

# ***Cytoprotective and Polyphenol-Rich Botanicals that Provide Antioxidant Activity, Reduce Oxidation & Modulate Inflammation***

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## ***Discussion***

### **CELLULAR PROTECTION: POLYPHENOL-RICH HERBS**

Stress-resistance capacity is a hallmark of longevity and survival throughout the plant and animal kingdoms. All plants naturally produce many biochemical compounds that support their health and survival. Time-proven traditional herbs provide a protective role in helping prevent diseases and promote wellness. Today, as researchers look to the plant world for safe, efficacious remedies, they are examining these same plants and discovering more about their role in human health, disease and aging.

These powerful botanicals are now known to be especially rich in plant micronutrients known as polyphenols. Polyphenols are a vast family of naturally-occurring biochemical compounds produced by plants as part of their defense system. Vegetables, fruits, whole grains and herbs provide a complex diversity and abundance of polyphenols. Of over 10,000 known polyphenolic compounds, almost half are flavonoids. Flavonoids are further divided into six major subgroups: flavones, flavonols, isoflavones, flavanones, anthocyanidins and flavanols (catechins and proanthocyanadins).<sup>1</sup> Diets high in plant polyphenols are found to correlate with increased health and decreased incidence of chronic degenerative disease.<sup>2,3</sup>

Polyphenols are classified according to their chemical structure, which defines their functions and activity. Research clearly reveals that polyphenolic compounds act as antioxidants that work through multiple pathways. They exert a powerful influence on normalizing cell signaling and support healthy cellular function. They also exert anti-inflammatory and immuno-modulatory effects. Many of the phenolic compounds in plants are being studied for their role in preventing both occurrence and progression of tumor growth. It is scientifically well-known that excess generation of ROS (reactive oxygen species) and other radicals at the cellular level causes lipid oxidation and reduces cellular membrane fluidity. This can cause loss of enzyme and

receptor activity and – since it damages proteins in the cellular membrane – can cause cell inactivation. As the free radicals attack and damage cellular DNA, mutational changes occur that can lead to cancer.<sup>4,5</sup> This damage from oxidative stress can also manifest as degenerative disease, immuno-deficiency, inflammatory conditions and neurological or metabolic disorders. Natural plant foods and medicinals are of great interest to researchers because of their well-known antioxidant capacities and because polyphenolic compounds are found to inhibit mutagenesis and carcinogenesis in humans.<sup>4,5</sup>

Polyphenols and their subgroup, flavonoids, are widely studied and known to support health and help prevent degenerative disease when included as part of our regular diet. Botanical medicinals contain a wide variety of polyphenols including catechins, curcuminoids, resveratrol, quercetin and OPCs (oligomeric proanthocyanadins) along with other beneficial compounds.

#### ***Actions of Plant Polyphenols:***

- non-specific, normalizing action
- modulate cell-signaling pathways
- protect cells and neurons
- exert strong antioxidant activity
- offer cardio-protective ability
- inhibit neurodegeneration
- promote healthy cellular behavior
- anti-inflammatory

Polyphenols are found to be cardio-protective, neuro-protective and cyto-protective. Epidemiological studies demonstrate an inverse relationship between a polyphenolic-rich diet and risk of chronic human diseases<sup>3</sup> including cardiovascular, diabetes, osteoporosis, chronic inflammation, cancer and neurodegenerative conditions.<sup>2,3</sup> Plant polyphenols protect cellular health through many actions such as scavenging free radicals, antioxidant and anti-inflammatory activity, and enhancing normal cell function. Normal cell function includes cell-signaling processes, apoptosis (normal cell death), cellular metabolism and maintenance of healthy cellular structure.<sup>2</sup>

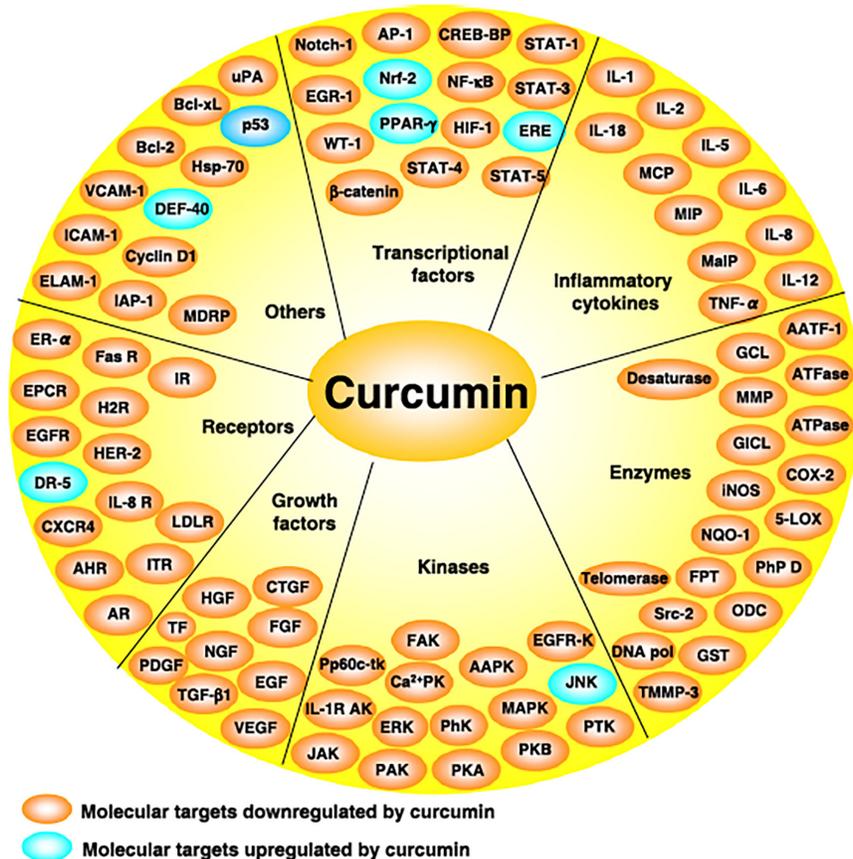
## CHRONIC INFLAMMATION

The body's protective inflammatory response to acute infection is mediated by the immune system to promote healing and recovery. Chronic inflammation, caused by multiple factors, is intensely studied because it is widely recognized as being linked to most chronic disease

conditions including autoimmune, neurodegenerative, cardiovascular and many more.<sup>3,7</sup>

Studies show that inflammation and oxidative stress at the cellular level are a root cause of most disease processes.<sup>2,5</sup> Herbs with high polyphenolic content are currently of great interest because they offer profound antioxidant and anti-inflammatory activity.<sup>6</sup> They exert antioxidant influence through multiple pathways. They neutralize free radicals through donation of an electron or hydrogen atom. They are also able to suppress formation of free radicals through several pathways, can act to chelate metals, and can help prevent lipid peroxidation. These high polyphenolic botanicals support regeneration of beneficial vitamins and promote antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. They demonstrate an ability to modulate enzyme response to decrease oxidative stress, and also modulate cell-signaling pathways.<sup>2,4,6-8</sup>

Specialized cytokine proteins modulate the inflammatory



This diagram, while it focuses on curcumin, illustrates the fact that plant polyphenolic compounds work through multiple pathways to modulate cellular health and function.

Anand P, Sundaram C, et al. Curcumin and cancer: An "old-age" disease with an "age-old" solution. Cancer Letters 267 (2008) 133-164.

response. Cytokines such as IL-1 and IL-6 (interleukin 1 and 6) and TNF (tumor necrosis factor) provoke an inflammatory response that involves multiple response mechanisms, complex interactions and cell signaling processes. In this process, many pathways become dysregulated or dysfunctional.<sup>6-8</sup> NF-kB (nuclear factor kappa-beta) is a key player in inflammatory response and as a regulator of gene expression that influences cell health.<sup>7</sup> When

NF-kB is activated, it is found to promote expression of proinflammatory factors.<sup>8</sup> Many contemporary studies and treatments are focused on blocking the NF-kB pathway as a means to prevent or mediate chronic inflammation. A great deal of research is focused on the role and efficacy of botanicals in this capacity to support the return of dysregulated biochemical pathways to normal, and thus restore health.<sup>7,8</sup>

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## **Botanicals that Provide Antioxidant Activity, Reduce Oxidation, and Modulate Inflammation**



### **Turmeric (*Curcuma longa*)**

Turmeric is world-renowned as a cooking spice, food, herbal medicine and dye. Yogis revered Turmeric for its ability to nourish the blood and help keep ligaments and joints flexible to enhance their practice. Chinese and Ayurvedic medicines value Turmeric to move the blood and the Qi (energy), supporting circulation and warming the metabolism.

Curcuminoids, the active constituents in Turmeric, are yellowish-orange, lipid-soluble natural phenolic compounds. Highly-researched, they demonstrate many protective health benefits and offer powerful anti-inflammatory, antioxidant, antineoplastic, antiviral and immune-modulating activity.<sup>9</sup>

Curcumin works to calm inflammatory pathways including NF-kB, TNF (tumor necrosis factor), multiple IL (interleukin) factors<sup>10,11</sup> and inhibits COX-2 and 5-LOX.<sup>12-17</sup> NF-kB is a protein that induces an abnormal inflammatory response that can lead to multiple disorders including arthritis and cellular disturbances.<sup>18,19</sup> COX-2 and 5-LOX are well-known inflammatory markers.

Curcumin shows hepato-protective, cyto-protective and antioxidant properties.<sup>11,20</sup> It is found to modulate glutathione (GSH) activity in animals.<sup>21</sup> Curcumin modulates cell-signaling pathways, supports normal cell function and death (apoptosis) and regulates cell-cycle-gene expression.<sup>16,17</sup> Curcumin also demonstrates neuro-protective qualities.<sup>22-24</sup>



### **Green Tea (*Camellia sinensis*)**

Tea (*Camellia sinensis*) is a true botanical treasure with a 5,000-year history as a beverage and medicine in Chinese culture. Today tea is one of the most widely consumed beverages in the world. In Chinese,

Japanese and other Asian cultures the tea ceremony celebrates quietude and contemplation. Even in daily use, tea is revered for its ability to promote calmness and clarity. Using ancient methods, black, green, oolong and pu'er teas are all produced from varieties of *Camellia sinensis*. Tea is highly studied for its calming and healing qualities.

Green tea is produced by steaming the fresh leaves, which preserves the highly-prized polyphenols. Comprising 30% to 40% of the green tea leaves, these polyphenols include the flavonoids known as flavonols and flavanols (catechins) – including epigallocatechin-3-gallate (EGCG). These factors impart significant antioxidant and anti-inflammatory activity.<sup>25-28</sup>

Tea polyphenols benefit cell cycle regulation and are found to be cell-protective.<sup>29-31</sup> EGCG, the main catechin in green tea extract, inhibits VEGF (vascular endothelial growth factor)<sup>32,33</sup> implicated in abnormal cell behavior, cell signaling and angiogenesis.<sup>33-36</sup>



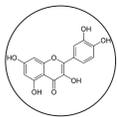
### **Japanese Knotweed / Resveratrol (*Polygonum cuspidatum*)**

Japanese Knotweed has been used widely for centuries in Chinese medicine to prevent and treat disease. In modern research it is found to exert antimicrobial, anti-inflammatory, neuro-protective and cardio-protective functions. Japanese Knotweed contains quercetin, catechin and resveratrol, which demonstrate powerful antioxidant and anti-inflammatory properties. Knotweed extract is found to inhibit inflammatory pathways including TNF-a, NFkB and COX-2 expression.<sup>37,38</sup>

Japanese Knotweed standardized to 50% resveratrol has been extensively researched over several decades for its multiple profound health benefits. Numerous studies investigate its role in preventing age-related disorders

including diabetes, cardiovascular, cancer and neurodegenerative<sup>39,40</sup>, which share a common foundation of inflammatory processes with cellular dysregulation. Research reports that resveratrol binds to numerous cell-signaling molecules, activates transcription factors, induces antioxidant enzymes, modulates cell-cycle regulation and inhibits expression of inflammatory processes.<sup>41</sup> Japanese Knotweed is well-recognized for its cardiovascular benefits as it supports endothelial health, inhibits low-density lipoprotein oxidation, and suppresses platelet aggregation.<sup>42-44</sup>

Due to its inherent properties as a polyphenolic compound, resveratrol is neuro-protective and can help inhibit progression of age-related neurological decline and disease. One reason for this is that due to the high rate of oxygen consumption of the brain, with concurrently very low levels of antioxidant enzymes, the brain is particularly susceptible to free-radical damage. A potent antioxidant, resveratrol works through multiple cellular pathways to support normal function.<sup>45</sup> Recent studies report that resveratrol, which crosses the blood-brain barrier, decreases aging-dependent cognitive decline, and helps stabilize even lower levels of amyloid-beta proteins in those with mild to moderate Alzheimer's disease.<sup>39,46,47</sup>



#### Quercetin (Dihydrate)

Quercetin is a flavonol abundantly found in many foods including onions, curly kale, leeks, apples and green, black and red teas.<sup>1,48,49</sup> Quercetin benefits those suffering from allergies primarily due to its anti-histamine activity.<sup>50</sup> It is anti-inflammatory, antioxidant and exerts free-radical scavenging activities.<sup>51</sup>

Quercetin benefits cellular health and inhibits abnormal cell growth. Widely researched for its ability to inhibit abnormal cell growth, it is reported to be anti-angiogenic and able to induce normal apoptosis.<sup>52-58</sup>

Like many polyphenolic compounds, quercetin is found to be neuro-protective.<sup>59-61</sup> It inhibits free-radical damage and lipid peroxidation.<sup>62</sup> Quercetin also modulates inflammatory pathways including COX-2 and 5-LOX.<sup>63-66</sup> Studies find it down-regulates NFkB and EGF (epidermal growth factor) expression<sup>66-68</sup> and improves cell-signaling.<sup>69,70</sup>



#### Grape Seed & Skin (*Vitis vinifera*)

Grape fruit, seed and skin are rich in resveratrol, anthocyanins, catechins and quercetin, which are widely known to be cyto-protective, anti-inflammatory and antioxidant.<sup>71-74</sup> These compounds act as free-radical scavengers in the brain and whole body. They are anti-inflammatory, inhibiting COX-2 and NF-kappaB

pathways.<sup>75,76</sup> Studies find these natural compounds modulate signal transduction pathways<sup>77-79</sup> and promote apoptosis.<sup>80</sup>



#### Amla (*Emblica officinalis*)

Amla fruit, sometimes called Indian Gooseberry, is a valued Ayurvedic restorative and rejuvenative tonic. Used for thousands of years as food and medicine it supplies a rich source of vitamin C, flavonoids and carotenoids.<sup>81</sup> Amla fruit is traditionally given to relieve circulatory, digestive and respiratory conditions.

Studies find it to possess potent antioxidant and anti-inflammatory activity.<sup>82-84</sup> Amla has an ORAC (oxygen radical absorbance capacity) value of 1770 – twice that of Acai berry and about 17 times that of pomegranate fruit.<sup>85</sup>

Amla fruit is shown to be hepato-protective<sup>86-88</sup> and to reduce serum fatty acids.<sup>89</sup> It contains gallic acid, ellagic acid, and sesquiterpenoids, which are found to be free-radical scavenging, antioxidant, anti-inflammatory, anti-mutagenic and immunomodulatory.<sup>90-92</sup>



#### Holy Basil (*Ocimum sanctum*)

Holy Basil, known as Tulsi in the Ayurvedic tradition, is a sacred plant revered for its healing qualities. Traditionally, it is considered calming and healing to the nervous system with the ability to promote clarity and serenity. Ayurvedic practitioners use Tulsi to strengthen the respiratory and cardiovascular systems and as a digestive aid.

Compounds in Tulsi include volatile oils such as eugenol, and the triterpenoids ursolic acid and rosmarinic acid (phenylpropanoid). It also contains some carotenoids, vitamin C, calcium, iron, zinc and chlorophyll.<sup>93</sup> Ursolic acid is known for its anti-inflammatory, anti-microbial and anti-viral properties, and for exerting hepatoprotective influence.<sup>94-95</sup>

Tulsi is considered adaptogenic as it lowers the stress-induced release of adrenal hormones<sup>96-98</sup> and is found to increase physical performance.<sup>99</sup> It modulates inflammation and inhibits COX-2 expression.<sup>95</sup> Tulsi also exhibits antioxidant activity and modulates glutathione and antioxidant enzymes.<sup>95,100-103</sup>



#### Ginger (*Zingiber officinale*)

This world-renowned and well-loved herb has been used as cooking spice, herbal remedy and revered medicine for centuries. It is a daily household remedy for digestive upset, sore throat, colds and flu. Known as a valuable anti-nausea remedy it is also a digestive carminative. Ginger aids circulation and is used to warm the system during cold weather. Herbalists also use Ginger to enhance

the effectiveness of other herbs in a formula by supporting digestion and circulating the herbs.<sup>104</sup> The active ingredients are its many volatile oils.<sup>105-107</sup>

Ginger has a thermogenic and diaphoretic effect.<sup>108,109</sup> Modern studies find it beneficial for many types of nausea<sup>109-112</sup>, which is one of its traditional uses. It demonstrates impressive antioxidant<sup>113-116</sup> and anti-inflammatory activity.<sup>117,118</sup>



### Rosemary (*Rosmarinus officinalis*)

Traditional European herbalists called Rosemary the “Herb of Remembrance”. They valued it as a tonic for the heart, brain and nervous system. It was used to increase circulation, mental outlook and vitality. Dr. Rudolf Weiss, highly regarded as the founding father of German phytotherapy, used Rosemary extract to treat cerebral arteriosclerosis.

Rosemary possesses powerful antioxidant activity, containing numerous antioxidant compounds that are neuro-protective, hepato-protective and anti-inflammatory. It contains at least six phenolic diterpenoids with antioxidant activity. The most potent of these is carnosic acid, which transforms into another antioxidant compound called carnosol while it quenches free radicals. This transformation or cascade of antioxidant activity repeats several times. Rosemary inhibits ROS-induced mutagenicity and cell mediated oxidation of low-density lipoproteins (LDL).<sup>119,120</sup>

Rosemary contains significant amounts of rosmarinic acid - a phenolic acid. This is a water-soluble antioxidant that scores extremely high on the ORAC (oxygen radical scavenging activity) analysis, a method used to measure dietary antioxidant capacity of substances. Rosmarinic acid is anti-inflammatory and works to inhibit COX-2.<sup>121</sup> Some of Rosemary’s other antioxidants including limonene, terpinene and thymol, are shown to inhibit aging of the brain through acetylcholinesterase inhibition.<sup>122</sup>



### Bromelain (*Ananus comosus*)

Bromelain, a proteolytic enzyme, is a component of pineapple commonly used as a digestive aid. It demonstrates anti-edematous, anti-inflammatory and fibrinolytic activities. It is also an immuno-modulator that modulates cytokines.<sup>123,124</sup> Well-absorbed orally, therapeutic effects are enhanced with higher doses.<sup>125</sup>



### Long Pepper (*Piper longum*)

Long Pepper, one of the world’s oldest culinary and medicinal spices, is the fruit of a flowering vine that is indigenous to the hot and moist parts of India. In ancient times, until around the 14th century, Long Pepper

was much more widely known, used and traded than Black Pepper (*P. nigrum*). Highly prized for its sweet and pungent flavor in the Roman Empire, it traded for three times the cost of Black Pepper.<sup>126</sup> It was known to both Hippocrates and to the Greek botanist Theophrastus. Called Pippali in Ayurvedic medicine, it is one of their most esteemed herbs. It is the primary ingredient in the famous Ayurvedic formula Trikatu (“Three Pungents”), which contains three warming digestive herbs: Long Pepper, Black Pepper and Ginger Root. This formula has been used for thousands of years to enhance the digestion and assimilation of nutrients.

Modern studies find that Long Pepper exerts antioxidant activity, decreases lipid peroxide levels and modulates glutathione levels. Found to be anti-inflammatory and immunomodulatory, it is being studied for cytotoxic activity.<sup>126-130</sup> Long Pepper contains about 3% to 5% content of the pungent alkaloid piperine.<sup>129</sup> Known as an agent that enhances bioavailability of many nutrients, piperine improves the bioavailability of EGCG (epigallocatechin), the primary catechin found in Green Tea,<sup>131</sup> and of resveratrol and curcumin.<sup>132,133</sup>

*For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email [info@naturaedu.com](mailto:info@naturaedu.com).*

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