the primary components of pomegranate extract is ellagic acid. Ellagic acid feeds the recently discovered, highly beneficial bacteria *Akkermansia muciniphila*.<sup>233,234</sup> The gut microbiota convert ellagic acid into Urolithins A and B. Urolithin A impacts metabolic dysfunction because of its immunomodulatory properties.<sup>235</sup> This is one of the first components that is produced by the microbiota that displays a strong influence or cross-talk with the cellular mitochondria.<sup>236</sup>

□ **Glutamine** is the most abundant amino acid in the body, and is present in nearly every biochemical pathway.<sup>237</sup> It plays a wide array of important health-supporting roles throughout the human body. Examples include: 1) Serves as a primary precursor for the synthesis of glutathione (GSH), the major antioxidant produced in the human body. GSH offers protection against oxidative injury and cell death.<sup>238</sup> 2) Supports healthy cell development and appropriate response to abnormal cell development;<sup>239</sup> 3) Is associated with up-regulation of NK cell activity;<sup>240</sup> 4) Demonstrates protective effect on liver by attenuating inflammatory response;<sup>241</sup>

□ **N Acetylcysteine** (NAC) is well respected as a valuable antioxidant.<sup>242,243</sup> It is a rich source of cysteine, another important amino acid that is recognized as “conditionally essential” under circumstances in which the body requires more than it can produce. This is especially true when oxidative stress is severe.<sup>244</sup> Among NAC’s varied benefits, its provision of cysteine may be its most valuable contribution to overall human health. Cysteine is a key precursor (substance from which another usually more active substance is formed) in the body’s own production of glutathione. Glutathione, the most powerful antioxidant made by the body, plays critical roles in many physiologic processes, including healthy brain, metabolic and immune function, as well as detoxification.<sup>245,246,247,248</sup> It also provides a critical defense system for the protection of cells from many forms of stress,<sup>249</sup> and offers antioxidant protection against environmental influences and progression of changes associated with aging.<sup>250,251</sup> NAC has been clearly shown to increase glutathione levels,<sup>252,253</sup> but beyond that, it is respected for a number of other benefits. Examples of these include: 1) support of more effective respiratory function in a variety of respiratory challenges;<sup>254,255,256</sup> 2) support of the body’s defense functions in chronic health challenges;<sup>257,258</sup> 3) support of the body’s defense functions toward abnormal cell development;<sup>259</sup> 4) support of the body’s defense functions in face of infection;<sup>260,261</sup> 5) protection of cell function and viability in varied forms of toxicity;<sup>262,263</sup> 6) support of sustained muscle integrity in the face of aging;<sup>264,265</sup> and 7) may offer support for healthy mental function.<sup>266</sup>



**Black pepper extract** is a standardized extract from *Piper longum* L. The active component, piperine, is recognized most for its enhancement of the bioavailability of many nutrients,<sup>267</sup> including curcumin.<sup>268</sup> Piperine is rapidly absorbed by the gastrointestinal tract<sup>269</sup> and enhances gastrointestinal absorption of other nutrients through a combination of processes.<sup>270</sup> Other recognized benefits of piperine include: 1) immune support;<sup>271,272</sup> 2) improved joint health,<sup>273</sup> and 3) support of mood state and cognitive function.<sup>274</sup>

## ENDNOTES

<sup>1</sup> **Process for obtaining transfer factor from colostrum transfer factor so obtained and use thereof.** Wilson, GB, Paddock GV. US Patent Number 4816563; Mar. 28, 1989. <http://www.patentstorm.us/patents/4816563/fulltext.html>

<sup>2</sup> **The cellular transfer of cutaneous hypersensitivity to tuberculin in man.** Lawrence HS, Proc Soc Exp Biol Med. 1949 Aug;71(4):516-22. <http://www.ncbi.nlm.nih.gov/pubmed/18139800> [PubMed - OLDMEDLINE] Full text in PDF documents for NRR website folder.

<sup>3</sup> **A new basis for the immunoregulatory activities of transfer factor—an arcane dialect in the language of cells.** Lawrence HS, Borkowsky W. Cell Immunol. 1983; 82:102-16. <http://www.ncbi.nlm.nih.gov/pubmed/6227395> Full text in PDF in NRR website library.

<sup>4</sup> **Effect of in vitro produced transfer factor on the immune response of cancer patients.** Pizza G, Viza D, Boucheix C, Corrado F. Eur J Cancer. 1977 Sep;13(9):917-23. <http://www.ncbi.nlm.nih.gov/pubmed/578792> Available in PDF for purchase at Science Direct: [http://www.sciencedirect.com/science?\\_ob=ArticleURL&\\_udi=B7GGP-4C11C1J-1FS&\\_user=10&\\_coverDate=09%2F30%2F1977&\\_rdoc=1&\\_fmt=high&\\_orig=search&\\_sort=d&\\_docanchor=&\\_view=c&\\_searchStrId=1280914440&\\_rerunOrigin=google&\\_acct=C000050221&\\_version=1&\\_urlVersion=0&\\_userid=10&md5=262f45625cce13bac93422406d644b09](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B7GGP-4C11C1J-1FS&_user=10&_coverDate=09%2F30%2F1977&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&_view=c&_searchStrId=1280914440&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=262f45625cce13bac93422406d644b09)

<sup>5</sup> **In vitro studies during long-term oral administration of specific Transfer Factor.** Pizza C, De Vinci C, Fornarola V~ Palareti A, Baricordi O, Viza D. *Biotherapy* 1996; 9(1-3): 175-85. <http://www.ncbi.nlm.nih.gov/pubmed/8993778> PDF full text available for purchase at: <http://www.springerlink.com/content/wt8657697055k611/>

<sup>6</sup> **Transfer factor 1993: New frontiers.** Judenbert HH, Pizza G. Progress in Drug Research. Vol. 42. © 1994 Birkhäuser Verlag Basel (Switzerland). <http://www.ncbi.nlm.nih.gov/pubmed/8085011>

<sup>7</sup> **Transfer factor in malignancy.** Pizza, G, De Vinci C, Fudenberg HH. Prog Drug Res. 1994;42:401022. <http://www.ncbi.nlm.nih.gov/pubmed/8085013>

<sup>8</sup> **Enhanced Transfer Factor**, 3rd edition, p.11. Hennen WJ., Ph.D., Woodland Publishing, 2005. <http://www.discovertransferfactor.com/ebooks.htm>

<sup>9</sup> **[The biological activity of the transfer factor induced by bacterial antigens].** Liubchenko TA, Holeva OH, Kholodna LS, et al. *Mikrobiol Z.* 1997 Sep-Oct;59(5):83-100. [Article in Ukrainian] <http://www.ncbi.nlm.nih.gov/pubmed/9480022>

<sup>10</sup> **A new basis for the immunoregulatory activities of transfer factor—an arcane dialect in the language of cells.** Lawrence HS, Borkowsky W. Cell Immunol. 1983 Nov;82(1):102-116. <http://www.ncbi.nlm.nih.gov/pubmed/6227395>

<sup>11</sup> **Transfer Factor current status and future prospects.** Lawrence HS, Borkowsky W.: *Biotherapy* 1996, 9(1-3), 1-5. <http://www.ncbi.nlm.nih.gov/pubmed/8993750>

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- <sup>12</sup> **Methodological Letter\_14/231 Transfer Factors Use in Immunorehabilitation After Infectious-Inflammatory and Somatic Diseases.** Vorobiev AA, Telnuikh IuV, Khalturina EO, et al. Reviewed by Tutelian BA, Karaulov AV. Ministry of Health and Social Development of the Russian Federation. Moscow, 30 Jul 2004. <http://www.discovertransferfactor.com/ebooks.htm>
- <sup>13</sup> **Increased tumor necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers.** See D, Mason S, Roshan R. Immunol Invest. 2002 May;31(2):137-53. <http://www.ncbi.nlm.nih.gov/pubmed/12148949>
- <sup>14</sup> **Methodological Letter\_14/231 Transfer Factors Use in Immunorehabilitation After Infectious-Inflammatory and Somatic Diseases.** Vorobiev AA, Telnuikh IuV, Khalturina EO, et al. Reviewed by Tutelian BA, Karaulov AV. Ministry of Health and Social Development of the Russian Federation. Moscow, 30 Jul 2004. <http://www.discovertransferfactor.com/ebooks.htm>
- <sup>15</sup> **The Abundant NK Cells in Human Secondary Lymphoid Tissues Require Activation to Express Killer Cell Ig-Like Receptors and Become Cytolytic.** Ferlazzo G., Thomas D, Lin SL, et al, *The Journal of Immunology*, 2004, 172: 1455-1462. <http://www.ncbi.nlm.nih.gov/pubmed/14734722>; Free full text: <http://www.jimmunol.org/cgi/content/full/172/3/1455>
- <sup>16</sup> Hennen WJ., Ph.D., **Enhanced Transfer Factor**, 3rd edition, p.13. Woodland Publishing, 2005. <http://www.discovertransferfactor.com/ebooks.htm>
- <sup>17</sup> Hennen WJ., Ph.D., **Enhanced Transfer Factor**, 3rd edition, p.15. Woodland Publishing, 2005. <http://www.discovertransferfactor.com/ebooks.htm>
- <sup>18</sup> **Cell mediated immunity to meet the avian influenza A (H5N1) challenge.** Pizza G, Amadori M, Ablashi D, De Vinci C, Viza D. Med Hypotheses. 2006;67(3):601-8. PMID: 16603322 [PubMed - indexed for MEDLINE] <http://www.ncbi.nlm.nih.gov/pubmed/16603322>
- <sup>19</sup> **Methodological Letter\_14/231 Transfer Factors Use in Immunorehabilitation After Infectious-Inflammatory and Somatic Diseases.** Vorobiev AA, Telnuikh IuV, Khalturina EO, et al. Reviewed by Tutelian BA, Karaulov AV. Ministry of Health and Social Development of the Russian Federation. Moscow, 30 Jul 2004. <http://www.discovertransferfactor.com/ebooks.htm>
- <sup>20</sup> **Protection of cells against HIV infection by the dialyzable leukocyte extract prior to cell culture duplication.** Fernández-Ortega C, Dubed M, Álvarez, et al. *Biotechnologia Aplicada* 2008; 25: 145-148. Full text PDF: [www.elfoscientiaecigb.edu.cu/PDFs/BA/2008/25/2/BA002502OL145-148.pdf](http://www.elfoscientiaecigb.edu.cu/PDFs/BA/2008/25/2/BA002502OL145-148.pdf)
- <sup>21</sup> **Transfer factors as immunotherapy and supplement of chemotherapy in experimental pulmonary tuberculosis.** Fabrae R A, Pérez T M, Aguilar L D, et al. *Clin Exp Immunol*. 2004 May; 136(2): 215–223. <http://www.ncbi.nlm.nih.gov/pubmed/15086383>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809022/>
- <sup>22</sup> **A proline-rich polypeptide complex (PRP) isolated from ovine colostrum. Modulation of H2O2 and cytokine induction in human leukocytes.** Zablocka A, Janusz M, Macala J, et al. *Int Immunopharmacol*. 2007 Jul;7(7):981-8. <http://www.ncbi.nlm.nih.gov/pubmed/17499201>
- <sup>23</sup> [Therapeutic properties of proteins and peptides from colostrum and milk]. **Zimecki M, Artym J.** *Postepy Hig Med Dosw (Online)*. 2005;59:309-23. <http://www.ncbi.nlm.nih.gov/pubmed/15995598>
- <sup>24</sup> **Proline-rich polypeptide (PRP)—an immunomodulatory peptide from ovine colostrum.** Janusz M, Lisowski J. *Arch Immunol Ther Exp (Warsz)*. 1993;41(5-6):275-9. <http://www.ncbi.nlm.nih.gov/pubmed/8010865>
- <sup>25</sup> **Cytokine-inducing activity of a proline-rich polypeptide complex (PRP) from ovine colostrum and its active nonapeptide fragment analogs.** Zablocka M, Janusz K, Rybka I, et al. *European Cytokine Network*. Volume 12, Number 3, 462-7, September 2001. <http://www.ncbi.nlm.nih.gov/pubmed/11566627>; Free full text: [http://www.john-libbey-eurotext.fr/en/revues/bio\\_rech/ecn/e-docs/00/01/60/E3/article.phtml](http://www.john-libbey-eurotext.fr/en/revues/bio_rech/ecn/e-docs/00/01/60/E3/article.phtml)
- <sup>26</sup> **Proline-rich polypeptide (PRP)—an immunomodulatory peptide from ovine colostrum.** Janusz M, Lisowski J. *Arch Immunol Ther Exp (Warsz)*. 1993;41(5-6):275-9. <http://www.ncbi.nlm.nih.gov/pubmed/8010865>
- <sup>27</sup> **The effect of a proline-rich polypeptide (PRP) on the humoral immune response. II. PRP induces differentiation of helper cells from glass-nonadherent thymocytes (NAT) and suppressor cells from glass-adherent thymocytes (GAT).** Zimecki M, Lisowski J, Hrabata T, et al. *Arch Immunol Ther Exp (Warsz)*. 1998;32(2):197-201. <http://www.ncbi.nlm.nih.gov/pubmed/6237628>
- <sup>28</sup> **Colostrin decreases hypersensitivity and allergic responses to common allergens.** Boldogh I, Aguilera-Aguirre L, Bacsí A, et al. *Int Arch Allergy Immunol*. 2008;146(4):298-306. Epub 2008 Mar 26. <http://www.ncbi.nlm.nih.gov/pubmed/18367843>
- <sup>29</sup> **Milk-derived proteins and peptides of potential therapeutic and nutritive value.** Zimecki M, Kruzel ML. *J Exp Ther Oncol*. 2007;6(2):89-106. <http://www.ncbi.nlm.nih.gov/pubmed/17407968>

- 
- <sup>30</sup> **Cytokine-inducing activity of a proline-rich polypeptide complex (PRP) from ovine colostrum and its active nonapeptide fragment analogs.** Zablocka M, Janusz K, Rybka I, et al. European Cytokine Network. Volume 12, Number 3, 462-7, September 2001. <http://www.ncbi.nlm.nih.gov/pubmed/11566627>
- <sup>31</sup> **Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes.** Inglot A, Janusz M, Lisowski J. Arch Immunol Ther Exp (Warsz), 1996;44(4):215-224. <http://www.ncbi.nlm.nih.gov/pubmed/9017161>
- <sup>32</sup> **Colostrinin: an oxidative stress modulator for prevention and treatment of age-related disorders.** Boldough I, Kruzel M. J Alzheimers Dis. 2008 Apr;13(3): 303-321. <http://www.ncbi.nlm.nih.gov/pubmed/18430998>
- <sup>33</sup> **Colostrinin proline-rich polypeptide complex from ovine colostrum—a long-term study of its efficacy in Alzheimer's disease.** Leszek J, Inglot A, Janusz M, et al. Med Sci Monit. 2002 Oct;8(10):193-6. <http://www.ncbi.nlm.nih.gov/pubmed/12388930>
- <sup>34</sup> **A structural framework for understanding the multifunctional character of lactoferrin.** Baker E, Baker H. Biochimie 91 (2009) 3-10. <http://www.ncbi.nlm.nih.gov/pubmed/18541155>
- <sup>35</sup> **Immunomodulatory effects of lactoferrin on antigen presenting cells.** Puddu P, Valenti P, Gessani S. Biochemi 91 (2009) 11-18. <http://www.ncbi.nlm.nih.gov/pubmed/18539153>
- <sup>36</sup> **Antimicrobial properties of lactoferrin.** Jenssen H, Hancock R. Biochimie 91 (2009) 19-29. <http://www.ncbi.nlm.nih.gov/pubmed/>
- <sup>37</sup> **Twenty-five years of research on bovine lactoferrin applications.** Tomita M, Wakabayashi H, Shin K, et al. Biochimie 91 (2009) 52-57. <http://www.ncbi.nlm.nih.gov/pubmed/18573312>
- <sup>38</sup> **The role of lactoferrin in the proper development of newborns.** Artym J, Zimecki M. Postepy Hig Med Dosw (Online) 2005; 59:421-32 (online article in Polish) <http://www.ncbi.nlm.nih.gov/pubmed/16106243>
- <sup>39</sup> **Iron-binding Proteins in Milk and Resistance of Escherichia coli Infection in Infants.** Bullen j, Rogers H, Leigh L. Brit Med J 8 Jan 1972. <http://www.ncbi.nlm.nih.gov/pubmed/4550126>; Full text access: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1789269/?tool=pubmed>
- <sup>40</sup> **The role of lactoferrin in the proper development of newborns.** Artym J, Zimecki M. Postepy Hig Med Dosw (Online) 2005; 59:421-32 (online article in Polish) <http://www.ncbi.nlm.nih.gov/pubmed/16106243>
- <sup>41</sup> **The role of lactoferrin in the proper development of newborns.** Artym J, Zimecki M. Postepy Hig Med Dosw (Online) 2005; 59:421-32 (online article in Polish) <http://www.ncbi.nlm.nih.gov/pubmed/16106243>
- <sup>42</sup> **The role of lactoferrin in the proper development of newborns.** Artym J, Zimecki M. Postepy Hig Med Dosw (Online) 2005; 59:421-32 (online article in Polish) <http://www.ncbi.nlm.nih.gov/pubmed/16106243>
- <sup>43</sup> **Lactoferrin in Infant Formulas: Effect on Oxidation.** Satué-Gracia M, Frankel E, Rangavajhyala N, German B. J Agric Food Chem. 2000, 48, 4984-4990. <http://www.ncbi.nlm.nih.gov/pubmed/11052766>
- <sup>44</sup> **Lactoferrin is a potent regulator of bone cell activity and increases Bone formation in vivo.** Cornish J, Callon K, Naot D, et al. Endocrinology 145(9):4366–4374. <http://www.ncbi.nlm.nih.gov/pubmed/15166119>; Full text access: <http://endo.endojournals.org/cgi/content/full/145/9/4366>
- <sup>45</sup> **Colostrum and its benefits: a review.** Uruakpa F, Ismonda M, Akobundu E. Nut Res Volume 22, Issue 6, Pages 755-767 (June 2002). <http://www.nrjournal.com/article/S0271-5317%2802%2900373-1/abstract> (Full text available for purchase at same website.)
- <sup>46</sup> **Wound healing and expression of antimicrobial peptides/polypeptides in human keratinocytes, a consequence of common growth factors.** Sørensen OE, Cowland JB, J Immunol. 2003 Jun 1;170(11):5583-9. <http://www.ncbi.nlm.nih.gov/pubmed/12759437>; Free full text: <http://www.jimmunol.org/cgi/content/full/170/11/5583>.
- <sup>47</sup> **Antimicrobial peptides derived from growth factors.** Malmsten M, Davoudi M, Walse B, et al. Growth Factors. 2007 Feb;25(1):60-70. <http://www.ncbi.nlm.nih.gov/pubmed/17454151>.
- <sup>48</sup> **An Opinion on "Staging" of Infant Formula: A Developmental Perspective on Infant Feeding.** Lönnerdal B, Hernell O. J Pediatr Gastroenterol Nutr. 2016 Jan;62(1):9-21. <https://pubmed.ncbi.nlm.nih.gov/25844707/>
- <sup>49</sup> **Human Milk Microbiota and Oligosaccharides: A Glimpse into Benefits, Diversity, and Correlations.** Moubareck CA. Nutrients. 2021 Mar 29;13(4):1123. doi: 10.3390/nu13041123. <https://pubmed.ncbi.nlm.nih.gov/33805503/>
- <sup>50</sup> **Human milk oligosaccharides: every baby needs a sugar mama.** Bode L. Glycobiology 2012 Sep;22(9):1147-62. <10.1093/glycob/cws074>
- <sup>51</sup> **Human milk oligosaccharides: every baby needs a sugar mama.** Bode L. Glycobiology 2012;22:1147-62. <https://pubmed.ncbi.nlm.nih.gov/22513036/>

- 
- <sup>52</sup> **[Recent advances in the bio-production of human milk oligosaccharides 2'-FL and 3-FL].** Xu Z, Li N, Chen Y, Zhang W, Zhu W, Sheng W, Gong Cheng Xue Bao. 2020 Dec 25;36(12):2767-2778. <https://pubmed.ncbi.nlm.nih.gov/33398971/> Free article. Review.
- <sup>53</sup> **Biotechnological Production of 2'-Fucosyllactose: A Prevalent Fucosylated Human Milk Oligosaccharide.** Zhou W, Jiang H, Wang L, Liang X, Mao X. ACS Synth Biol. 2021 Mar 19;10(3):447-458. <https://pubmed.ncbi.nlm.nih.gov/33687208/>
- <sup>54</sup> **2'-fucosyllactose: an abundant, genetically determined soluble glycan present in human milk.** Castanys-Muñoz E, Martín MJ, Prieto PA. Nutr Rev. 2013 Dec;71(12):773-89. <https://pubmed.ncbi.nlm.nih.gov/24246032/> Free article. Review.
- <sup>55</sup> **Systematic Characterization and Longitudinal Study Reveal Distinguishing Features of Human Milk Oligosaccharides in China.** Wu J, Wu S, Huo J, Ruan H, Xu X, Hao Z, Wei Y. Curr Dev Nutr. 2020 Jul 2;4(8):nzaa113. <https://pubmed.ncbi.nlm.nih.gov/32734137/> Free PMC article.
- <sup>56</sup> **Blends of Human Milk Oligosaccharides Confer Intestinal Epithelial Barrier Protection in Vitro.** Natividad JM, Rytz A, Keddani S, Bergonzelli G, Garcia-Rodenas CL. Nutrients. 2020 Oct 5;12(10):3047. <https://pubmed.ncbi.nlm.nih.gov/33027993/> Free PMC article.
- <sup>57</sup> **Anti-Pathogenic Functions of Non-Digestible Oligosaccharides In Vitro.** Asadpoor M, Peeters C, Henricks PAJ, Varasteh S, Pieters RJ, Folkerts G, Braber S. Nutrients. 2020 Jun 16;12(6):1789. doi: 10.3390/nu12061789. PMID: 32560186 Free PMC article. Review. <https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32560186/>
- <sup>58</sup> **Protection of Galacto-Oligosaccharide against E. coli O157 Colonization through Enhancing Gut Barrier Function and Modulating Gut Microbiota.** Zou Y, Wang J, Wang Y, Peng B, Liu J, Zhang B, Lv H, Wang S. Foods. 2020 Nov 21;9(11):1710. <https://pubmed.ncbi.nlm.nih.gov/33233359/>
- <sup>59</sup> **Galacto-oligosaccharides ameliorate dysbiotic Bifidobacteriaceae decline in Japanese patients with type 2 diabetes.** Gonai M, Shigehisa A, Kigawa I, Kurasaki K, Chonan O, Matsuki T, Yoshida Y, Aida M, Hamano K, Terauchi Y. Benef Microbes. 2017 Oct 13;8(5):705-716. <https://pubmed.ncbi.nlm.nih.gov/28884590/>
- <sup>60</sup> **Leaky brain in neurological and psychiatric disorders: Drivers and consequences.** Morris G, Fernandes BS, Puri BK, Walker AJ, Carvalho AF, Berk M. Aust N Z J Psychiatry. 2018 Oct;52(10):924-948. <https://pubmed.ncbi.nlm.nih.gov/30231628/Review>.
- <sup>61</sup> **A review of dietary and microbial connections to depression, anxiety, and stress.** Taylor AM, Holscher HD. Nutr Neurosci. 2020 Mar;23(3):237-250. <https://pubmed.ncbi.nlm.nih.gov/29985786/>
- <sup>62</sup> **Toxicological evaluation of fucoidan extracted from Laminaria japonica in Wistar rats.** Li N, Zhang Q, Song J. Food Chem Toxicol. 2005 Mar;43(3):421-6. <http://www.ncbi.nlm.nih.gov/pubmed/15680677>
- <sup>63</sup> **Toxicological evaluation of fucoidan from Cladosiphon okamuranus.** Gideon TP, Rengasamy R. J Med Food. 2008 Dec;11(4):638-42. <http://www.ncbi.nlm.nih.gov/pubmed/15680677>
- <sup>64</sup> **Defensive effects of a fucoidan from brown alga Undaria pinnatifida infection.** Hayashi K, Nakano T, Hashimoto M, et al. Int Immunopharmacol. 2008 Jan;8(1):109-16. <http://www.ncbi.nlm.nih.gov/pubmed/18068106> against herpes simplex virus
- <sup>65</sup> **The role of NK cells in antitumor activity of dietary fucoidan from Undaria pinnatifida sporophylls (Mekabu).** Maruyama H, Tamauchi H, Iizuka M, Nakano T. Planta Med. 2006 Dec;72(15):1415-7. <http://www.ncbi.nlm.nih.gov/pubmed/17054048>
- <sup>66</sup> **Immunostimulatory effects of fucoidan on bone marrow-derived dendritic cells.** Kim MH, Joo HG. Immunol Lett. 2008 Jan 29;115(2):138-43. <http://www.ncbi.nlm.nih.gov/pubmed/18077003>
- <sup>67</sup> **A new procedure for the isolation of anti-HIV compounds (polysaccharides and polyphenols) from the marine alga Fucus vesiculosus.** Béress A, Wassermann O, Tahhan S, Bruhn T, Béress L, Kraiselburd EN, Gonzalez LV, de Motta GE, Chavez PI. J Nat Prod. 1993 Apr;56(4):478-88. <http://www.ncbi.nlm.nih.gov/pubmed/7684438>
- <sup>68</sup> **Inhibition of reverse transcriptase activity of HIV by polysaccharides of brown algae.** Queiroz KC, Medeiros VP, Queiroz LS, Abreu LR, Rocha HA, Ferreira CV, Jucá MB, Aoyama H, Leite EL. Biomed Pharmacother. 2008 Jun;62(5):303-7. <http://www.ncbi.nlm.nih.gov/pubmed/18455359>
- <sup>69</sup> **Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk Sea Fucus evanescens brown alga.** Alekseyenko TV, Zhanayeva SY, Venediktova AA, et al. Bull Exp Biol Med. 2007 Jun;143(6):730-2. PMID: 18239813 [PubMed - indexed for MEDLINE] <http://www.ncbi.nlm.nih.gov/pubmed/18239813>
- <sup>70</sup> **A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds.** Cumashi A, Ushakova NA, Preobrazhenskaya ME. Glycobiology vol. 17 no. 5 pp. 541-552, 2007. <http://www.ncbi.nlm.nih.gov/pubmed/17296677>



- 
- <sup>71</sup> **Apoptosis inducing activity of fucoidan in HCT-15 colon carcinoma cells.** Hyun JH, Kim SC, Kang JI, Kim MK, Boo HJ, Kwon JM, Koh YS, Hyun JW, Park DB, Yoo ES, Kang HK. *Biol Pharm Bull.* 2009 Oct;32(10):1760-4. <http://www.ncbi.nlm.nih.gov/pubmed/19801840> Free full text: [http://www.jstage.jst.go.jp/article/bpb/32/10/32\\_1760/article](http://www.jstage.jst.go.jp/article/bpb/32/10/32_1760/article)
- <sup>72</sup> **Fucoidan: Structure and Bioactivity.** Li B, Lu F, Wei X, et al. *Molecules* **2008**, 13, 1671-1695. <http://www.ncbi.nlm.nih.gov/pubmed/18794778>
- <sup>73</sup> **A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds.** Cumashi A, Ushakova NA, Preobrazhenskaya ME. *Glycobiology* vol. 17 no. 5 pp. 541–552, 2007. <http://www.ncbi.nlm.nih.gov/pubmed/17296677>
- <sup>74</sup> **Improved coagulation in bleeding disorders by Non-Anticoagulant Sulfated Polysaccharides (NASP).** Liu T, Scallan CD, Broze GJ Jr, Thromb Haemost. 2006 Jan;95(1):68-76. PMID: 16543964 [PubMed - indexed for MEDLINE] <http://www.ncbi.nlm.nih.gov/pubmed/16543964>
- <sup>75</sup> **A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds.** Cumashi A, Ushakova NA, Preobrazhenskaya ME. *Glycobiology* vol. 17 no. 5 pp. 541–552, 2007. <http://www.ncbi.nlm.nih.gov/pubmed/17296677>
- <sup>76</sup> **Fucoidin prevents Clostridium difficile toxin-A-induced ileal enteritis in mice.** Barreto AR, Cavalcante IC, Castro MV, et al. *Dig Dis Sci.* 2008 Apr;53(4):990-6. <http://www.ncbi.nlm.nih.gov/pubmed/17805968>
- <sup>77</sup> **Radioprotective effects of fucoidan in mice treated with total body irradiation.** Lee J, Kim J, Moon C, Kim SH, *Phytother Res.* 2008 Aug 6. <http://www.ncbi.nlm.nih.gov/pubmed/18683851>
- <sup>78</sup> **In vitro chemopreventive potential of fucophlorethols from the brown alga Fucus vesiculosus L. by anti-oxidant activity and inhibition of selected cytochrome P450 enzymes.** Parys S, Kehraus S, Krick A, Glombitza KW, Carmeli S, Klimo K, Gerhäuser C, König GM. *Phytochemistry.* 2010 Feb;71(2-3):221-9.
- <sup>79</sup> **Crucial role of neutrophils in the development of mechanical inflammatory hypernociception.** Cunha TM, Verri WA Jr., SchivoIR, et al. *Journal of Leukocyte Biology.* 2008;83:824-832. <http://www.ncbi.nlm.nih.gov/pubmed/18203872>; Full text: <http://www.jleukbio.org/cgi/content/full/83/4/824>
- <sup>80</sup> **The effects of fucoidan extracts on CCl(4)-induced liver injury.** Kang KS, Kim ID, Kwon RH, et al. *Arch Pharm Res.* 2008 May;31(5):622-7. <http://www.ncbi.nlm.nih.gov/pubmed/18481019>
- <sup>81</sup> **Mitochondrial dysfunction in an animal model of hyperoxaluria: a prophylactic approach with fucoidan.** Veena CK, Josephine A, Preetha SP, Rajesh NG, Varalakshmi P. *Eur J Pharmacol.* 2008 Jan 28;579(1-3):330-6 <http://www.ncbi.nlm.nih.gov/pubmed/18001705>
- <sup>82</sup> **Inhibitory Effects of Fucoidan in 3T3-L1 Adipocyte Differentiation.** Kim MJ, Chang UJ, Lee JS. *Mar Biotechnol (NY).* 2008 Dec 10. <http://www.ncbi.nlm.nih.gov/pubmed/19067076>
- <sup>83</sup> **Increased effect of fucoidan on lipoprotein lipase secretion in adipocytes.** Yokota T, Nagashima M, Ghazizadeh M, Kawanami O. *Life Sci.* 2009 Apr 10;84(15-16):523-9. <http://www.ncbi.nlm.nih.gov/pubmed/19302807>
- <sup>84</sup> **Lipoprotein Lipase: From Gene to Obesity.** Wang H, Eckel RH. *Am J Physiol Endocrinol Metab.* 2009 Mar 24. <http://www.ncbi.nlm.nih.gov/pubmed/19318514>
- <sup>85</sup> **Brown kelp modulates endocrine hormones in female sprague-dawley rats and in human luteinized granulosa cells.** Skibola CF, Curry JD, VandeVoort C, Conley A, Smith MT. *J Nutr.* 2005 Feb;135(2):296-300. <http://www.ncbi.nlm.nih.gov/pubmed/15671230> ; Free full text access: <http://jn.nutrition.org/cgi/content/full/135/2/296>
- <sup>86</sup> Skibola CF. The effect of Fucus vesiculosus, an edible brown seaweed, upon menstrual cycle length and hormonal status in three premenopausal women: a case report. *BMC Complement Altern Med.* 2004 Aug 4;4:10. <http://www.ncbi.nlm.nih.gov/pubmed/15294021>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC514561/?tool=pubmed>
- <sup>87</sup> **Oligosaccharides and Viral Infection: Human Milk Oligosaccharides versus Algal Fucan-Type Polysaccharides.** Hanisch F-G, Aydogan C. *Nestle Nutr Inst Workshop Ser* 2020;94:124-132. <https://pubmed.ncbi.nlm.nih.gov/32176880/>
- <sup>88</sup> **Vitamin B12** Linus Pauling Institute, Micronutrient Information Center. <https://lpi.oregonstate.edu/mic/vitamins/vitamin-B12> and references therein.
- <sup>89</sup> **Ascorbic acid and the immune system.** Ottoboni F, Ottoboni A. *The Journal of Orthomolecular Medicine.* 2005; 20(3): 179-183. Full text access: <http://www.orthomolecular.org/library/jom/2005/toc3.shtml>
- <sup>90</sup> Jones K. **Reishi: Ancient Herb for Modern Times.** Healing Arts Press. 1995.
- <sup>91</sup> **Vitamin C supplementation could reverse diabetes-induced endothelial cell dysfunction in mesenteric microcirculation in STZ-rats.** Sridulyakul P, Chakraphan D, Patumraj S. *Clin Hemorrhheol Microcirc* 2006;34(1-2):315-21. <http://www.ncbi.nlm.nih.gov/pubmed/16543652>

- 
- <sup>92</sup> **Long-term effects of oral vitamin C supplementation on the endothelial dysfunction in the iris microvessels of diabetic rats.** Jariyapongskul A, Rungjaroen T, Kasetsuwan N, et al. *Microvasc Res.* 2007 Jul;74(1):32-8. Epub 2007 Mar 23. <http://www.ncbi.nlm.nih.gov/pubmed/17467747>
- <sup>93</sup> **Ascorbic acid--important for iron metabolism.** Atanassova BD, Tzatchev KN. *Folia Med (Plovdiv).* 2008 Oct-Dec;50(4):11-6. <http://www.ncbi.nlm.nih.gov/pubmed/19209525>
- <sup>94</sup> **Reduced bactericidal activity in neutrophils from scorbutic animals and the effect of ascorbic acid on these target bacteria in vivo and in vitro.** Goldschmidt MC. *Am J Clin Nutr.* 1991 Dec;54(6 Suppl):1214S-1220S. [www.ncbi.nlm.nih.gov/pubmed/1962573](http://www.ncbi.nlm.nih.gov/pubmed/1962573); Full text: <http://www.ajcn.org/cgi/reprint/54/6/1214S>
- <sup>95</sup> **Enhancement of natural killer cell activity and T and B cell function by buffered vitamin C in patients exposed to toxic chemicals: the role of protein kinase-C.** Heuser G, Vojdani A. *Immunopharmacol Immunotoxicol.* 1997 Aug;19(3):291-312. <http://www.ncbi.nlm.nih.gov/pubmed/9248859>
- <sup>96</sup> **The effect of ascorbic acid supplementation on some parameters of the human immunological defence system.** Prinz W, Bortz R, Bregin B, Hersch M. *Int J Vitam Nutr Res.* 1977;47(3):248-57. <http://www.ncbi.nlm.nih.gov/pubmed/914459>
- <sup>97</sup> **Maitake D-Fraction: Apoptosis Inducer and Immune Enhancer.** Konno S. *Alternative and Complementary Therapies.* April 2001, Vol. 7, No. 2:102-107. <http://www.liebertonline.com/doi/abs/10.1089/10762800151125137?prevSearch=allfield%253A%2528Maitake%25BD-Fraction%252C%252BKonno%2529&searchHistoryKey=>
- <sup>98</sup> **Emerging roles of vitamin D: More reasons to address widespread vitamin D insufficiency.** Harris S. *Molecular Aspects of Medicine* 29 (2008) 359-60. <http://www.ncbi.nlm.nih.gov/pubmed/18840460> full text available for purchase at: [http://www.sciencedirect.com/science?\\_ob=MIimg&\\_imagekey=B6T9P-4TG9HVK-1-1&\\_cdi=5120&\\_user=10&\\_pii=S0098299708000642&\\_orig=search&\\_coverDate=12%2F31%2F2008&\\_sk=999709993&\\_view=c&\\_wchp=dGLbVt-b-zSkWb&\\_md5=fb6f50903b581d6698bd4648693ad656&\\_ie=/sdarticle.pdf](http://www.sciencedirect.com/science?_ob=MIimg&_imagekey=B6T9P-4TG9HVK-1-1&_cdi=5120&_user=10&_pii=S0098299708000642&_orig=search&_coverDate=12%2F31%2F2008&_sk=999709993&_view=c&_wchp=dGLbVt-b-zSkWb&_md5=fb6f50903b581d6698bd4648693ad656&_ie=/sdarticle.pdf)
- <sup>99</sup> **Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials.** Autier P, Gandini S. *Arch Intern Med.* 2007 Sep 10;167(16):1730-7. <http://www.ncbi.nlm.nih.gov/pubmed/17846391>; Full text access: <http://archinte.ama-assn.org/cgi/reprint/167/16/1730>
- <sup>100</sup> **25-hydroxyvitamin D levels and the risk of mortality in the general population.** Melamed ML, Michos ED, Post W, Astor B. *Arch Intern Med.* 2008 Aug 11;168(15):1629-37. <http://www.ncbi.nlm.nih.gov/pubmed/18695076>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677029/?tool=pubmed>
- <sup>101</sup> **Vitamin D Deficiency.** Holick MF. *NEJM* Volume 357:266-281 July 19, 2007 Number 3. <http://www.ncbi.nlm.nih.gov/pubmed/17634462>; Freefull text access: <http://content.nejm.org/cgi/content/extract/357/3/266>
- <sup>102</sup> **Update in vitamin D.** Adams JS, Hewison M. *J Clin Endocrinol Metab.* 2010 Feb;95(2):471-8. <http://www.ncbi.nlm.nih.gov/pubmed/20133466>;
- <sup>103</sup> **Vitamin D Deficiency.** Holick MF. *NEJM* Volume 357:266-281 July 19, 2007 Number 3. <http://www.ncbi.nlm.nih.gov/pubmed/17634462>; Free full text access: <http://content.nejm.org/cgi/content/extract/357/3/266>
- <sup>104</sup> **Large-scale in silico and microarray-based identification of direct 1,25-dihydroxyvitamin D3 target genes.** Wang TT, Tavera-Mendoza LE, Laperriere D, et al. *Mol Endocrinol.* 2005 Nov;19(11):2685-95. <http://www.ncbi.nlm.nih.gov/pubmed/16002434>; Free full text: <http://mend.endojournals.org/cgi/content/full/19/11/2685>
- <sup>105</sup> **Molecular actions of vitamin D contributing to cancer prevention.** Fleet JC.. *Mol Aspects Med.* 2008 Dec;29(6):388-96. <http://www.ncbi.nlm.nih.gov/pubmed/18755215>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2613446/?tool=pubmed>
- <sup>106</sup> **Vitamin D regulation of cathelicidin in the skin: toward a renaissance of vitamin D in dermatology?** Segaert S. *J Invest Dermatol.* 2008 Apr;128(4):773-5. <http://www.ncbi.nlm.nih.gov/pubmed/18337709>; Free full-text access: <http://www.nature.com/jid/journal/v128/n4/abs/jid200835a.html>
- <sup>107</sup> **Vitamin D signaling, infectious diseases, and regulation of innate immunity.** White JH. *Infect Immun.* 2008 Sep;76(9):3837-43. <http://www.ncbi.nlm.nih.gov/pubmed/18505808>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2519414/?tool=pubmed>
- <sup>108</sup> **Vitamin D-Directed Rheostatic Regulation of Monocyte Antibacterial Responses.** Adams JS, Ren S, Liu PT, et al. *J Immunol* 2009 182 (7), p. 4289. <http://www.ncbi.nlm.nih.gov/pubmed/19299728>; Free full text: <http://www.jimmunol.org/cgi/content/full/182/7/4289>
- <sup>109</sup> **Immunomodulatory effects of 1,25-dihydroxyvitamin D3 on TH1/TH2 cytokines in inflammatory bowel disease: an in vitro study.** Ardizzone S, Cassinotti A, Trabattoni D, et al. *Int J Immunopathol Pharmacol.* 2009 Jan-Mar;22(1):63-71. <http://www.ncbi.nlm.nih.gov/pubmed/19309553>

- 110 **Vitamin D-Directed Rheostatic Regulation of Monocyte Antibacterial Responses.** Adams JS, Ren S, Liu PT, et al. *J Immunol* 2009 182 (7), p. 4289. <http://www.ncbi.nlm.nih.gov/pubmed/19299728>; Free full text: <http://www.jimmunol.org/cgi/content/full/182/7/4289>
- 111 **Control of autoimmune diseases by the vitamin D endocrine system.** Adorini L, Penna G. *Nat Clin Pract Rheumatol.* 2008 Aug;4(8):404-12. <http://www.ncbi.nlm.nih.gov/pubmed/18594491>
- 112 **Vitamin D and innate immunity.** Hewison M. *Curr Opin Investig Drugs.* 2008 May;9(5):485-90. <http://www.ncbi.nlm.nih.gov/pubmed/18465658>
- 113 **Vitamin D as a defensin.** Adams JS. *J Musculoskelet Neuronol Interac* 2006; 6(4):344-46. <http://www.ncbi.nlm.nih.gov/pubmed/17185816>
- 114 **Control of autoimmune diseases by the vitamin D endocrine system.** Adorini L, Penna G. *Nat Clin Pract Rheumatol.* 2008 Aug;4(8):404-12. <http://www.ncbi.nlm.nih.gov/pubmed/18594491>
- 115 **Calcium and 1 alpha,25-dihydroxyvitamin D target the TNF-alpha pathway to suppress experimental inflammatory bowel disease.** Zhu Y, Mahon BD, Froicu M, Cantorn MT. *Eur J Immunol* 2005;35:217-24. <http://www.ncbi.nlm.nih.gov/pubmed/15593122>
- 116 **Vitamin D-vitamin D receptor system regulates antithrombogenicity in vivo.** Aihara K, Azuma H, Matsumoto T. *Clin Calcium.* 2006 Jul;16(7):1173-79. [Article in Japanese] <http://www.ncbi.nlm.nih.gov/pubmed/16816478>
- 117 **Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier.** Kong J, Zhang Z, Musch MW, et al. *Am J Physiol Gastrointest Liver Physiol.* 2008 Jan;294(1):G208-16. <http://www.ncbi.nlm.nih.gov/pubmed/17962355>; Free full text: <http://ajpgi.physiology.org/cgi/content/full/294/1/G208>
- 118 **Zinc in Human Health: Effect of Zinc on Immune Cells.** Prasad A, *Mol Med.* 2008 May-Jun; 14(5-6): 353-357. <http://www.ncbi.nlm.nih.gov/pubmed/18385818>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2277319/?tool=pubmed>
- 119 **Zinc, metallothioneins, immune responses, survival and ageing.** Mocchegiani E, Muzzioli M, Giacconi R. *Biogerontology* 1: 133-143, 2000. <http://www.ncbi.nlm.nih.gov/pubmed/11707929>
- 120 **Zinc, Human diseases and aging.** Fabris N, Mocchegiani E. *Aging (Milano).* 1995 Apr;7(2):77-93. <http://www.ncbi.nlm.nih.gov/pubmed/7548268>
- 121 **Zinc and immune function: the biological basis of altered resistance to infection.** Shankar A, Prasad A. *Am J Clin Nutr* 1999;68(suppl):447S-63S. <http://www.ncbi.nlm.nih.gov/pubmed/9701160>; Free full-text access: <http://www.ajcn.org/cgi/reprint/68/2/447S>
- 122 **Therapeutic Application of Zinc in Human Immunodeficiency Virus against Opportunistic Infections.** Mocchegiani E, Mario M. *J Nutr.* 2000 May;130(5S Suppl):1424S-31S. <http://www.ncbi.nlm.nih.gov/pubmed/10801955>; Free full-text access: <http://jn.nutrition.org/cgi/content/full/130/5/1424S>
- 123 **Zinc, Human diseases and aging.** Fabris N, Mocchegiani E. *Aging (Milano).* 1995 Apr;7(2):77-93. <http://www.ncbi.nlm.nih.gov/pubmed/7548268>
- 124 **Zinc in Human Health: Effect of Zinc on Immune Cells.** Prasad A. *Mol Med.* 2008 May-Jun; 14(5-6): 353-357. <http://www.ncbi.nlm.nih.gov/pubmed/18385818>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2277319/?tool=pubmed>
- 125 **Zinc: Mechanisms of Host Defense.** Prasad A. *J Nutr.* 2007 May;137(5):1345-9. <http://www.ncbi.nlm.nih.gov/pubmed/17449604>; Free full-text access: <http://jn.nutrition.org/cgi/content/full/137/5/1345>
- 126 **Clinical, immunological, anti-inflammatory and antioxidant roles of zinc.** Prasad AS. *Exp Gerontol.* 2008 May;43(5):370-7. <http://www.ncbi.nlm.nih.gov/pubmed/18054190>
- 127 **Zinc in Human Health: Effect of Zinc on Immune Cells.** Prasad A. *Mol Med.* 2008 May-Jun; 14(5-6): 353-357. <http://www.ncbi.nlm.nih.gov/pubmed/18385818>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2277319/?tool=pubmed>
- 128 **Yeast whole glucan particle (WGP) beta-glucan in conjunction with antitumour monoclonal antibodies to treat cancer.** Yan J, Allendorf DJ, Brandley B. *Expert Opin Biol Ther.* 2005 May;5(5):691-702. <http://www.ncbi.nlm.nih.gov/pubmed/15934844>
- 129 **Beta-Glucans in promoting health: prevention against mutation and cancer.** Mantovani MS, Bellini MF, Angeli JP, Oliveira RJ, et al. *Mutat Res.* 2008 Mar-Apr;658(3):154-61. <http://www.ncbi.nlm.nih.gov/pubmed/17827055>
- 130 **Beta Glucan Research.** <http://www.betaglucan.org/>
- 131 **Therapeutic potential of various beta-glucan sources in conjunction with anti-tumor monoclonal antibody in cancer therapy.** Driscoll M, Hansen R, Ding C, et al. *Cancer Biol Ther.* 2009 Mar 3;8(3). <http://www.ncbi.nlm.nih.gov/pubmed/19106638>
- 132 **Anthrax-protective effects of yeast beta 1,3 glucans.** Kournikakis B, Mandeville R, Brousseau P, Ostroff G. *MedGenMed.* 2003 Mar 21;5(1):1. <http://www.ncbi.nlm.nih.gov/pubmed/12827062>
- 133 **Combined yeast-derived beta-glucan with anti-tumor monoclonal antibody for cancer immunotherapy.** Liu J, Gunn L, Hansen R, Yan J. *Exp Mol Pathol.* 2009 Jun;86(3):208-14. <http://www.ncbi.nlm.nih.gov/pubmed/19454271>
- 134 **Beta Glucan Research.** <http://www.betaglucan.org/>

<sup>135</sup> **Questions and Answers on Beta 1,3/1,6 Glucan.** Jordan FM. IMMUNITION™ Report© Volume II No. 4.

<http://www.nsc24.com/questions.htm>

<sup>136</sup> **Beta Glucan Research: An Arsenal of Immune Defense: “The Role of Beta.-Glucan Receptors on Blood and Tissue Leukocytes in Phagocytosis and Metabolic Activation.”** Czop, Joyce K., Pathology and Immunopathology Research; 5:286-296. Harvard Medical School. 1986. PMID: 3037509 [PubMed - indexed for MEDLINE]

<sup>137</sup> **Beta-Glucans in promoting health: prevention against mutation and cancer.** Mantovani MS, Bellini MF, Angeli JP, Oliveira RJ, et al. *Mutat Res.* 2008 Mar-Apr;658(3):154-61. <http://www.ncbi.nlm.nih.gov/pubmed/17827055>

<sup>138</sup> **Immunomodulatory Activities Associated with  $\beta$ -Glucan Derived from *Saccharomyces cerevisiae*.** PELIZON AC, KANENO R, SOARES AMVC, et al. *Physiol. Res.* 54: 557-564, 2005. [www.ncbi.nlm.nih.gov/pubmed/16238470](http://www.ncbi.nlm.nih.gov/pubmed/16238470) (includes access to full text).

<sup>139</sup> **Supplemental vitamin C and yeast cell wall  $\beta$ -glucan as growth enhancers in newborn pigs and as immunomodulators after an endotoxin challenge after weaning.** Eicher SD, McKee CA, Carroll JA and Pajor EA. *J Anim Sci* 2006. 84:2352-2360.

<http://www.ncbi.nlm.nih.gov/pubmed/16908637> Full text: <http://jas.fass.org/cgi/content/full/84/9/2352>.

<sup>140</sup> **Beta Glucan Research.** <http://www.betaglucan.org/>

<sup>141</sup> **Yeast beta-glucan amplifies phagocyte killing of iC3b-opsonized tumor cells via complement receptor 3-Syk-phosphatidylinositol 3-kinase pathway.** Li B, Allendorf DJ, Hansen R, et al. *J Immunol.* 2006 Aug 1;177(3):1661-9. PMID:

<http://www.ncbi.nlm.nih.gov/pubmed/16849475>; free full text <http://www.jimmunol.org/cgi/content/full/177/3/1661>.

<sup>142</sup> **Yeast whole glucan particle (WGP) beta-glucan in conjunction with antitumour monoclonal antibodies to treat cancer.** Yan J, Allendorf DJ, Brandley B. *Expert Opin Biol Ther.* 2005 May;5(5):691-702. <http://www.ncbi.nlm.nih.gov/pubmed/15934844>

<sup>143</sup> **“The Role of Beta.-Glucan Receptors on Blood and Tissue Leukocytes in Phagocytosis and Metabolic Activation”.** Czop JK. *An Arsenal of Immune Defense: Pathology and Immunopathology Research*; 5:286-296. Harvard Medical School. 1986.

<http://www.ncbi.nlm.nih.gov/pubmed/3037509>.

<sup>144</sup> **Anthrax-Protective Effects of Yeast Beta1,3 Glucans.** Kournikakis B, Mandeville R, Brousseau P, Ostroff, G. *GenMed.* 2004 Mar 21;5(1):1. <http://www.ncbi.nlm.nih.gov/pubmed/12827062>

<sup>145</sup> **The Use of Glucan as Immunostimulant in the Treatment of Paracoccidioidomycosis.** Meira, D.A., Pereira PC, Marcondes-Machado J, et al; *Am J Trop Med Hyg* 55(5), 496-503; 1996. <http://www.ncbi.nlm.nih.gov/pubmed/8940980>

<sup>146</sup> **The biological activity of beta-glucans.** [No authors listed] *Minerva Med.* 2009 Jun;100(3):237-245.

<http://www.ncbi.nlm.nih.gov/pubmed/19571787>

<sup>147</sup> <sup>147</sup> **Antiviral effect of *Saccharomyces cerevisiae* beta-glucan to swine influenza virus by increased production of interferon-gamma and nitric oxide.** Jung K, Ha Y, Ha SK, et al. *J Vet Med B Infect Dis Vet Public Health.* 2004 Mar;51(2):72-6.

<http://www.ncbi.nlm.nih.gov/pubmed/15030604>

<sup>148</sup> **Beta-Glucans in promoting health: prevention against mutation and cancer.** Mantovani MS, Bellini MF, Angeli JP, et al. *Mutat Res.* 2008 Mar-Apr;658(3):154-61. <http://www.ncbi.nlm.nih.gov/pubmed/17827055>

<sup>149</sup> **Yeast cell wall polysaccharides as antioxidants and antimutagens: can they fight cancer?** Kogan G, Pajtinka M, Babincova M, et al. *Neoplasma.* 2008;55(5):387-93. <http://www.ncbi.nlm.nih.gov/pubmed/18665748>

<sup>150</sup> **Beta-Glucans in promoting health: prevention against mutation and cancer.** Mantovani MS, Bellini MF, Angeli JP, Oliveira RJ, et al. *Mutat Res.* 2008 Mar-Apr;658(3):154-61. <http://www.ncbi.nlm.nih.gov/pubmed/17827055>

<sup>151</sup> **Anti-tumor metastatic activity of beta-glucan purified from mutated *Saccharomyces cerevisiae*.** Yoon TJ, Kim TJ, Lee H, et al. *Int Immunopharmacol.* 2008 Jan;8(1):36-42. Epub 2007 Oct 30. <http://www.ncbi.nlm.nih.gov/pubmed/18068098>

<sup>152</sup> **Immune Response Enhancement: The Use of Glucan as Immunostimulant in the Treatment of Paracoccidioidomycosis;** Meira, D.A., et al; *Am J. Trop Med Hyg* 55(5), 496-503; 1996. <http://www.ncbi.nlm.nih.gov/pubmed/8940980>

<sup>153</sup> **Yeast cell wall polysaccharides as antioxidants and antimutagens: can they fight cancer?** Kogan G, Pajtinka M, Babincova M, et al. *Neoplasma.* 2008;55(5):387-93. <http://www.ncbi.nlm.nih.gov/pubmed/18665748>

<sup>154</sup> **Acetaminophen-induced toxicity is prevented by beta-D-glucan treatment in mice.** Toklu HZ, Sehirli AO, Velioglu-Ogüncü A, et al. *Eur J Pharmacol.* 2006 Aug 14;543(1-3):133-40. <http://www.ncbi.nlm.nih.gov/pubmed/16822497>

<sup>155</sup> **Yeast cell wall polysaccharides as antioxidants and antimutagens: can they fight cancer?** Kogan G, Pajtinka M, Babincova M, et al. *Neoplasma.* 2008;55(5):387-93. <http://www.ncbi.nlm.nih.gov/pubmed/18665748>

<sup>156</sup> **Enhancement of radioprotection and anti-tumor immunity by yeast-derived beta-glucan in mice.** Gu YH, Takagi Y, Nakamura T, *J Med Food.* 2005 Summer;8(2):154-8. <http://www.ncbi.nlm.nih.gov/pubmed/16117606>

<sup>157</sup> **Beta-glucan inhibits the genotoxicity of cyclophosphamide, adriamycin and cisplatin.** Tohamy AA, El-Ghor AA, Noshay MM. *Mutat Res.* 2003 Nov 10;541(1-2):45-53. <http://www.ncbi.nlm.nih.gov/pubmed/14568293>

<sup>158</sup> **The biological activity of beta-glucans.** Rondanelli M, Opizzi A, Monteferrario F. *Minerva Med.* 2009 Jun;100(3):237-245. <http://www.ncbi.nlm.nih.gov/pubmed/19571787>

<sup>159</sup> **Effects of yeast-derived beta-glucans on blood cholesterol and macrophage functionality.** Vetvicka V, Vetvickova J. *J Immunotoxicol.* 2009 Mar;6(1):30-5. <http://www.ncbi.nlm.nih.gov/pubmed/19519160>

<sup>160</sup> **Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients.** Reyna NY, Cano C, Bermúdez VJ, et al. *Am J Ther.* 2003 Nov-Dec;10(6):438-43. <http://www.ncbi.nlm.nih.gov/pubmed/14624282>

<sup>161</sup> **Beta-glucans in the treatment of diabetes and associated cardiovascular risks.** Chen J, Raymond K. *Vasc Health Risk Manag.* 2008;4(6):1265-72. <http://www.ncbi.nlm.nih.gov/pubmed/19337540>; free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2663451/?tool=pubmed>.

- <sup>162</sup> **Beta-glucans in the treatment of diabetes and associated cardiovascular risks.** Chen J, Raymond K. *Vasc Health Risk Manag.* 2008;4(6):1265-72. <http://www.ncbi.nlm.nih.gov/pubmed/19337540>; free full text article: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2663451/?tool=pubmed>.
- <sup>163</sup> **Conjugation of protein antigen to microparticulate beta-glucan from *Saccharomyces cerevisiae*: a new adjuvant for intradermal and oral immunizations.** Berner VK, Sura ME, Hunter KW Jr. *Appl Microbiol Biotechnol.* 2008 Oct;80(6):1053-61. <http://www.ncbi.nlm.nih.gov/pubmed/18677470>
- <sup>164</sup> **Immunomodulating Activity of *Agaricus brasiliensis* KA21 in Mice and in Human Volunteers.** Liu Y, Fukuwatari Y, Okumura K, et al. *Evid Based Complement Alternat Med.* 2008 Jun;5(2):205-219. <http://www.ncbi.nlm.nih.gov/pubmed/18604247>  
Free Full text: <http://ecam.oxfordjournals.org/cgi/content/full/5/2/205>
- <sup>165</sup> **Tumor-specific cytotoxic and immunopotentiating effects of relatively low molecular weight products derived from the basidiomycete, *Agaricus blazei* Murill.** Fujimiya Y, Suzuki Y, Katakura R, Ebina T. *Anticancer Res.* 1999 Jan-Feb;19(1A):113-8. <http://www.ncbi.nlm.nih.gov/pubmed/10226531>
- <sup>166</sup> **Polysaccharides from *Agaricus blazei* stimulate lymphocyte T-cell subsets in mice.** Mizuno M et al. *Biosci Biotechnol Biochem.* 62, 30:434-7, 1998. <http://www.ncbi.nlm.nih.gov/pubmed/9571772> ; Full text: [http://www.jstage.jst.go.jp/article/bbb/62/3/62\\_434/article](http://www.jstage.jst.go.jp/article/bbb/62/3/62_434/article)
- <sup>167</sup> **Effects of the medicinal mushroom *Agaricus blazei* Murill on immunity, infection and cancer.** Hetland G, Johnson E, Lyberg T, ET AL. *Scand J Immunol.* 2008 Oct;68(4):363-70. <http://www.ncbi.nlm.nih.gov/pubmed/18782264>
- <sup>168</sup> **Immunomodulating Activity of *Agaricus brasiliensis* KA21 in Mice and in Human Volunteers.** Liu Y, Fukuwatari Y, Okumura K, et al. *Evid Based Complement Alternat Med.* 2008 Jun;5(2):205-219. <http://www.ncbi.nlm.nih.gov/pubmed/18604247>  
Free Full text: <http://ecam.oxfordjournals.org/cgi/content/full/5/2/205>
- <sup>169</sup> **Immunomodulating Activity of *Agaricus brasiliensis* KA21 in Mice and in Human Volunteers.** Liu Y, Fukuwatari Y, Okumura K, et al. *Evid Based Complement Alternat Med.* 2008 Jun;5(2):205-219. <http://www.ncbi.nlm.nih.gov/pubmed/18604247>  
Free Full text: <http://ecam.oxfordjournals.org/cgi/content/full/5/2/205>
- <sup>170</sup> **The mushroom *Agaricus blazei* Murill extract normalizes liver function in patients with chronic hepatitis B.** Hsu CH, Hwang KC, Chiang YH, Chou P. *J Altern Complement Med.* 2008 Apr;14(3):299-301. <http://www.ncbi.nlm.nih.gov/pubmed/18370584>
- <sup>171</sup> **Interleukin-12- and interferon-gamma-mediated natural killer cell activation by *Agaricus blazei* Murill.** Yuminamochi E, Koike T, Takeda K, Horiuchi I, Okumura K. *Immunology.* 2007 Jun;121(2):197-206. Epub 2007 Mar 7. <http://www.ncbi.nlm.nih.gov/pubmed/17346284>;  
Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2265935/?tool=pubmed>
- <sup>172</sup> **Tumoricidal effects of beta-glucans: mechanisms include both antioxidant activity plus enhanced systemic and topical immunity.** Gu Y, Fujimiya Y, Itokawa Y, et al. *Nutr Cancer.* 2008;60(5):685-91. <http://www.ncbi.nlm.nih.gov/pubmed/18791933>
- <sup>173</sup> **Inhibitory action of a (1->6)-beta-D-glucan-protein complex (F III-2-b) isolated from *Agaricus blazei* Murill ("*himematsutake*") on Meth A fibrosarcoma-bearing mice and its antitumor mechanism.** Itoh H, Ito H, Amano H, Noda H. *Jpn J Pharmacol.* 1994 Oct;66(2):265-71. <http://www.ncbi.nlm.nih.gov/pubmed/7869611> ; Full text: [http://www.journalarchive.jst.go.jp/english/jnlabstract\\_en.php?cdjournal=jphs1951&cdvol=66&noissue=2&startpage=265](http://www.journalarchive.jst.go.jp/english/jnlabstract_en.php?cdjournal=jphs1951&cdvol=66&noissue=2&startpage=265)
- <sup>174</sup> **Immuno-stimulating effect of the endo-polysaccharide produced by submerged culture of *Inonotus obliquus*.** Kim YO, Han SB, Lee HW, et al. *Life Sci.* 2005 Sep 23;77(19):2438-56. <http://www.ncbi.nlm.nih.gov/pubmed/15970296>
- <sup>175</sup> **Chaga mushroom (*Inonotus obliquus*) induces G0/G1 arrest and apoptosis in human hepatoma HepG2 cells.** Youn MJ, Kim JK, Park SY, et al. *World J Gastroenterol.* 2008 Jan 28;14(4):511-7. <http://www.ncbi.nlm.nih.gov/pubmed/18203281>; Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681140/?tool=pubmed>
- <sup>176</sup> **Identification of a novel blocker of IKBA kinase activation that enhances apoptosis and inhibits proliferation and invasion by suppressing nuclear factor-KB.** Sung B, Pandey M, Nakajima Y, et al. *Mol Cancer Ther* 2008;7(1), 191-201. <http://www.ncbi.nlm.nih.gov/pubmed/18202022>; Full text: <http://mct.aacrjournals.org/content/7/1/191.long>
- <sup>177</sup> **Identification of a novel blocker of IKBA kinase activation that enhances apoptosis and inhibits proliferation and invasion by suppressing nuclear factor-KB.** Sung B, Pandey M, Nakajima Y, et al. *Mol Cancer Ther* 2008;7(1), 191-201. <http://www.ncbi.nlm.nih.gov/pubmed/18202022>; Full text: <http://mct.aacrjournals.org/content/7/1/191.long>
- <sup>178</sup> **Antioxidant effect of *Inonotus obliquus*.** Cui Y, Kim D, Park K. *J Ethnopharmacol.* 2005 Jan 4;96(1-2):79-85. <http://www.ncbi.nlm.nih.gov/pubmed/15588653>
- <sup>179</sup> **Chaga mushroom extract inhibits oxidative DNA damage in human lymphocytes as assessed by comet assay.** Park YK, Lee HB, Jeon EJ, et al. *Biofactors.* 2004;21(1-4):1090-112. <http://www.ncbi.nlm.nih.gov/pubmed/15630179>
- <sup>180</sup> **The immunomodulator PSK induces in vitro cytotoxic activity in tumour cell lines via arrest of cell cycle and induction of apoptosis.** Jiménez-Medina E, Berruguilla E, Romero I, et al. *BMC Cancer.* 2008 Mar 24;8:78. <http://www.ncbi.nlm.nih.gov/pubmed/18366723>;  
Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291471/?tool=pubmed>

- <sup>181</sup> **Activation of human natural killer cells by the protein-bound polysaccharide PSK independently of interferon and interleukin 2.** Kariya Y, Inoue N, Kihara T, et al. *Immunol Lett.* 1992 Feb 15;31(3):241-5. <http://www.ncbi.nlm.nih.gov/pubmed/1372283>
- <sup>182</sup> **Protein-bound polysaccharide (PSK) induces cytotoxic activity in the NKL human natural killer cell line.** Pedrinaci S, Algarra I, Garrido F. *Int J Clin Lab Res.* 1999;29(4):135-40. <http://www.ncbi.nlm.nih.gov/pubmed/10784373>
- <sup>183</sup> **Involution of the thymus in tumor-bearing mice and its restoration by PSK. II. Mechanism of the involution and its restoration.** Oguchi Y, Morita I, Fujii T, et al. *J Clin Lab Immunol.* 1987 Oct;24(2):93-99. <http://www.ncbi.nlm.nih.gov/pubmed/3437442>
- <sup>184</sup> **Antimetastatic Effects of P5K (Krestin), a Protein-bound Polysaccharide Obtained from Basidiomycetes: An Overview.** Kobayashi H, Matsunaga K, Y Oguchi. *Cancer Epidemiology, Biomarkers & Prevention* 1995 Apr-May;4(3):275-281. [Free full text auto-download: cebp.aacrjournals.org/content/4/3/275.full.pdf](http://cebp.aacrjournals.org/content/4/3/275.full.pdf)
- <sup>185</sup> **A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae).** Ng TB. *Gen Pharmacol.* 1998 Jan;30(1):1-4. <http://www.ncbi.nlm.nih.gov/pubmed/9457474>
- <sup>186</sup> **Triterpene acids from *Poria cocos* and their anti-tumor-promoting effects.** Akihisa T, Nakamura Y, Tokuda H, et al. *J Nat Prod.* 2007 Jun;70(6):948-53. <http://www.ncbi.nlm.nih.gov/pubmed/17488130>
- <sup>187</sup> **Induction of apoptosis in prostate cancer cells by pachymic acid from *Poria cocos*.** Gapter L, Wang Z, Glinski J, Ng KY. *Biochem Biophys Res Commun.* 2005 Jul 15;332(4):1153-61. <http://www.ncbi.nlm.nih.gov/pubmed/15913545>
- <sup>188</sup> **Induction of apoptosis in prostate cancer cells by pachymic acid from *Poria cocos*.** Gapter L, Wang Z, Glinski J, Ng KY. *Biochem Biophys Res Commun.* 2005 Jul 15;332(4):1153-61. <http://www.ncbi.nlm.nih.gov/pubmed/15913545>
- <sup>189</sup> **Cytotoxic and Anti-oxidant Activities of Lanostane-Type Triterpenes Isolated from *Poria cocos*.** Zhou L, Zhang Y, Gapter LA, et al. *Chem Pharm Bull (Tokyo).* 2008 Oct;56(10):1459-62. <http://www.ncbi.nlm.nih.gov/pubmed/18827390>; Full text access: [http://www.jstage.jst.go.jp/article/cpb/56/10/56\\_1459/article](http://www.jstage.jst.go.jp/article/cpb/56/10/56_1459/article)
- <sup>190</sup> **Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1.** Sagar SM, Yance D, Wong RK. *Curr Oncol.* 2006 Feb;13(1):14-26. <http://www.ncbi.nlm.nih.gov/pubmed/17576437>; Full text access: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1891166/?tool=pubmed>
- <sup>191</sup> **Herbal formula FBD extracts prevented brain injury and inflammation induced by cerebral ischemia-reperfusion.** Lin Z, Zhu D, Yan Y, Yu B. *J Ethnopharmacol.* 2008 Jun 19;118(1):140-7. <http://www.ncbi.nlm.nih.gov/pubmed/18486376>.
- <sup>192</sup> **Effect of the basidiomycete *Poria cocos* on experimental dermatitis and other inflammatory conditions.** Cuellar MJ, Giner RM, Recio MC, Just MJ, Mañez S, Rios JL. *Chem Pharm Bull (Tokyo).* 1997 Mar;45(3):492-4. <http://www.ncbi.nlm.nih.gov/pubmed/9085556>.
- <sup>193</sup> **An Antioxidant Phytotherapy to Rescue Neuronal Oxidative Stress.** Lin Z, Zhu D, Yan Y, et al. *Evid Based Complement Alternat Med.* 2008 Aug 7. Free full text: <http://ecam.oxfordjournals.org/cgi/content/full/nen053v1>.
- <sup>194</sup> ***Poria cocos* water extract (PCW) protects PC12 neuronal cells from beta-amyloid-induced cell death through antioxidant and antiapoptotic functions.** Park YH, Son IH, Kim B, et al. *Pharmazie.* 2009 Nov;64(11):760-4. <http://www.ncbi.nlm.nih.gov/pubmed/20099523>.
- <sup>195</sup> **Oral administration of submerged cultivated *Grifola frondosa* enhances phagocytic activity in normal mice.** Wang L, Ha CL, Cheng TL, et al. *J Pharm Pharmacol.* 2008 Feb;60(2):237-43. <http://www.ncbi.nlm.nih.gov/pubmed/18237472>
- <sup>196</sup> **Enhancement of cytotoxicity of NK cells by D-Fraction, a polysaccharide from *Grifola frondosa*.** Kodama N, Asakawa A, Inui A, et al. *Oncol Rep.* 2005 Mar;13(3):497-502. <http://www.ncbi.nlm.nih.gov/pubmed/15706424>
- <sup>197</sup> **Enhancement of cytotoxicity of NK cells by D-Fraction, a polysaccharide from *Grifola frondosa*.** Kodama N, Asakawa A, Inui A, et al. *Oncol Rep.* 2005 Mar;13(3):497-502. <http://www.ncbi.nlm.nih.gov/pubmed/15706424>
- <sup>198</sup> **Inhibitory effect of MD-Fraction on tumor metastasis: involvement of NK cell activation and suppression of intercellular adhesion molecule (ICAM)-1 expression in lung vascular endothelial cells.** Masuda Y, Murata Y, Hayashi M, et al. *Biol Pharm Bull.* 2008 Jun;31(6):1104-8. <http://www.ncbi.nlm.nih.gov/pubmed/18520039>; Free full text access: [http://www.jstage.jst.go.jp/article/bpb/31/6/31\\_1104/article](http://www.jstage.jst.go.jp/article/bpb/31/6/31_1104/article)
- <sup>199</sup> **The immune effects of edible fungus polysaccharides compounds in mice.** Yin Y, Fu W, Fu M, et al. *Asia Pac J Clin Nutr.* 2007;16 Suppl 1:258-60. <http://www.ncbi.nlm.nih.gov/pubmed/17392115>
- <sup>200</sup> **Inhibition of hepatitis B virus by D-fraction from *Grifola frondosa*: synergistic effect of combination with interferon-alpha in HepG2 2.2.15.** Gu CQ, Li J, Chao FH. *Antiviral Res.* 2006 Nov;72(2):162-5. <http://www.ncbi.nlm.nih.gov/pubmed/16846649>

- 
- 201 **Characterization and immunomodulating activities of polysaccharide from *Lentinus edodes*.** Zheng R, Jie S, Hanchuan D, Moucheng W. *Int Immunopharmacol.* 2005 May;5(5):811-20. <http://www.ncbi.nlm.nih.gov/pubmed/15778117>
- 202 **Lentinan has a stimulatory effect on innate and adaptive immunity against murine *Listeria monocytogenes* infection.** Kupfahl C, Geginat G, Hof H. *Int Immunopharmacol.* 2006 Apr;6(4):686-96. <http://www.ncbi.nlm.nih.gov/pubmed/16504933>
- 203 **The shiitake mushroom-derived immuno-stimulant lentinan protects against murine malaria blood-stage infection by evoking adaptive immune-responses.** Zhou LD, Zhang QH, Zhang Y, et al. *Int Immunopharmacol* 2009 Apr;9(4):455-62. <http://www.ncbi.nlm.nih.gov/pubmed/19189863>
- 204 **Hepatoprotective effect of extracts from *Lentinus edodes* mycelia on dimethylnitrosamine-induced liver injury.** Akamatsu S, Watanabe A, Tamesada M, *Biol Pharm Bull.* 2004 Dec;27(12):1957-60. <http://www.ncbi.nlm.nih.gov/pubmed/15577212>; Free full text access: [http://www.jstage.jst.go.jp/article/bpb/27/12/27\\_1957/article](http://www.jstage.jst.go.jp/article/bpb/27/12/27_1957/article)
- 205 **Protection against D-galactosamine-induced acute liver injury by oral administration of extracts from *Lentinus edodes* mycelia.** Watanabe A, Kobayashi M, Hayashi S, et al. *Biol Pharm Bull.* 2006 Aug;29(8):1651-4. <http://www.ncbi.nlm.nih.gov/pubmed/1688062>; Free full-text access: [http://www.jstage.jst.go.jp/article/bpb/29/8/29\\_1651/article](http://www.jstage.jst.go.jp/article/bpb/29/8/29_1651/article)
- 206 **Inhibition of human colon carcinoma development by lentinan from shiitake mushrooms (*Lentinus edodes*).** Ng ML, Yap AT.). *J Altern Complement Med.* 2002 Oct;8(5):581-9. <http://www.ncbi.nlm.nih.gov/pubmed/12470439>
- 207 **An examination of antibacterial and antifungal properties of constituents of Shiitake (*Lentinula edodes*) and oyster (*Pleurotus ostreatus*) mushrooms.** Hearst R, Nelson D, McCollum G, et al. *Complement Ther Clin Pract.* 2009 Feb;15(1):5-7. <http://www.ncbi.nlm.nih.gov/pubmed/19161947>
- 208 **Reishi polysaccharides induce immunoglobulin production through the TLR4/TLR2-mediated induction of transcription factor Blimp-1.** Lin K, Kao Y, Kuo H, et al. *J Biol Chem.* 2006 Aug 25;281(34):24111-23. <http://www.ncbi.nlm.nih.gov/pubmed/16798741>; Free full text: <http://www.jbc.org/content/281/34/24111.long>.
- 209 **Reishi immuno-modulation protein induces interleukin-2 expression via protein kinase-dependent signaling pathways within human T cells.** Hsu H, Hua K, Wu W, et al. *J Cell Physiol.* 2008 Apr;215(1):15-26. <http://www.ncbi.nlm.nih.gov/pubmed/18189229>.
- 210 **Reishi polysaccharides induce immunoglobulin production through the TLR4/TLR2-mediated induction of transcription factor Blimp-1.** Lin K, Kao Y, Kuo H, et al. *J Biol Chem.* 2006 Aug 25;281(34):24111-23. <http://www.ncbi.nlm.nih.gov/pubmed/16798741>; Free full text: <http://www.jbc.org/content/281/34/24111.long>.
- 211 ***Ganoderma lucidum* polysaccharides enhance the function of immunological effector cells in immunosuppressed mice.** Zhu XL, Chen AF, Lin ZB. *J Ethnopharmacol.* 2007 May 4;111(2):219-26. <http://www.ncbi.nlm.nih.gov/pubmed/17182202>.
- 212 **Polysaccharide purified from *Ganoderma lucidum* induced activation and maturation of human monocyte-derived dendritic cells by the NF-kappaB and p38 mitogen-activated protein kinase pathways.** Lin YL, Liang YG, Lee SS, Chiang BL. *L Leukoc Biol.* 2005 Aug;78(2):533-43. <http://www.ncbi.nlm.nih.gov/pubmed/15894585>; Free full text: <http://www.jleukbio.org/cgi/content/full/78/2/533>.
- 213 **Indian medicinal mushrooms as a source of antioxidant and antitumor agents.** Aith A, Janardhanan K. *J Clin Biochem Nutr.* 2007 May;40(3):157-62. <http://www.ncbi.nlm.nih.gov/pubmed/18398492>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2275760/?tool=pubmed>.
- 214 **Dihydrolipoic acid inhibits tetrachlorohydroquinone-induced tumor promotion through prevention of oxidative damage.** Wang YJ, Yang MC, Pan MH. *Food Chem Toxicol.* 2008 Dec;46(12):3739-48. [www.ncbi.nlm.nih.gov/pubmed/18951944](http://www.ncbi.nlm.nih.gov/pubmed/18951944)
- 215 **Lipoic acid as an anti-inflammatory and neuroprotective treatment for Alzheimer's disease.** Maczurek A, Hager K, Kenkies M, et al. *Adv Drug Deliv Rev.* 2008 Oct-Nov;60(13-14):1463-70. <http://www.ncbi.nlm.nih.gov/pubmed/18655815>
- 216 **Dihydrolipoic acid activates oligomycin-sensitive thiol groups and increases ATP synthesis in mitochondria.** Zimmer G, Mainka L, Krüger E. *Arch Biochem Biophys.* 1991 Aug 1;288(2):609-13. [www.ncbi.nlm.nih.gov/pubmed/1832845](http://www.ncbi.nlm.nih.gov/pubmed/1832845)
- 217 **Cardioprotective effects of dihydrolipoic acid and tocopherol in right heart hypertrophy during oxidative stress.** Thürich T, Bereiter-Hahn J, Schneider M, Zimmer G. *Arzneimittelforschung.* 1998 Jan;48(1):13-21. [www.ncbi.nlm.nih.gov/pubmed/9522025](http://www.ncbi.nlm.nih.gov/pubmed/9522025)
- 218 **Neuroprotection by the metabolic antioxidant alpha-lipoic acid.** Packer L, Tritschler HJ, Wessel K. *Free Radic Biol Med.* 1997;22(1-2):359-78. [www.ncbi.nlm.nih.gov/pubmed/8958163](http://www.ncbi.nlm.nih.gov/pubmed/8958163)
- 219 **Immunomodulatory activity of curcumin: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production in vitro.** Gao X, Kuo J, Jiang H, et al. *Biochem Pharmacol.* 2004 Jul 1;68(1):51-61. <http://www.ncbi.nlm.nih.gov/pubmed/15183117>
- 220 **Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.** Aggarwal BB, Sung B.

- 
- 221 **Curcumin, an atoxic antioxidant and natural NFκB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases.** Bengmark S. *JPEN J Parenter Enteral Nutr.* 2006 Jan-Feb;30(1):45-51. <http://www.ncbi.nlm.nih.gov/pubmed/16387899>
- 222 **Curcumin, quercetin, and tBHQ modulate glutathione levels in astrocytes and neurons: importance of the glutamate cysteine ligase modifier subunit.** Lavoie S, Chen Y, Dalton TP, et al. *J Neurochem.* 2009 Mar;108(6):1410-22. <http://www.ncbi.nlm.nih.gov/pubmed/19183254>
- 223 **Curcumin ameliorates acute thioacetamide-induced hepatotoxicity.** Shapiro H, Ashkenazi M, Weizman N, et al. *J Gastroenterol Hepatol.* 2006 Feb;21(2):358-66. <http://www.ncbi.nlm.nih.gov/pubmed/16509859>
- 224 **Pharmacological basis for the use of turmeric in gastrointestinal and respiratory disorders.** Gilani AH, Shah AJ, Ghayur MN, Majeed K. *Life Sci.* 2005 May 13;76(26):3089-105. <http://www.ncbi.nlm.nih.gov/pubmed/15850601>
- 225 **Curcumin inhibits neurotensin-mediated interleukin-8 production and migration of HCT116 human colon cancer cells.** Wang X, Wang Q, Ives KL, Evers BM. *Clin Cancer Res.* 2006 Sep 15;12(18):5346-55. <http://www.ncbi.nlm.nih.gov/pubmed/17000667>; Full text: <http://clincancerres.aacrjournals.org/content/12/18/5346.long>
- 226 **Antidepressant activity of curcumin: involvement of serotonin and dopamine system.** Kulkarni SK, Bhutani MK, Bishnoi M. *Psychopharmacology (Berl).* 2008 Dec;201(3):435-42. <http://www.ncbi.nlm.nih.gov/pubmed/18766332>
- 227 **In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice.** Seeram NP, Adams LS, Henning SM, et al. *J Nutr Biochem.* 2005 Jun;16(6):360-7. <http://www.ncbi.nlm.nih.gov/pubmed/15936648>
- 228 **Protective effect of pomegranate-derived products on UVB-mediated damage in human reconstituted skin.** Afaq F, Zaid MA, Khan N, et al. *Exp Dermatol.* 2009 Mar 3. <http://www.ncbi.nlm.nih.gov/pubmed/19320737>
- 229 **Immune-suppressive activity of punicalagin via inhibition of NFAT activation.** Lee SI, Kim BS, Kim KS, et al. *Biochem Biophys Res Commun.* 2008 Jul 11;371(4):799-803. <http://www.ncbi.nlm.nih.gov/pubmed/18466764>
- 230 **The flavonoid ellagic acid from a medicinal herb inhibits host immune tolerance induced by the hepatitis B virus-e antigen.** Kang EH, Kwon TY, Oh GT, et al. *Antiviral Res.* 2006 Nov;72(2):100-6. <http://www.ncbi.nlm.nih.gov/pubmed/16720052>
- 231 **Pomegranate juice: a heart-healthy fruit juice.** Basu A, Penugonda K. *Nutr Rev.* 2009 Jan;67(1):49-56. <http://www.ncbi.nlm.nih.gov/pubmed/19146506>
- 232 **Pomegranate fruit components modulate human thrombin.** Cuccioloni M, Mozzicafreddo M, Sparapani L, et al. *Fitoterapia.* 2009 Apr 6. <http://www.ncbi.nlm.nih.gov/pubmed/19358882>
- 233 **Pomegranate ellagitannins stimulate the growth of *Akkermansia muciniphila* in vivo.** Henning SM, Summanen PH, Lee RP, Yang J, Finegold SM, Heber D, Li Z. *Anaerobe.* 2017 Feb;43:56-60. <https://pubmed.ncbi.nlm.nih.gov/27940244/>
- 234 **Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers.** Li Z, Henning SM, Lee RP, Lu QY, Summanen PH, Thames G, Corbett K, Downes J, Tseng CH, Finegold SM, Heber D. *Food Funct.* 2015 Aug;6(8):2487-95. <https://pubmed.ncbi.nlm.nih.gov/26189645/>
- 235 **Immunomodulatory Role of Urolithin A on Metabolic Diseases.** Toney AM, Fox D, Chaidez V, Ramer-Tait AE, Chung S. *Biomedicines.* 2021 Feb 15;9(2):192. <https://pubmed.ncbi.nlm.nih.gov/33671880/> Free PMC article. Review.
- 236 **Urolithin A, a Gut Metabolite, Improves Insulin Sensitivity Through Augmentation of Mitochondrial Function and Biogenesis.** Toney AM, Fan R, Xian Y, Chaidez V, Ramer-Tait AE, Chung S. *Obesity (Silver Spring).* 2019 Apr;27(4):612-620. <https://pubmed.ncbi.nlm.nih.gov/30768775/>
- 237 **Effect of dietary glutamine on tumor glutathione levels and apoptosis-related proteins in DMBA-induced breast cancer of rats.** Todorova VK, Harms SA, Kaufmann Y, et al. *Breast Cancer Res Treat.* 2004 Dec;88(3):247-56. <http://www.ncbi.nlm.nih.gov/pubmed/15609127>
- 238 **Effect of dietary glutamine on tumor glutathione levels and apoptosis-related proteins in DMBA-induced breast cancer of rats.** Todorova VK, Harms SA, Kaufmann Y, et al. *Breast Cancer Res Treat.* 2004 Dec;88(3):247-56. <http://www.ncbi.nlm.nih.gov/pubmed/15609127>
- 239 **Glutamine prevents DMBA-induced squamous cell cancer.** Lim V, Korourian D, Todorova VK, et al. *Oral Oncol.* 2009 Feb; 45(2):148-55. <http://www.ncbi.nlm.nih.gov/pubmed/18635390>
- 240 **Glutamine prevents DMBA-induced squamous cell cancer.** Lim V, Korourian D, Todorova VK, et al. *Oral Oncol.* 2009 Feb; 45(2):148-55. <http://www.ncbi.nlm.nih.gov/pubmed/18635390>



- 
- 241 **Protective effects of glutamine dipeptide and alpha-tocopherol against ischemia-reperfusion injury in the isolated rat liver.** Schuster H, Blanc MC, Bonnefont-Rousselot D, et al. *Clin Nutr.* 2009 Jun;28(3):331-7. <http://www.ncbi.nlm.nih.gov/pubmed/19324476>
- 242 **N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility.** Dodd S, Dean O, Copolov DL, et al. *Expert Opin Biol Ther.* 2008 Dec;8(12):1955-62. <http://www.ncbi.nlm.nih.gov/pubmed/18990082>
- 243 **The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid.** Aruoma OI, Halliwell B, Hoey BM, Butler J. *Free Radic Biol Med.* 1989;6(6):593-7. <http://www.ncbi.nlm.nih.gov/pubmed/2546864>
- 244 **Glutathione deficiency leads to mitochondrial damage in brain.** Jain A, Mårtensson J, Stole E, et al. *Proc Natl Acad Sci U S A.* 1991 Mar 1;88(5):1913-7. <http://www.ncbi.nlm.nih.gov/pubmed/2000395>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC51136/?tool=pubmed>
- 245 **Glutathione: overview of its protective roles, measurement, and biosynthesis.** Forman HJ, Zhang H, Rinna A. *Mol Aspects Med.* 2009 Feb-Apr;30(1-2):1-12. Epub 2008 Aug 30. <http://www.ncbi.nlm.nih.gov/pubmed/18796312>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2696075/?tool=pubmed>
- 246 **Environmental toxicity, redox signaling and lung inflammation: the role of glutathione.** Biswas SK, Rahman I. *Mol Aspects Med.* 2009 Feb-Apr;30(1-2):60-76. Epub 2008 Aug 8. <http://www.ncbi.nlm.nih.gov/pubmed/18760298>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699458/?tool=pubmed>
- 247 **N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility.** Dodd S, Dean O, Copolov DL, et al. *Expert Opin Biol Ther.* 2008 Dec;8(12):1955-62. <http://www.ncbi.nlm.nih.gov/pubmed/18990082>
- 248 **The protective mechanism of antioxidants in cadmium-induced ototoxicity in vitro and in vivo.** Kim SJ, Jeong HJ, Myung NY, et al. *Environ Health Perspect.* 2008 Jul;116(7):854-62. <http://www.ncbi.nlm.nih.gov/pubmed/18629305>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2453151/?tool=pubmed>
- 249 **The effects of stress and aging on glutathione metabolism.** Maher P. *Ageing Res Rev.* 2005 May;4(2):288-314. <http://www.ncbi.nlm.nih.gov/pubmed/15936251>
- 250 **Extracellular redox state: refining the definition of oxidative stress in aging.** Jones DP. *Rejuvenation Res.* 2006 Summer(92):169-81. <http://www.ncbi.nlm.nih.gov/pubmed/16706639>
- 251 **The deficit in low molecular weight thiols as a target for antiageing therapy.** Dröge W, Kinscherf R, Hildebrandt W, Schmitt T. *Curr Drug Targets.* 2006 Nov;7(11):1505-12. <http://www.ncbi.nlm.nih.gov/pubmed/17100590>
- 252 **N-Acetylcysteine--a safe antidote for cysteine/glutathione deficiency.** Atkuri KR, Mantovani JJ, Herzenberg LA, Herzenberg LA. *Curr Opin Pharmacol.* 2007 Aug;7(4):355-9. Epub 2007 Jun 29. <http://www.ncbi.nlm.nih.gov/pubmed/17602868>
- 253 **Use of N-acetyl cysteine to increase intracellular glutathione during the induction of antitumor responses by IL-2.** Yim CY, Hibbs JB Jr, McGregor JR, et al. *J Immunol.* 1994 Jun 15;152(12):5796-805. <http://www.ncbi.nlm.nih.gov/pubmed/8207209>
- 254 **Antioxidant therapeutic advances in COPD.** Rahman I. *Ther Adv Respir Dis.* 2008 Dec;2(6):351-74. <http://www.ncbi.nlm.nih.gov/pubmed/19124382>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2744584/?tool=pubmed>
- 255 **Role of N-acetylcysteine in the management of COPD.** Sadowska AM, Verbraecken J, Darquennes K, De Backer WA. *Int J Chron Obstruct Pulmon Dis.* 2006;1(4):425-34. <http://www.ncbi.nlm.nih.gov/pubmed/18044098>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2707813/?tool=pubmed>
- 256 **N-acetylcysteineamide (NACA) prevents inflammation and oxidative stress in animals exposed to diesel engine exhaust.** Banerjee A, Trueblood MB, Zhang X, et al. *Toxicol Lett.* 2009 Jun 22;187(3):187-93. Epub 2009 Mar 13. <http://www.ncbi.nlm.nih.gov/pubmed/19429263>
- 257 **Antioxidant properties of N-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease.** Dekhuijzen PN. *Eur Respir J.* 2004 Apr;23(4):629-36. <http://www.ncbi.nlm.nih.gov/pubmed/15083766>; Free full text: <http://erj.ersjournals.com/cgi/content/full/23/4/629>
- 258 **Comparative study of the anti-HIV activities of ascorbate and thiol-containing reducing agents in chronically HIV-infected cells.** Harakeh S, Jariwalla RJ. *Am J Clin Nutr.* 1991 Dec;54(6 Suppl):1231S-1235S. <http://www.ncbi.nlm.nih.gov/pubmed/1720598>; Free full text access: <http://www.ajcn.org/cgi/reprint/54/6/1231S>
- 259 **Antioxidants Suppress Lymphoma and Increase Longevity in Atm-Deficient Mice.** Ramune Reliene and Robert H. Schiestl. *The American Society for Nutrition J. Nutr.* 137:229S-232S, January 2007. <http://www.ncbi.nlm.nih.gov/pubmed/17182831>; Free full text access: <http://jn.nutrition.org/cgi/content/full/137/1/229S>

- 
- 260 **Protective effects of N-acetylcysteine and beta-glucan pretreatment on oxidative stress in cecal ligation and puncture model of sepsis.** Senoglu N, Yuzbasioglu MF, Aral M, et al. *J Invest Surg.* 2008 Sep-Oct;21(5):237-43. <http://www.ncbi.nlm.nih.gov/pubmed/19160131>
- 261 **Use of N-acetylcysteine for postnecrosectomy peripancreatic collections in a patient with severe, acute pancreatitis.** **Narasimhan S, Khwaja HA, Dutta S,** et al. *Can J Surg.* 2008 Dec;51(6):E133-4. <http://www.ncbi.nlm.nih.gov/pubmed/19057727>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2592585/?tool=pubmed>
- 262 **N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility.** Dodd S, Dean O, Copolov DL, et al. *Expert Opin Biol Ther.* 2008 Dec;8(12):1955-62. <http://www.ncbi.nlm.nih.gov/pubmed/18990082>
- 263 **Potentiation of lead-induced cell death in PC12 cells by glutamate: protection by N-acetylcysteine amide (NACA), a novel thiol antioxidant.** Penugonda S, Mare S, Lutz P, et al. *Toxicol Appl Pharmacol.* 2006 Oct 15;216(2):197-205. <http://www.ncbi.nlm.nih.gov/pubmed/16781745>
- 264 **Redox regulation in anabolic and catabolic processes.** Dröge W. *Curr Opin Clin Nutr Metab Care.* 2006 May;9(3): 190-5. <http://www.ncbi.nlm.nih.gov/pubmed/16607115>
- 265 **Oxidative stress and ageing: is ageing a cysteine deficiency syndrome?** Dröge W. *Philos Trans R Soc Lond B Biol Sci.* 2005 Dec 29;360(1464):2355-72. <http://www.ncbi.nlm.nih.gov/pubmed/16321806>; Free full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1569588/?tool=pubmed>
- 266 **N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility.** Dodd S, Dean O, Copolov DL, et al. *Expert Opin Biol Ther.* 2008 Dec;8(12):1955-62. <http://www.ncbi.nlm.nih.gov/pubmed/18990082>
- 267 **Black pepper and its pungent principle-piperine: a review of diverse physiological effects.** Srinivasan K. *Crit Rev Food Sci Nutr.* 2007;47(8):735-48. <http://www.ncbi.nlm.nih.gov/pubmed/17987447>
- 268 **Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers.** Shoba G, Joy D, Joseph T, et al. *Planta Med.* 1998 May;64(4):353-6. <http://www.ncbi.nlm.nih.gov/pubmed/9619120>
- 269 **Permeability characteristics of piperine on oral absorption--an active alkaloid from peppers and a bioavailability enhancer.** Khajuria A, Zutshi U, Bedi KL. *Nutr. Biochem.* (2000) 11: 109-113. <http://www.ncbi.nlm.nih.gov/pubmed/9536651>
- 270 **Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics.** Khajuria A, Thusu N, Zutshi U. *Phytomedicine.* 2002 Apr;9(3):224-31. <http://www.ncbi.nlm.nih.gov/pubmed/12046863>
- 271 **Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis.** Manoharan S, Balakrishnan S, Menon V, et al. *Singapore Med J.* 2009 Feb;50(2):139-46. Abstract and free full text access: <http://www.ncbi.nlm.nih.gov/pubmed/19296028>
- 272 **Piperine inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in the ovalbumin-induced asthma model.** Kim SH, Lee YC. *J Pharm Pharmacol.* 2009 Mar;61(3):353. <http://www.ncbi.nlm.nih.gov/pubmed/19222908>
- 273 **Anti-inflammatory and anti-arthritis effects of piperine in human interleukin-1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models.** Bang JS, Oh DH, Choi HM, et al. *Arthritis Res Ther.* 2009 Mar 30;11(2):R49. <http://www.ncbi.nlm.nih.gov/pubmed/19327174>; Free full text: <http://arthritis-research.com/content/11/2/R49>.
- 274 **Piperine, the potential functional food for mood and cognitive disorders.** Wattanathorn J, Chonpathompikunlert P, Muchimapura S, et al. *Food Chem Toxicol.* 2008 Sep;46(9):3106-10. <http://www.ncbi.nlm.nih.gov/pubmed/18639606>.