The Immunomodulatory and Anti-Inflammatory Role of Polyphenols

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Abstract: This review offers a systematic understanding about how polyphenols target multiple inflammatory components and lead to anti-inflammatory mechanisms. It provides a clear understanding of the molecular mechanisms of action of phenolic compounds. Polyphenols regulate immunity by interfering with immune cell regulation, proinflammatory cytokines’ synthesis, and gene expression. They inactivate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and modulate mitogen-activated protein Kinase (MAPk) and arachidonic acids pathways. Polyphenolic compounds inhibit phosphatidylinositol 3-kinases/protein kinase B (PI3K/Akt), inhibitor of kappa kinase/c-Jun amino-terminal kinases (IKK/JNK), mammalian target of rapamycin complex 1 (mTORC1) which is a protein complex that controls protein synthesis, and JAK/STAT. Their antioxidant activity and ability to inhibit enzymes involved in the production of eicosanoids contribute as well to their anti-inflammation properties. They inhibit certain enzymes involved in reactive oxygen species ROS production like xanthine oxidase and NADPH oxidase (NOX) while they upregulate other endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase (Px). Furthermore, they inhibit phospholipase A2 (PLA2), cyclooxygenase (COX) and lipoxygenase (LOX) leading to a reduction in the production of prostaglandins (PGs) and leukotrienes (LTs) and inflammation antagonism. The effects of these biologically active compounds on the immune system are associated with extended health benefits for different chronic inflammatory diseases. Studies of plant extracts and compounds show that polyphenols can play a beneficial role in the prevention and the progress of chronic diseases related to inflammation such as diabetes, obesity, neurodegeneration, cancers, and cardiovascular diseases, among other conditions.

Keywords: polyphenols; immune system; inflammation; molecular mechanisms; nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); arachidonic acid; mitogen-activated protein Kinase (MAPK); cytokines; oxidative stress; reactive oxygen species (ROS); cyclooxygenase (COX); nitric oxide synthase (NOS); lipoxygenase (LOX); superoxide dismutase (SOD); inhibitor of kappa kinase (IKK); extra-cellular signal regulated kinases (ERK); cancer; anti-inflammation; anti-tumorigenic; chronic inflammatory conditions; macrophages; T helper 1 (Th1); Th17; Treg

1. Introduction

Numerous studies have attributed to polyphenols a broad range of biological activities including but not limited to anti-inflammatory, immune-modulatory, antioxidant, cardiovascular protective and anti-cancer actions [1–5]. Polyphenols are ubiquitously made by plants and are present either as glycosides esters or as free aglycones [6]. More than 8000 structural variants exist in the polyphenol
family. Polyphenols are bioactive compounds found in fruits and vegetables contributing to their color, flavor, and pharmacological activities [1]. They are classified according to their chemical structures into flavonoids such as flavones, flavonols, isoflavones, neoflavonoids, chalcones, anthocyanidins, and proanthocyanidins and nonflavonoids, such as phenolic acids, stilbenoids, and phenolic amides [7]. The majority of these molecules are metabolites of plants, they are made of several aromatic rings with hydroxyl moieties [8]. Their chemical structures contribute to their classification into different classes. Considering gastrointestinal digestion, some—but not all—polyphenols are absorbed in the small intestine, for example, anthocyanins and the majority of remaining polyphenols except flavonoids are usually stable; these later are unstable in the duodenum. Unabsorbed polyphenols must be hydrolyzed first by digestive enzymes then glycosides with high lipid contents are absorbed by epithelial cells [9,10].

In recent years, consumers prefer using natural food ingredients as additives because of their safety and availability. Applications of phenolic compounds to multiple fresh perishable foods show that they are worthy to be used as preservatives in foods and can be creditable alternatives to synthetic food additives. In this sense, polyphenolic compounds start to substitute chemical additives in food. Different methods like spraying, coating and dipping treatment of food are currently applied in food technology preceding packaging as effective alternatives [11]. Grape seeds and olive oil polyphenols’ rich extracts can be used as food additives for their anti-oxidant properties [12]. Various polyphenols like grape polyphenols demonstrate an efficient role as additives in fish and fish products for their anti-oxidant properties in order to prevent lipid oxidation and quality deterioration of polyunsaturated fatty acids [13]. In addition polyphenolic compounds like flavonols, p-coumaric, and caffeic acids can be used as food preservatives for their antimicrobial activity [11].

Back to inflammation, continuous inflammation is known to be a major cause linked to different human disorders involving cancer, diabetes type II, obesity, arthritis, neurodegenerative diseases, and cardiovascular diseases [14,15]. Polyphenols derived from botanic origin have shown anti-inflammatory activity in vitro and in vivo highlighting their beneficial role as therapeutic tools in multiple acute and chronic disorders [16–20]. Accordingly, many epidemiological and experimental researches have been studying the anti-inflammatory and immune modulation activities of dietary polyphenols [15,21]. The ability of these natural compounds to modify the expression of several pro-inflammatory genes like multiple cytokines, lipoxygenase, nitric oxide synthases cyclooxygenase, in addition to their anti-oxidant characteristics such as ROS (reactive oxygen species) scavenging contributes to the regulation of inflammatory signaling [22,23]. This review will discuss the immunomodulatory effects of dietary polyphenols, their anti-inflammatory abilities, the different mechanisms and pathways involved in reducing inflammation and their contribution to protect from different chronic inflammatory diseases with a focus on their anti-cancer activity.

2. Polyphenols and Inflammation

The immune modulation effect of polyphenols is supported by different studies: some polyphenols impact on immune cells populations, modulate cytokines production, and pro-inflammatory genes expression [24,25]. For example, cardioprotective effects of resveratrol present in red wine grape and nuts were mainly attributed to its anti-inflammatory properties. In vivo and in vitro studies demonstrate that resveratrol can inhibit COX, inactivate peroxisome proliferator-activated receptor gamma (PPARγ) and induce eNOS (endothelial nitric oxide synthase) in murine and rat macrophages [26–28]. Likewise, a resveratrol analog, RVSA40, inhibits the pro-inflammatory cytokines TNF-α (Tumor necrosis factor alpha) and IL-6 (interleukin-6) in RAW (Murine macrophages cell line) 264.7 macrophages [29]. Another example is the non-flavonoid curcumin found in turmeric plants and mustard. Curcumin was shown to reduce the expression of inflammatory cytokines: TNF and IL-1, adhesion molecules like ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) in human umbilical vein endothelial cells and inflammatory mediators like prostaglandins and leukotriens. It also inhibits certain
enzymes involved in inflammation like COX in mice (cyclooxygenase), LOX (lipoxygenase) in, human endothelial cells MAPK (mitogen-activated protein Kinase), and IKK (inhibitor of kappa kinase). Moreover, curcumin downregulates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and STAT3 (signal transducer and activator of transcription) and reduces the expression of TLR-2 (toll-like receptor-2) and 4 while, in vivo, it upregulates PPARγ (Peroxisome proliferator-activated receptor gamma) in male adult rats [30–35]. Caffeic acid phenethyl ester suppresses TLR4 activation and LPS-mediated NF-κB in macrophages, Quercetin was also shown to inhibit leukotriens biosynthesis in human polymorphonuclear leukocytes [36,37]. COX2 expression is also attenuated by ECGC (Epigallocatechin gallate) in colon cancer cell and androgen-independent PC-3 cells of human prostate cancer, gingerol in and piceatannol (EGCG analog found in Norway spruces) leading to NFκB inactivation [30,38–40]. Furthermore, polyphenols, such as Gingerol and Quercetin can activate the production of adiponectin known for its anti-inflammatory effects [30,39]. Similarly, EGC blocks NFκB activation in human epithelial cells and downregulates the expression of iNOS (inducible nitric oxide synthase), NO (nitric oxide) production in macrophages resulting in its immunomodulation [38,40,41]. A series of in vitro studies found that other polyphenols like oleanolic acid, curcumin, kaempferol-3-O-sophoroside, ECGC and lycopene inhibit high mobility group box1 protein, an important chromatin protein that interacts with nucleosomes, transcription factors, and histones regulating transcription and playing a key role in inflammation [35]. All of these examples support the anti-inflammatory effects of polyphenols.

Polyphenols’ use is associated with a direct change in the count and differentiation of specific immune cells. An increase in T helper 1(Th1), natural killer (NK), macrophages and dendritic cells (DCs) in Peyer’s patches and spleen is associated with oral administration of polyphenols extracted from the fruit date in male C3H/HeN mice [24]. In humans, the count of regulatory T cells (Treg or suppressor T cells) characterized by the (CD4 + CD25 + Foxp3+) phenotype and involved in immune tolerance and autoimmune control can be boosted by polyphenols [42–44]. In vivo, Epigallocatechin-3-gallate, found in green tea and injected to Laboratory inbred strain (BALB/c mice, rises the number of functional Treg in spleens, pancreatic lymph nodes, and mesenteric lymph nodes [45]. Similarly, in vitro treatment of Jurkat T cells with EGC or green tea upsurges the expression of Foxp3 and IL10. Baicalin, a flavone, extracted from Huangqin herb, induces Foxp3 expression in HEK 293 T cells and triggers functional Treg from splenic CD4 + CD25− T cells [46]. Additionally, flavonoids show an agonistic effect of aryl hydrocarbon receptor (AhR) and bind xenobiotic-responsive elements in promoter regions of certain genes, including Foxp3 rising its expression [47].

Th1 and Th17 populations are also affected by polyphenols: EGCG reduces the differentiation of Th1 and reduces the numbers of Th17 and Th9 cells in specific pathogen-free C57/BL6 female mice [48]. Other polyphenols like Baicalin show a reduction of Th17 differentiation in vitro and a diminution of IL-17 expression [49].

Macrophages are affected by polyphenols as well. Macrophages are known to be a key player in the inflammatory response. They initiate inflammation by secreting pro-inflammatory mediators and cytokines like IL-6 and TNF-α [50]. Polyphenols repress macrophages by inhibiting cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), thus they reduce the production of TNF-α, interleukine-1-beta (IL-1-β) and IL-6 expression [51]. Chinese propolis [52] containing ferulic acid and coumaric acid, an extract of Lonicera japonica Thunb) [53] or Kalanchoe gracilis [54] are a good example in this case as per demonstrated by in vitro studies using RAW 264.7 cells.

3. Polyphenol and Cytokine Modulation

Cytokines are important mediators’ proteins, essential in networking communication for immune system. Cytokines can be produced by lymphocytes (lymphokines), or monocytes (monokines) with pro-inflammatory and anti-inflammatory effects. Cytokines with chemotactic activities are termed chemokines. The equilibrium between pro-inflammatory cytokines (IL-1β, IL-2, TNFα, IL-6, IL-8, IFN-γ . . . ) and anti-inflammatory cytokines (IL-10, IL-4, TGFβ) are thought to be an important
parameter in immune response homeostasis and inflammation underlining many disease [55]. In vivo and in vitro studies demonstrate that polyphenols affect macrophages by inhibiting multiple key regulators of inflammatory response such as the inhibition of TNF-α, IL-1-β, and IL-6 [51].

In humans, consumption of bilberries is associated with a decreased inflammation score in patients’ blood, reflected by decreasing serum levels of IL-6, IL-12, and high sensitivity C reactive protein [56]. Moreover, clinical trials have shown the ability of polyphenol-enriched extra virgin olive oil to reduce IL-6 and C-reactive protein expression in stable coronary heart disease patients [57].

In lipopolysaccharide (LPS)-treated BALB/c mice, a model system of inflammation olive vegetation water show ability to inhibit the production of tumor necrosis factor-alpha usually activated by inflammation [58]. Flavonoids, as well, play an important anti-inflammatory effect by influencing cytokines’ secretion. Several flavonoids are found able to inhibit the expression of various pro-inflammatory cytokines and chemokines like TNFα, IL-1β, IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1) in multiple cell types such as LPS-activated mouse primary macrophages, activated human mast cell line, activated human astrocytes, human synovial cells, and human peripheral blood mononuclear cells [59–64]. In murine RAW 264.7 macrophages stimulated by LPS, Chinese propolis as well as extract of Lonicera japonica Thunb (Caprifoliaceae) or Kalanchoe gracilis demonstrated inhibitory effects on TNF-α, IL-1-β, and IL-6 [52–54]. Similarly, certain polyphenol analogs, like curcumin analog EF31, have shown the ability to inhibit the expression and secretion of TNF-α, IL-1-β, and IL-6 in mouse Raw 264.7 macrophages [65].

Likewise, reduction of the secretion of TNF-α and IL-6 without IL-1β modulation is observed with extracts of chamomile, meadowsweet, willow bark, and isolated polyphenols such as quercetin existing in these extracts in THP1 macrophages [66]. Extract of Cydonia oblonga inhibits TNF-α and Interleukin 8 while it increases IL-10 and IL-6 in THP-1 monocytes stimulated with LPS. The reduction in TNF-α levels limits the acute inflammatory response [67,68]. Other cytokines like IFNγ might also be inhibited by certain polyphenols. For example, kaempferol reduces the production of IFN-γ in a dose-dependent manner in spleen cells and T cell lines [69].

Certain polyphenols exert their effects on the balance between pro- and anti-inflammatory cytokines production such as quercetin and catechins, they enhance IL-10 release while they inhibit TNFα and IL-1β [59,70]. Extract of Cydonia oblonga also inhibits the effects of TNF-α and Interleukin 8 (IL-8) while it raises IL-10 in the same type of monocytes [67,68]. Modulation of inflammatory cytokines is one of many common mechanisms by which polyphenols in general exert their immunomodulatory effects.

4. Polyphenols, Inflammation, and Modulation of Different Signaling Pathways

4.1. NFκB Signaling Pathway

NF-κB or nuclear factor kappa-light-chain-enhancer of activated B cells is a complex protein that plays a key role in deoxyribonucleic acid (DNA) transcription, cytokine production and cell survival. It controls immune, inflammation, stress, proliferation and apoptotic responses of a cell to multiple stimuli [58].

The expression of a large number of genes involved in inflammation is controlled by NF-κB such as COX-2, VEGF (vascular endothelial growth Factor), pro-inflammatory cytokines (IL-1, IL-2, IL-6, and TNFα), chemokines (e.g., IL-8, MIP-1α, and MCP-1), adhesion molecules, immuno-receptors, growth factors, and other agents involved in proliferation and invasion [71].

NFκB is located in the cytoplasm, it exists as an inactive non-DNA-binding form. Ik B proteins (Ik Bs), are inhibitors proteins that are associated with NFκB resulting in its inactivation. Ik Bs include Ik Ba, Ik Bβ, Ik Bγ, Ik Bε, Bcl-3, precursors p100 and p105 [72]. Under stimulatory conditions, Ik B kinase (IKK) phosphorylate IkB proteins leading to successive ubiquitination, consequent degradation of the inhibitory proteins and release of NFκB dimer. This later can translocate into the nucleus and prompts the expression of particular genes [72]. Different mechanisms regulate NFκB activity as per
the accumulation and degradation of IkB, the phosphorylation of NFkB, the hyper-phosphorylation of IKK, and the processing of NFkB precursors [73–75]. Thus, the inhibition of NFkB can be of a great benefit in controlling inflammatory conditions [76]. Several polyphenols modulate NFkB activation and reduce inflammation [77,78]. Quercetin blocks the nuclear translocation of p50 and p65 subunits of NFkB and represses the expression of pro-inflammatory associated genes, NOS and COX-2 in RAW264.7 macrophages [79]. It inhibits the phosphorylation of IkB protein both in vitro (using macrophages) and in vivo (using dextran sulfate sodium (DSS) rat colitis model) leading to inactivation of the NFkB pathway [80]. In human mast cells, quercetin prevents the degradation of IkBα, as well as the nuclear translocation of p65 resulting in reduction of TNFα, IL-1β, IL-6 and IL-8 [63]. It can modulate chromatin remodeling, for example it blocks the recruitment of a histone acetyl transferase called CBP/p300 to the promoters of interferon-inducible protein 10 (IP-10) and macrophage inflammatory protein-2 (MIP-2) genes in primary murine small intestinal epithelial cell. As a result, it inhibits the expression of these pro-inflammatory cytokines [81]. Quercetin can block the activation of IKK, NFkB, and it reduces the ability of NFkB to bind DNA in microglia treated by LPS and IFN-γ in mouse BV-2 microglia [82]. Luteolin, too, blocks NFkB activation and inhibits pro-inflammatory genes expression and the cytokines production in murine macrophages RAW 264.7 and mouse alveolar macrophages; it also inhibits IKKs in LPS-induced epithelial and dendritic cells [83]. In addition, in co-cultured intestinal epithelial Caco-2 and macrophage RAW 264.7 cells, luteolin represses NF-kB activation and TNF-α secretion [84]. Likewise, Genistein represses LPS-induced activation of NF-kB in monocytes and reduces the inflammation by inhibiting NF-kB activation upon adenosine monophosphate activated protein kinase stimulation in LPS-stimulated macrophages RAW 264.7 [85,88]. Galangin, as well, stops the degradation of IkBα and the translocation of p65 NF-kB, repressing the expression of TNF-α, IL-6, IL-1β, and IL-8 in mast cell [86]. EGCG counteracts the activation of IKK and the degradation of IkBα and inhibits NFkB in culture respiratory epithelial cells and in vivo in male Wistar rats [87,88]. Furthermore, EGCG blocks DNA binding of NFkB which reduces the expression of IL-12p40 and iNOS in murine peritoneal macrophages [89,90]. Catechin and epicatechin reduce NFkB activity in PMA-induced Jurkat T cells. Flavonoids can modulate NFkB activation cascade at early phases by affecting IKK activation and regulation of oxidant levels or at late phases by affecting binding of NF-kB to DNA in jurkat T cells [91]. Hydroxytyrosol, and resveratrol inhibit NFkB activation, and the expression of VCAM-1 in LPS-stimulated human umbilical vein endothelial cells [92]. In summary, polyphenols can modulate NFkB activation cascade at different steps such as by affecting IKK activation and regulating of the oxidant levels or by affecting binding of NF-kB to DNA leading to an important anti-inflammatory effect responsible for their potential value in treating chronic inflammatory conditions (Figure 1).

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

The mitogen-activated protein kinases (MAPK) are a highly conserved family of serine/threonine protein kinases. They play a key role in a range of fundamental cellular processes like cell growth, proliferation, death and differentiation. They regulate gene transcription and transcription factor activities involved in inflammation. Extracellular signal-related kinases, like (extracellular signal-related kinases (ERK))-1/2, c-Jun amino-terminal kinases (JNK1/2/3), p38-MAP kinase (α, β, δ, and γ), and ERK5 are different groups of MAPKs expressed in mammals. These are later activated by MAP kinase kinases (MAPKK) which might be triggered by some MAPKK kinases (MAPKKK) [93].

MAPK, in its turn, cross-talks with other pathways such as NFκB, thus the complexity of the MAPK signaling pathway and its interactions. Stress and mitogens activate MAPK signaling: For example, ERK1/2 route is triggered by mitogens and growth factors while JNK and p38 cascade are stimulated by stress [94–97]. Preclinical data propose an anti-inflammatory role of JNK and p38 cascades inhibitors [98,99].

Polyphenols’ activity is specific, it depends on the cell types as well as the structure of the polyphenol itself [100]. Polyphenols can block TNFα release by modulating MAPK pathway at different levels of the signaling pathway. Luteolin reduces TNFα liberation by LPS-activated mouse macrophages, it blocks ERK1/2 and p38 phosphorylation [100]. In epithelial cells, luteolin, as well as other polyphenols such as chrysins and kaempferol block TNFα triggered ICAM-1 expression by inhibiting ERK, JNK and P38 [100,101]. Quercitin blocks the phosphorylation of ERK, JNK in THP-1 activated human monocytes, while in murine macrophages RAW 246.7 triggered by LPS it blocks the phosphorylation and the activation of JNK/SAPK (stress activated protein kinases), ERK1/2, and p38 leading to a reduction in the transcription and expression of TNF-α expression [102]. EGCG reduces inflammation in various cell types by exerting an anti-MAPK activity. It reduces IL-12 expression in LPS-activated murine macrophages by prohibiting p38 MAPK phosphorylation [89,103]. In addition, EGCG is found to play a protective role in autoimmune-induced tissue damage caused by Sjogren’s syndrome: it protects human salivary glands from TNF-α induced cytotoxicity by acting on p38 MAPK1. In vivo, in female ICR mice, EGCG inhibits phorbol ester-induced activation of NFκB and CREB (cAMP response element-binding protein—a cellular transcription factor) in mouse skin by blocking the activation of p38 MAPK [104]. Polyphenols concentration plays as well a role in their modulatory activities on signaling pathways: in human coronary artery endothelial cells, the activation of the MAPKs pathways (p38, ERK1/2, and JNK) and the repression of the plasminogen activator inhibitor by catechin and quercetin is time and dose dependent [105]. The ability of polyphenolic compounds to block MAPK pathways (Figure 1) endowed these bioactive substances with therapeutic potential to protect against inflammation.

4.3. Arachidonic Acid Signaling Pathway

Arachidonic acid (AA) is liberated by membrane phospholipids upon phospholipase A2 (PLA2) cleavage. Cyclooxygenase (COX) or lipoxygenase (LOX) metabolize it and produce, respectively, prostaglandins (PGs) and thromboxane A2 (TXA2) by COX, and hydroxyeicosatetraenoic acids and leukotrienes (LTs) by LOX [106]. The COX family involves different members (COX1, COX-2, and COX-3). COX-2 is responsible of the production of important quantity of prostaglandins, its expression is triggered by lipopolysaccharide and pro-inflammatory cytokines [107]. The ability of polyphenols to reduce the release of arachidonic acid, prostaglandins, and leukotrienes is considered one of their most important anti-inflammatory mechanisms (Figure 1). Their action is mainly realized by their ability to inhibit cellular enzymes, such as PLA2, COX, and LOX [21,108–111]. Quercetin blocks COX and LOX in various cell types such as rat peritoneal leukocyte, murine leukocytes, and guinea pig epidermis [110,112,113]. Similarly, red wine reduces COX-2 expression in old male F344 rats [114].

In LPS activated murine macrophages, green tea polyphenols not only suppress NF-κB and MAPK pathways but also constrain the expression of COX-2 and the release of prostaglandin (PGE2) in RAW 264.7 macrophages [115,116]. Equally, a reduction in the release of PGE2 is observed with
other polyphenols, such as kaempferol in culture of LPS-stimulated human whole blood cells [117]. Extra virgin olive oil rich with more than 30 phenolic compounds inhibit 5-LOX in human activated leukocytes reducing leukotriene B4 and suppresses eicosanoids production by animal and human cells in vitro [118,119]. Finally, certain polyphenols show structural and functional similarities with specific anti-inflammatory drugs. A phenolic compound—oleocanthal—demonstrates a natural anti-inflammatory property and exhibits structural similarities to the ibuprofen (a well-known anti-inflammatory drug). Oleocanthal—like ibuprofen—inhibits COX-1 and COX-2 activities in a dose-dependent manner [120].

5. Polyphenols, Oxidative Stress, and Inflammation

Higher production of reactive oxygen species (ROS) is associated with oxidative stress and protein oxidation [121]. In its turn inflammatory molecules and different inflammatory signals (i.e., peroxiredoxin2) are triggered by protein oxidations [122]. Furthermore, overproduction of ROS can prompt tissue injury that might initiates the inflammatory process [123–127]. Therefore, the classical antioxidant actions of polyphenols undoubtedly contribute to their anti-inflammatory roles by interrupting the ROS-inflammation cycle (Figure 2). Polyphenols are known for their antioxidant activities; they scavenge a wide-ranging selection of ROS. Polyphenols can scavenge radicals and chelate metal ions, for example quercetin chelates iron ion [128]. They also inhibit multiple enzymes responsible of ROS generation [129]. In fact, free metal ions, as well as highly reactive hydroxyl radical release, is increased by the formation of ROS. To the opposite, polyphenols are able to chelate metal ions like Fe$^{2+}$, Cu$^{2+}$, and free radicals which lead to a reduction of highly oxidizing free radicals [130].

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

Transition metal ions, like Fe$^{2+}$, Cu$^{2+}$, Co$^{2+}$, Ti$^{3+}$, or Cr$^{5+}$, results in OH$^-$ formation from H$_2$O$_2$ [131,132]. Curcumin is able to chelate transition metal (Cu$^{2+}$ and Fe$^{2+}$) ions. Alike, EGCG and quercetin chelate Fe$^{2+}$ (iron ion) [128]. Polyphenols like apocynin, reservatol, and curcumin can inhibit NOX (NADPH oxidase) causing a reduction in the generation of O$_2^*$ during infections consecutively in endothelial cells in THP1-monocytes [133–135]. Additionally, polyphenols can attenuate the mitochondrial ATP synthesis by blocking the mitochondrial respiratory chain and ATPase. As a result, ROS production is diminished. Curcumin [136], EGCG [137], phenolic acids [138], capsaicin [139], quercetins [140], anthocyanins [140], and resveratrol analogs [141] inhibit xanthine oxidase. Thus, they reduce ROS production. Polyphenols affect the activity of cyclooxygenase,
lipoxygenase, and NOS (nitric oxide synthase) as per found in RAW 264.7 macrophes [142]. These enzymes are known to metabolize arachidonic acid and their inhibition moderates the production of key mediators of inflammation (prostaglandins, leukotrienes, and NO . . . ) [142]. Polyphenols can also restrain LPS-induced iNOS gene expression in cultured macrophages, decreasing oxidative harm [143]. Finally, they may act by upregulating endogenous antioxidant enzymes. In vivo, curcumin can stimulate antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase (Px) which lead to ROS detoxification [144]. Likewise, EGCG rises SOD and GSH-Px activities with augmented amount of cellular glutathione [145]. In conclusion, polyphenols exert the anti-inflammatory action by different mechanisms: Radical scavenging, metal chelating, NOX inhibition, tempering the mitochondrial respiratory chain, inhibition of certain enzymes involved in ROS production, like xanthine oxidase and upregulation of endogenous antioxidant enzymes.

6. Polyphenols, Chronic Diseases and Cancer

Referring to the previously cited roles of polyphenols in maintaining tissue homeostasis by targeting different signaling pathways and referring to their antioxidant, anti-inflammation, and protection against pro-inflammation properties; polyphenols play a beneficial role in the prevention and the process of chronic diseases related to inflammation.

Various polyphenolic compounds show protective actions in diabetes, obesity, neurodegeneration, cancers, and cardiovascular diseases, among other conditions [30,146–154].

6.1. Polyphenols and Insulin Resistance

Polyphenols reduce insulin resistance. They promote glycolysis by activation of AMPK (AMP-activated protein kinase) or inhibition of mTORC1 and PI3K/Akt in vivo (in rats), ex vivo (in rats’ muscles strips) and in vitro (in C2C12 myoblasts and HELA cells) [148,149,155,156]. Additionally, AMPK activation by polyphenols increases glucose uptake by positively affecting eNOS imitating muscle contraction and in vivo activity of insulin [148–150]. Similarly, it is found that polyphenols lower insulin resistance by inhibiting PI3K/Akt and JNK of activation of the AMPK-SirT1-PGC1α axis (i.e., gingerol and anthocyanins, and their ability to protect from diabetes and reduce insulin resistance using in vivo, ex vivo and in vitro studies [26–28,148,149,155]. In addition, polyphenols attenuate glucose intake from carbohydrates by inhibiting rats’ α-glucosidase [157]. Lastly, polyphenols, like flavonoids, can improve insulin secretion by reducing apoptosis of pancreatic β-cells [145].

6.2. Polyphenols and Inflammatory Cardiovascular Diseases (CVD)

Meta-analysis studies have reported that an intake of three cups of tea per day reduces CVD by 11% [151] while adequate intake of red wine is associated with 32% lower risk of cardiovascular disease (CVD) [158]. Soy and cocoa flavonoids contribute to the prevention of CVD as per meta-analysis of randomized controls trial [159]. Polyphenols exert their protective effects in CVD due to their anti-hypertensive potentials. Resveratrol inhibits ACE (angiotensin converting enzyme) and PDE (phosphodiesterase) and upregulates eNOS (endothelial NOS) resulting in a reduction in high blood pressure as per multiple in vivo and in vitro studies [26–28,155,156,160]. In addition, flavanols and flavonoids exert their CVD prevention role by reducing the manifestations of age-related vascular injury. They reduce nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by affecting MAPK signaling and downregulating NF-κB in aged rats [161–163]. At the end, the antioxidant action of polyphenols and their ability to suppress LDL oxidation leads to endothelium-protective activity [164].

Certain polyphenols like resveratrol and anthocyanins protect from CVD by multiple mechanisms; they have (1) anti hypertensive properties, they inhibit eNOS, and (2) inhibit NFκB mediated expression of VCAM and ICAM expression as per previously discussed [39,165]. Polyphenols can also reduce LDL oxidation or improve LDL/HDL ratio. For example, flavanones such as hesperetin in orange juice reduce LDL/HDL ratio while quercetin inhibits LDL oxidation with elevated paraoxonase and eliminate atherogenic lesions referring to in vitro and in vivo studies (using human male subjects) [166].
6.3. Polyphenols and Inflammatory Neurological Diseases

Polyphenols show protective effects in neurological disease [152,153]. High flavonoid intake can reduce by 50% dementia and aging. More precisely, it lowers the incidence of Parkinson’s and delays the onset of Alzheimer’s disease as per different epidemiological studies [167–170]. EGCG has neuroprotective properties due to its antioxidant (SOD, GSHPx) activities and cellular GSH contents and ability to reduce ROS contents. Similarly, anthocyanins neuroprotective characteristics are related to the improvement of oxidative stress and reduction of Aβ deposition [38,171,172]. Other mechanisms of polyphenols protection in neurodegenerative diseases is modulation of neuronal and glial signaling pathways [173]. Polyphenols can downregulate NF-κB related with iNOS generation in glial cells [174–176]. Moreover, their ability to inhibit monoamine oxidase plays a positive role in cognition, depression, and learning ability in vivo in male laca mice [172].

6.4. Polyphenols and Inflammatory Obesity

Polyphenols exert their anti-obesity effect by activation of AMPK (5’ adenosine monophosphate-activated protein kinase) leading to a reduction of cholesterol, fatty acid synthesis, and triglyceride formation by inhibiting HMG-CoA reductase and acetyl CoA carboxylase. Furthermore, they can inhibit genes involved in adipocyte differentiation and triglyceride accumulation. They block mTORC1 and repress specific signals associated with diminished levels of PPARγ and C/EBPα mRNA throughout adipogenesis (in an experimental model of sepsis) and in vitro [30,146]. They can improve energy expenditure, stop the maturation of preadipocytes into adipocytes and increase the expression of adiponectin (a hormonal protein with a role in regulating glucose levels and breaking down fatty acids). For example, capsaicin enhances the energy spending in adipose tissue. Capsaicin diminishes intracellular triglycerides and improves brown adipose tissue thermogenesis. Furthermore, in clinical studies, capsaicin is found able to increase satiety [30,177,178]. EGCG inhibits MEK/ERK and PI3K/AKT pathways leading to inactivation of preadipocytes maturation by downregulating the expression of different genes like PPARγ and C/EBPα that are associated with adipogenesis [38,41,146,179]. Certain polyphenols can increase adiponectin such as gingerol and curcumin in serum of human subjects based on randomized controlled trial [180,181].

6.5. Polyphenols and Cancer

Clinical and epidemiological studies have reported that polyphenols have chemo-preventive and anticancer efficacy [182–184]. Polyphenol compounds have the ability to inhibit the proliferation of different types of cancer such as prostate, bladder, lung, gastrointestinal, breast, and ovarian cancers [154]. For instance, quercetin, resveratrol, green tea polyphenols [185], epigallocatechin-3-gallate [186], and curcumin [187] have demonstrated efficacy as anticancer compounds. Several studies reported that polyphenols are able to prevent cancer initiation (cyto-protective), progression, recurrence, and metastasis to distant organs (cytotoxic) as per different epidemiological, in vitro, and in vivo studie [188–190]. However, a dichotomy exists between polyphenols’ antioxidant effects in normal cells, and their potential pro-oxidant effects in cancer cells [154,188].

Recent studies illustrated a direct correlation between ROS in intracellular signaling cascade and carcinogenesis [191]. Oxidative stress targets proteins, lipids, and DNA/RNA causing changes that increase the risks of mutagenesis. ROS/RNS (reactive nitrogen species) overproduction over a prolonged period of time damages cellular structure and functions and causes somatic mutations such as pre-neoplastic and neoplastic transformations that may lead to cell death by necrotic and apoptotic processes [192]. Polyphenols compounds contain hydroxyl groups that donate their protons to reactive oxygen species (ROS) [193]. Moreover, they reduce the activity of phase I enzymes, primarily cytochrome P450 enzymes (CYPs), such as CYP1A1 and CYP1B1 which lead to prevent the formation of reactive and carcinogenic metabolites in human bronchial epithelial cells [194]. They also can induce
phase II enzymes that initiate the formation of polar metabolites which are readily excreted from the body [195]. Certain dietary polyphenols such as flavonoids reduce cellular formation of ROS which protects from the oxidation of DNA [193].

In addition to their anti-oxidant properties, pro-oxidant characteristic of polyphenols is important in treating and preventing cancer. Pro-oxidant activity can be initiated by certain conditions such as superoxide leakage [196]. The pro-oxidant activities of polyphenols in cancer cells can result in inducing apoptosis [197], cell cycle arrest [198] and inhibiting the proliferation signaling pathways (i.e., epidermal growth factor receptor/mitogen activated protein kinase, phosphatidylinositol 3-kinases/protein kinase B, as well as NF-kB) [199]. For example, polyphenols from apple are able to inhibit the proliferation of human bladder transitional cell carcinoma (TCC, TSGH-8301 cells), inducing G2/M cell cycle arrest, and promoting apoptosis [200]. In human papilloma virus-18-positive HeLa cervical cancer cells, green tea polyphenols can induce cell cycle arrest at the subG1 phase and apoptosis through caspases activation [201]. Flavonoids, such as quercetin, induce apoptosis in many cancer cells such as leukemic U937 cell [202], prostate cancer cells [203], hepatic cancer cells [204], among other types. A combination of quercetin with resveratrol and catechin inhibits breast cancer progression in vitro and in vivo by inducing apoptosis in carcinogenic breast cells [205]. In addition, polyphenols can reduce cancer metastasis such as quercetin [206,207].

Sufficient studies have reported that NF-κB signaling pathways are closely related to cancer metastasis. Polyphenols can disrupt the metastatic potential of cancer by inhibiting NF-κB activity [208]. Curcumin is a good example [209–211] of decreasing cancer metastasis in mice by suppressing NF-κB expression and down-regulating VEGF (vascular endothelial growth factor), COX-2, and MMP-9 (matrix metallopeptidase-9) expression in tissues of the breast, brain, lung, liver, and spleen [212,213]. Moreover, the strength of metastasis is associated to the epithelial-to-mesenchymal transition (EMT) [214]. There is robust evidence that polyphenols compounds can modulate EMT and its related signaling pathways [215]. For example, EGCG, a flavan-3-ol, induces apoptosis and significantly reduces colony formation and cell migration in nasopharyngeal carcinoma (NPC) and cancer stem cells (CSC) in different cell lines [216]. Luteolin and quercetin reverse the migration and invasiveness of metastatic cells by reducing the expression of mesenchymal markers and transcriptional factors on the cell membrane (i.e., twist, snail, and N-cadherin) and upregulating adhesion molecules such as E-cadherin [217]. Thus, through variable mechanisms, polyphenols broadly downregulate inflammation origination, progression, and evolution to cancers (Figure 3).

**Figure 3.** Anti-tumorigenic activities of polyphenols. MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphatidylinositol 3-kinase; ERK: extracellular signal-related kinases; ROS: reactive oxygen species; COX: cyclooxygenase; EMT: epithelial mesenchymal transition; HIF-1α: hypoxia-inducible factor 1-alpha.
In order to emphasize on the beneficial health effects of polyphenols, different medications containing polyphenols are FDA-approved as pharmaceutical drugs. Polyphenon® E, a standardized green tea polyphenol preparation, is an FDA-approved medication to treat genital warts [218]. Another significant event in the use of polyphenols as pharmaceuticals is the FDA approval of crofelemer (a medication rich in oligomeric proanthocyanidin) to manage HIV associated non-infectious diarrhea.

7. Conclusions

In conclusion, the vast number of published studies proved the immunomodulatory role of polyphenols in vivo and in vitro. Different underlying regulatory mechanisms are now well elucidated. These data highlight the promising role of polyphenols in prevention and therapy of diseases with underlining inflammatory conditions, including cancer, neurodegenerative diseases, obesity, type II diabetes, and cardiovascular diseases. However, the role of polyphenols in modulating multiple inflammatory cellular pathways should be further investigated. Many questions remain unanswered about the usage of polyphenols in clinical setting. The role of the microbiota in degrading these polyphenols should be further studied. The notion of bioavailability and its impact on biofunctionality should also be revisited. It is generally believed that polyphenol activity is principally located in the gut where their immunoprotective and anti-inflammatory activities are initiated and subsequently ensuring systemic anti-inflammatory effects. Since different polyphenols can have multiple intracellular targets, additional data is needed to determine the consequences of the interaction or the synergistic effects between multiple polyphenolic compounds or polyphenols and commonly used medications. Moreover, further in vivo and meta-analysis studies in humans are necessary to fully reveal the mechanisms of action of polyphenols in several physiological conditions in order to produce important insights into their prophylactic and therapeutic uses.

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Abbreviations

ROS Reactive oxygen species
COX Cyclooxygenase
NOX NADPH oxidase
SOD Superoxide dismutase
GSH Glutathione
PxB Peroxidase
PLA2 Phospholipase A2
PGs Prostaglandins
LTs Leukotrienes
MAPK Mitogen-activated protein Kinase
IKK Inhibitor of kappa kinase
NFKB Nuclear factor kappa-light-chain-enhancer of activated B cells
T1 Helper 1
NK Natural killer
DCs Dendritic cells
ECGC Epigallocatechin gallate
Treg Regulatory T cells
References

1. Recio, M.; Andujar, I.; Rios, J. Anti-Inflammatory Agents from Plants: Progress and Potential. Curr. Med. Chem. 2012, 19, 2088–2103. [CrossRef] [PubMed]
2. Eberhardt, M.V.; Lee, C.Y.; Liu, R.H. Antioxidant Activity of Fresh Apples. Nature 2000, 405, 903–904. [CrossRef] [PubMed]
3. Spagnuolo, C.; Russo, M.; Bilotto, S.; Tedesco, I.; Laratta, B.; Russo, G.L. Dietary Polyphenols in Cancer Prevention: The Example of the Flavonoid Quercetin in Leukemia. Ann. N. Y. Acad. Sci. 2012, 1259, 95–103. [CrossRef] [PubMed]
4. Andriantsitohaina, R.; Auger, C.; Chataigneau, T.; Étienne-Selloum, N.; Li, H.; Martínez, M.C.; Schini-Kerth, V.B.; Laher, I. Molecular Mechanisms of the Cardiovascular Protective Effects of Polyphenols. Br. J. Nutr. 2012, 108, 1532–1549. [CrossRef] [PubMed]
5. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P.E. Polyphenols and Human Health: Prevention of Disease and Mechanisms of Action. Nutrients 2010, 2, 1106–1131. [CrossRef] [PubMed]
6. Ma, Y.; Kosinska-Cagnazzo, A.; Kerr, W.L.; Amarowicz, R.; Swanson, R.B.; Pegg, R.B. Separation and Characterization of Soluble Esterified and Glycoside-Bound Phenolic Compounds in Dry-Blanched Peanut Skins by Liquid Chromatography-Electrospray Ionization Mass Spectrometry. J. Agric. Food Chem. 2014, 62, 11488–11504. [CrossRef] [PubMed]
7. Tsao, R. Chemistry and Biochemistry of Dietary Polyphenols. *Nutrients* **2010**, *2*, 1231–1246. [CrossRef] [PubMed]
8. Cheynier, V. Polyphenols in Food Are More Complex Then Often Thought. *Am. J. Clin. Nutr.* **2005**, *81*, 223–229. [CrossRef] [PubMed]
9. Mosele, J.I.; Mancia, A.; Romero, M.-P.; Motilua, M.-J.; Rubio, L. Application of in Vitro Gastrointestinal Digestion and Colonic fermentation Models to Pomegranate Products (Juice, Pulp and Peel; extract) to Study the Stability and Catabolism of Phenolic Compounds. *J. Funct. Food* **2015**, *14*, 529–540. [CrossRef]
10. Correa-Betanzo, J.; Allen-Vercoe, E.; McDonald, J.; Schroeter, K.; Corredig, M.; Palijath, G. Stability and Biological Activity of Wild Blueberry (Vaccinium Angustifolium) Polyphenols during Simulated in Vitro Gastrointestinal Digestion. *Food Chem.* **2014**, *165*, 522–531. [CrossRef] [PubMed]
11. Martillanes, S.; Rocha-Pimienta, J.; Cabrera-Bañegil, M.; Martín-Vededor, D.; Delgado-Adámez, J. Application of Phenolic Compounds for Food Preservation: Food Additive and Active Packaging. In *Phenolic Compounds-Biological Activity*; InTech: London, UK, 2017.
12. Maqsood, S.; Benjakul, S.; Shahidi, F. Emerging Role of Phenolic Compounds as Natural Food Additives in Fish and Fish Products. *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 162–179. [CrossRef] [PubMed]
13. Maestre, R.; Micol, V.; Funes, L.; Medina, I. Incorporation and Interaction of Grape Seed Extract in Membranes and Relation with Efficacy in Muscle Foods. *J. Agric. Food Chem.* **2010**, *58*, 8365–8374. [CrossRef] [PubMed]
14. Kennedy, E.T. Evidence for Nutritional Benefits in Prolonging Wellness. *Am. J. Clin. Nutr.* **2006**, *8*, 1647004. [CrossRef] [PubMed]
15. Bengmark, S. Acute and “Chronic” Phase Reaction-a Mother of Disease. *Clin. Nutr.* **2004**, *23*, 1256–1266. [CrossRef] [PubMed]
16. Vissoli, F.; Galli, C. The Effect of Minor Constituents of Olive Oil on Cardiovascular Disease: New Findings. *Nutr. Rev.* **1998**, *56*, 142–147. [CrossRef] [PubMed]
17. Vissoli, F.; Galli, C. The Role of Antioxidants in the Mediterranean Diet. *Lipids* **2001**, *36*, S49–S52. [CrossRef] [PubMed]
18. Middleton, E., Jr.; Kandaswami, C.; Theoharides, T.C. The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer. *Pharmacol. Rev.* **2000**, *52*, 673–751. [PubMed]
19. Urquiaga, J.; Leighton, F. Plant Polyphenol Antioxidants and Oxidative Stress. *Biol. Res.* **2000**, *33*, 55–64. [CrossRef] [PubMed]
20. Scalbert, A.; Manach, C.; Morand, C.; Rémésy, C.; Jiménez, L. Dietary Polyphenols and the Prevention of Diseases. *Crit. Rev. Food Sci. Nutr.* **2005**, *45*, 287–306. [CrossRef] [PubMed]
21. Yoon, J.H.; Baek, S.J. Molecular Targets of Dietary Polyphenols with Anti-Inflammatory Properties. *Yonsei Med. J.* **2005**, *46*, 585–596. [CrossRef] [PubMed]
22. Malireddy, S.; Kotha, S.R.; Secor, J.D.; Gurney, T.O.; Abbott, J.L.; Maulik, G.; Maddipati, K.R.; Parinandi, N.L. Phytochemical Antioxidants Modulate Mammalian Cellular Epigenome: Implications in Health and Disease. *Antioxid. Redox Signal.* **2012**, *17*, 327–339. [CrossRef] [PubMed]
23. Santangelo, C.; Vari, R.; Scaccuzchio, B.; Di Benedetto, R.; Filesi, C.; Masella, R. Polyphenols, Intracellular Signalling and Inflammation. *Ann. Ist. Super. Sanita* **2007**, *43*, 394–405. [PubMed]
24. Karasawa, K.; Uzuhashi, Y.; Hirota, M.; Otani, H. A Matured Fruit Extract of Date Palm Tree (*Phoenix dactylifera* L.) Stimulates the Cellular Immune System in Mice. *J. Agric. Food Chem.* **2011**, *59*, 11287–11293. [CrossRef] [PubMed]
25. John, C.M.; Sandrasaigaran, P.; Tong, C.K.; Adam, A.; Ramasamy, R. Immunomodulatory Activity of Polyphenols Derived from Cassia Auriculata Flowers in Aged Rats. *Cell. Immunol.* **2011**, *271*, 474–479. [CrossRef] [PubMed]
26. Mohar, D.; Malik, S. The Sirtuin System: The Holy Grail of Resveratrol? *J. Clin. Exp. Cardiol.* **2012**, *3*, 216. [CrossRef] [PubMed]
27. Speciale, A.; Chirafisi, J.; Saija, A.; Cimino, F. Nutritional Antioxidants and Adaptive Cell Responses: An Update. *Curr. Mol. Med.* **2011**, *11*, 770–789. [CrossRef] [PubMed]
28. Biasutto, L.; Mattarei, A.; Zoratti, M. Resveratrol and Health: The Starting Point. *ChemBioChem* **2012**, *13*, 1256–1259. [CrossRef] [PubMed]
29. Capiralla, H.; Vingtdeux, V.; Venkatesh, J.; Drees-werringloer, U.; Zhao, H.; Davies, P.; Marambaud, P. Identification of Potent Small? Molecule Inhibitors of STAT3 with Anti? Inflammatory Properties in RAW 264.7 Macrophages. *FEBS J.* **2012**, *279*, 3791–3799. [CrossRef] [PubMed]
30. Leiherer, A.; Mündlein, A.; Drexel, H. Phytochemicals and Their Impact on Adipose Tissue Inflammation and Diabetes. *Vasc. Pharmacol.* 2013, *58*, 3–20. [CrossRef] [PubMed]

31. Siddiqui, A.M.; Cui, X.; Wu, R.; Dong, W.; Zhou, M.; Hu, M.; Simms, H.H.; Wang, P. The Anti-Inflammatory Effect of Curcumin in an Experimental Model of Sepsis Is Mediated by up-Regulation of Peroxisome Proliferator-Activated Receptor-γ. *Crit. Care Med.* 2006, *34*, 1874–1882. [CrossRef] [PubMed]

32. Marchiani, A.; Rozzo, C.; Fadda, A.; Delogu, G.; Ruzzu, P. Curcumin and Curcumin-like Molecules: From Spice to Drugs. *Curr. Med. Chem.* 2014, *21*, 204–222. [CrossRef] [PubMed]

33. Noorafshan, A.; Ashkani-Esfahani, S. A Review of Therapeutic Effects of Curcumin. *Curr. Pharm. Des.* 2013, *19*, 2032–2046. [PubMed]

34. Gupta, S.C.; Prasad, S.; Kim, J.H.; Patchva, S.; Webb, L.J.; Priyadarsini, I.K.; Aggarwal, B.B. Multitargeting by Curcumin as Revealed by Molecular Interaction Studies. *Nat. Prod. Rep.* 2011, *28*, 1937–1955. [CrossRef] [PubMed]

35. Bae, J. Role of High Mobility Group Box 1 in Inflammatory Disease: Focus on Sepsis. *Arch. Pharm. Res.* 2012, *35*, 1511–1523. [CrossRef] [PubMed]

36. Tsuda, S.; Egawa, T.; Ma, X.; Oshima, R.; Kurogi, E.; Hayashi, T. Coffee Polyphenol Caffeic Acid but Not Chlorogenic Acid Increases 5'AMP-Activated Protein Kinase and Insulin-Independent Glucose Transport in Rat Skeletal Muscle. *J. Nutr. Biochem.* 2012, *23*, 1403–1409. [CrossRef] [PubMed]

37. Akyol, S.; Ozturk, G.; Ginis, Z.; Amutcu, F.; Yigitoglu, M.; Akyol, O. In Vivo and in Vitro Anti-Inflammatory Actions of Caffeic Acid Phenethyl Ester (CAPE): Therapeutic Perspectives. *Nutr. Cancer* 2013, *65*, 1515–1526. [CrossRef] [PubMed]

38. Kanwar, J. Recent Advances on Tea Polyphenols. *Front. Biosci.* 2012, *E4*, 111–131. [CrossRef]

39. Domitrovic, R. The Molecular Basis for the Pharmacological Activity of Anthocyanins. *Curr. Med. Chem.* 2011, *18*, 4454–4469. [CrossRef] [PubMed]

40. Singh, B.; Shankar, S.; Srivastava, R. Green Tea Catechin, Epigallocatechin-3-Gallate (EGCG): Mechanisms, Perspectives and Clinical. *Biochem. Pharmacol.* 2011, *82*, 1807–1821. [CrossRef] [PubMed]

41. Landis-Piwowar, K.; Chen, D.; Foldes, R.; Chan, T.-H.; Hu, F. Molecular Mechanisms Underlying the In Vitro Anti-Inflammatory Effects of a Flavonoid-Rich Ethanol Extract from Chinese Propolis (Poplar Type). *Cell* 2013, *12*, 127672. [CrossRef] [PubMed]
53. Park, K.I.; Kang, S.R.; Park, H.S.; Lee, D.H.; Nagappan, A.; Kim, J.A.; Shin, S.C.; Kim, E.H.; Lee, W.S.; Chung, H.J.; et al. Regulation of Proinflammatory Mediators via NF-KB and P38 MAPK-Dependent Mechanisms in RAW 264.7 Macrophages by Polyphenol Components Isolated from Korea Lonicera Japonica THUNB. Evid.-Based Complement. Altern. Med. 2012, 2012, 22611435. [CrossRef] [PubMed]

54. Lai, Z.-R.; Ho, Y.-L.; Huang, S.-C.; Huang, T.-H.; Lai, S.-C.; Tsai, J.-C.; Wang, C.-Y.; Huang, G.-J.; Chang, Y.-S. Antioxidant, Anti-Inflammatory and Antiproliferative Activities of Kalanchoe gracilis (L.) DC Stem. Am. J. Chin. Med. 2011, 39, 1275–1290. [CrossRef] [PubMed]

55. Bohstam, M.; Asgary, S.; Kouhpayeh, S.; Shariati, L.; Khanhamad, H. Aptamers Against Pro- and Anti-Inflammatory Cytokines: A Review. Inflamm. Febr. 2017, 40, 340–349. [CrossRef] [PubMed]

56. Kolehmainen, M.; Mykkänen, O.; Kirjavainen, P.V.; Leppänen, T.; Moilanen, E.; Adriaens, M.; Laaksonen, D.E.; Hallikainen, M.; Puupponen-Pimiä, R.; Pulkkinen, L.; et al. Bilberries Reduce Low-Grade Inflammation in Individuals with Features of Metabolic Syndrome. Mol. Nutr. Food Res. 2012, 56, 1501–1510. [CrossRef] [PubMed]

57. Fitó, M.; Cladellas, M.; de la Torre, R.; Martí, J.; Muñoz, D.; Schröder, H.; Alcántara, M.; Pujadas-Bastardes, M.; Marrugat, J.; Ló-Sabater, M.C.; et al. Anti-Inflammatory Effect of Virgin Olive Oil in Stable Coronary Disease Patients: A Randomized, Crossover, Controlled Trial. Eur. J. Clin. Nutr. 2008, 62, 570–574. [CrossRef] [PubMed]

58. Bitler, C.M.; Viale, T.M.; Damaj, B.; Crea, R. Hydrolyzed Olive Vegetation Water in Mice Has Anti-Inflammatory Activity. J. Nutr. 2005, 135, 1475–1479. [CrossRef] [PubMed]

59. Comalada, M.; Ballester, I.; Bailon, E.; Sierra, S.; Xaus, J.; de Medina, F.; Zarzuelo, A. Inhibition of pro-Inflammatory Markers in Primary Bone Marrow-Derived Mouse Macrophages by Naturally Occurring Flavonoids: Analysis of the Structure-Activity Relationship. Biochem. Pharmacol. 2006, 72, 1010–1021. [CrossRef] [PubMed]

60. Blonska, M.; Czuba, Z.P.; Krol, W. Effect of Flavone Derivatives on Interleukin-1beta (IL-1beta) MRNA Expression and IL-1beta Protein Synthesis in Stimulated RAW 264.7 Macrophages. Scand. J. Immunol. 2003, 57, 162–166. [CrossRef] [PubMed]

61. Sharma, V.; Mishra, M.; Ghosh, S.; Tewari, R.; Basu, A.; Seth, P.; Sen, E. Modulation of Interleukin-1beta Mediated Inflammatory Response in Human Astrocytes by Flavonoids: Implications in Neuroprotection. Brain Res. Bull. 2007, 73, 55–63. [CrossRef] [PubMed]

62. Sato, M.; Miyazaki, T.; Kambe, F.; Maeda, K.; Seo, H. Quercetin, a Bioflavonoid, Inhibits the Induction of Interleukin 8 and Monocyte Chemoattractant Protein-1 Expression by Tumor Necrosis Factor-Alpha in Cultured Human Synovial Cells. J. Rheumatol. 1997, 24, 1680–1684. [PubMed]

63. Min, Y.; Choi, C.; Bark, H.; Son, H.; Park, H.; Lee, S.; Park, J.; Park, E.; Shin, H.; Kim, S. Quercetin Inhibits Expression of Inflammatory Cytokines through Attenuation of NFkappaB and P38 MAPK in HMC-1 Human Mast Cell Line. Inflamm. Res. 2007, 56, 210–215. [CrossRef] [PubMed]

64. Lyu, S.Y.; Park, W.B. Production of Cytokine and NO by RAW 264.7 Macrophages and PBMC in Vitro Incubation with Flavonoids. Arch. Pharm. Res. 2005, 28, 573–581. [CrossRef] [PubMed]

65. Olivera, A.; Moore, T.W.; Hu, F.; Brown, A.P.; Sun, A.; Liotta, D.C.; Snyder, J.P.; Yoon, Y.; Shim, H.; Marcus, A.I.; et al. Inhibition of the NF-KB Signaling Pathway by the Curcumin Analog, 3,5-Bis(2-Pyridinylmethylidene)-4-Piperidone (EF31): Anti-Inflammatory and Anti-Cancer Properties. Int. Immunopharmacol. 2012, 12, 368–377. [CrossRef] [PubMed]

66. Drummond, E.M.; Harbourne, N.; Marete, E.; Martyn, D.; Jacquier, J.C.; O’Riordan, D.; Gibney, E.R. Inhibition of Proinflammatory Biomarkers in THP1 Macrophages by Polyphenols Derived from Chamomile, Meadowsweet and Willow Bark. Phytomer. Res. 2013, 27, 588–594. [CrossRef] [PubMed]

67. Schindler, R.; Mancilla, J.; Endres, S.; GhORBani, R.; Clark, S.C.; Dinarello, C.A. Correlations and Interactions in the Production of Interleukin-6 (IL-6), IL-1, and Tumor Necrosis Factor (TNF) in Human Blood Mononuclear Cells: IL-6 Suppresses IL-1 and TNF. Blood 1990, 75, 40–47. [PubMed]

68. Essafi-Benkhadir, K.; Refai, A.; Riahi, I.; Fattouch, S.; Karoui, H.; Essafi, M. Quince (Cydonia oblonga Miller) Peel Polyphenols Modulate LPS-Induced Inflammation in Human THP-1-Derived Macrophages through NF-KB, P38MAPK and Akt Inhibition. Biochem. Biophys. Res. Commun. 2012, 418, 180–185. [CrossRef] [PubMed]
69. Okamoto, I.; Iwaki, K.; Koya-Miyata, S.; Tanimoto, T.; Kohno, K.; Ikeda, M.; Kurimoto, M. The Flavonoid Kaempferol Suppresses the Graft-versus-Host Reaction by Inhibiting Type 1 Cytokine Production and CD8+ T Cell Engraftment. *Clin. Immunol.* 2002, 103, 132–144. [CrossRef] [PubMed]

70. Crouvezier, S.; Powell, B.; Keir, D.; Yaqoob, P. The Effects of Phenolic Components of Tea on the Production of Pro- and Anti-Inflammatory Cytokines by Human Leukocytes in Vitro. *Cytokine* 2001, 13, 280–286. [CrossRef] [PubMed]

71. Nam, N. Naturally Occurring NF-kappa B Inhibitors. *Mini Rev. Med. Chem.* 2006, 6, 945–951. [CrossRef] [PubMed]

72. Hayden, M.S.; Ghosh, S. Signaling to NF-KappaB. *Genes Dev.* 2004, 18, 2195–2224. [CrossRef] [PubMed]

73. Haddad, J.J. Redox Regulation of pro-Inflammatory Cytokines and IkappaB-Alpha/NF-KappaB Nuclear Translocation And. *Biochem. Biophys. Res. Commun.* 2002, 296, 847–856. [CrossRef]

74. Karin, M.; Ben-Neriah, Y. Phosphorylation Meets Ubiquitination: The Control of NF-[Kappa]B Activity. *Annu. Rev. Immunol.* 2000, 18, 621–663. [CrossRef] [PubMed]

75. Perkins, N.D. Integrating Cell-Signalling Pathways with NF-KB and IKK Function. *Nat. Rev. Mol. Cell Biol.* 2007, 8, 49–62. [CrossRef] [PubMed]

76. Rahman, I.; Biswas, S.; Kirkham, P. Regulation of Inflammation and Redox Signaling by Dietary Polyphenols. *Biochem. Pharmacol.* 2006, 72, 1439–1452. [CrossRef] [PubMed]

77. Rahman, I.; Marwick, J.; Kirkham, P. Redox Modulation of Chromatin Remodeling: Impact on Histone Acetylation and Deacetylation, NF-KappaB and pro-Inflammatory Gene Expression. *Biochem. Pharmacol.* 2004, 68, 1255–1267. [CrossRef] [PubMed]

78. De Stefano, D.; Maiuri, M.C.; Simeon, V.; Grassia, G.; Socia, A.; Cinelli, M.P.; Carnuccio, R. Lycopene, Quercetin and Tyrosol Prevent Macrophage Activation Induced by Gliadin and IFN-γ. *Eur. J. Pharmacol.* 2005, 566, 192–199. [CrossRef] [PubMed]

79. Comalada, M.; Camuesco, D.; Sierra, S.; Ballester, I.; Xaus, J.; Galvez, J.; Zarzuelo, A. In Vivo Quercitrin Anti-Inflammatory Effect Involves Release of Quercetin, Which Inhibits Inflammation through down-Regulation of the NF-KB Pathway. *Eur. J. Immunol.* 2005, 35, 584–592. [CrossRef] [PubMed]

80. Ruiz, P.A.; Braun, A.; Hötzl, M., G.; Quintanilla-Fend, L.; Haller, D. Quercetin Inhibits TNF-Dependent NF-KB Transcription Factor Recruitment to Proinflammatory Gene Promoters in Murine Intestinal Epithelial Cells. *J. Nutr.* 2007, 137, 1208–1215. [CrossRef] [PubMed]

81. Chen, J.C.; Ho, F.M.; Chao, P.D.L.; Chen, C.P.; Jeng, K.C.G.; Hsu, H.B.; Lee, S.T.; Lin, W.W. Inhibition of INOS Gene Expression by Quercetin Is Mediated by the Inhibition of IκB Kinase, Nuclear Factor-Kappa B and STAT1, and Depends on Heme Oxygenase-1 Induction in Mouse BV-2 Microglia. *Eur. J. Pharmacol.* 2005, 521, 9–20. [CrossRef] [PubMed]

82. Gracia-Lafuente, A.; Guillamon, E.; Villares, A.; Rostagno, M.; Martinez, J. Flavonoids as Anti-Inflammatory Agents: Implications in Cancer and Cardiovascular Disease. *Inflamm. Res.* 2009, 58, 537–552. [CrossRef] [PubMed]

83. Aneja, R.; Hake, P.W.; Burroughs, T.J.; Denenberg, A.G.; Wang, H.R. Epigallocatechin-3-Gallate, a Green Tea-Derived Polyphenol, Inhibits IL-1 Beta-Dependent Proinflammatory Signal Transduction in Cultured Respiratory Epithelial Cells. *J. Nutr.* 2004, 134, 1039–1044. [CrossRef] [PubMed]

84. Kim, H.H.; Bae, Y.; Kim, S.H. Galangin Attenuates Mast Cell-Mediated Allergic Inflammation. *Food Chem. Toxicol.* 2013, 57, 209–216. [CrossRef] [PubMed]
89. Ichikawa, D.; Matsui, A.; Imai, M.; Sonoda, Y.; Kasahara, T. Effect of Various Catechins on the IL-12 p40 Production by Murine Peritoneal Macrophages and A. Biol. Pharm. Bull. 2004, 27, 1353–1358. [CrossRef] [PubMed]

90. Lin, Y.; Lin, J. Epigallocatechin-3-Gallate Blocks the Induction of Nitric Oxide Synthase by Down-Regulating Lipopolysaccharide-Induced Activity of Transcription Factor Nuclear Factor-xB. Mol. Pharmacol. 1997, 472, 465–472. [CrossRef]

91. Mackenzie, G.; Carrasquedo, F.; Delfino, J.; Keen, C.; Fraga, C.; Oteiza, P. Epicatechin, Catechin, and Dimeric Procyanidins Inhibit PMA-Induced NF-kappaB Activation at Multiple Steps in Jurkat T Cells. FASEB J. 2004, 18, 167–169. [CrossRef] [PubMed]

92. Carluccio, M.A.; Siculella, L.; Ancora, M.A.; Massaro, M.; Scoditti, E.; Storelli, C.; Visioli, F.; Distante, A.; De Caterina, R. Olive Oil and Red Wine Antioxidant Polyphenols Inhibit Endothelial Activation: Antiatherogenic Properties of Mediterranean Diet Phytochemicals. Arterioscler. Thromb. Vasc. Biol. 2003, 23, 622–629. [CrossRef] [PubMed]

93. Chang, L.; Karin, M. Mammalian MAP Kinase Signalling Cascades. Nature 2001, 410, 37–40. [CrossRef] [PubMed]

94. Khan, N.; Afaq, F.; Saleem, M.; Ahmad, N.; Mukhtar, H. Targeting Multiple Signaling Pathways by Green Tea Polyphenol (−)-Epigallocatechin-3-Gallate. Cancer Res. 2006, 66, 2500–2505. [CrossRef] [PubMed]

95. Kolch, W. Coordinating ERK/MAPK Signalling through Scaffolds and Inhibitors. Nat. Rev. Mol. Cell Biol. 2005, 6, 827–837. [CrossRef] [PubMed]

96. Lu, Z.; Xu, S. ERK1/2 MAP Kinases in Cell Survival and Apoptosis. IUBMB Life 2006, 58, 621–631. [CrossRef] [PubMed]

97. Mayor, F.; Jurado-Pueyo, M.; Campos, P.M.; Murga, C. Interfering with MAP Kinase Docking Interactions: Implications and Perspective for the P38 Route. Cell Cycle 2007, 6, 528–533. [CrossRef] [PubMed]

98. Kaminska, B. MAPK Signalling Pathways as Molecular Targets for Anti-Inflammatory Therapy—From Molecular Mechanisms to Therapeutic Benefits. Biochim. Biophys. Acta 2005, 1754, 253–262. [CrossRef] [PubMed]

99. Karin, M. Inflammation-Activated Protein Kinases as Targets for Drug Development. Proc. Am. Thorac. Soc. 2005, 2, 386–390. [CrossRef] [PubMed]

100. Xagorari, A.; Roussos, C.; Papapetropoulos, A. Inhibition of LPS-Stimulated Pathways in Macrophages by the Flavonoid Luteolin. Br. J. Pharmacol. 2002, 136, 1058–1064. [CrossRef] [PubMed]

101. Chen, C.; Chow, M.; Huang, W.; Lin, Y.; Chang, Y. Flavonoids Inhibit Tumor Necrosis Factor-Alpha-Induced up-Regulation of Intercellular Adhesion Molecule-1 (ICAM-1) in Respiratory Epithelial Cells through Activator Protein-1 and Nuclear Factor-KappaB Pathway—From Molecular Mechanisms to Therapeutic Benefits. Biochim. Biophys. Acta 2005, 1754, 253–262. [CrossRef] [PubMed]

102. Wadsworth, T.L.; McDonald, T.L.; Koop, D.R. Effects of Ginkgo Biloba Extract (EGb 761) and Quercetin on Lipopolysaccharide-Induced Signaling Pathways Involved in the Release of Tumor Necrosis Factor-Alpha. Biochem. Pharmacol. 2001, 62, 963–974. [CrossRef]

103. Cho, S.; Park, S.; Kwon, M.; Jeong, T.; Bok, S.; Choi, W.; Jeong, W.; Ryu, S.; Do, S.; Song, C.; et al. Quercetin Suppresses Proinflammatory Cytokines Production through MAP Kinases AndNF-Kappa B Pathway in Lipopolysaccharide-Stimulated Macrophage. Mol. Cell. Biochem. 2003, 243, 153–160. [CrossRef] [PubMed]

104. Kundu, J.K.; Suri, Y.J. Epigallocatechin Gallate Inhibits Phorbol Ester-Induced Activation of NF-KB and CREB in Mouse Skin Role of P38 MAPK. Ann. N. Y. Acad. Sci. 2007, 1095, 504–512. [CrossRef] [PubMed]

105. Pasten, C.; Olave, N.; Zhou, L.; Tabengwa, E.; Wolkowicz, P.; Grenett, H. Polyphenols Downregulate PAI-1 Gene Expression in Cultured Human Coronary Artery Endothelial Cells: Molecular Contributor to Cardiovascular Protection. Thromb. Res. 2007, 121, 59–65. [CrossRef] [PubMed]

106. Chandrasekharan, N.V.; Dai, H.; Roos, K.L.T.; Evanson, N.K.; Tomskij, J.; Elton, T.S.; Simmons, D.L. COX-3, a Cyclooxygenase-1 Variant Inhibited by Acetaminophen and Other Analgesic/Antipyretic Drugs: Cloning, Structure, and Expression. Proc. Natl. Acad. Sci. USA 2002, 99, 13926–13931. [CrossRef] [PubMed]

107. Needleman, P.; Isaixon, P. The Discovery and Function of COX-2. J. Rheumatol. Suppl. 2018, 49, 6–8.

108. Kim, H.P.; Son, K.H.; Chang, H.W.; Kang, S.S. Anti-Inflammatory Plant Flavonoids and Cellular Action Mechanisms. J. Pharmacol. Sci. 2004, 96, 229–245. [CrossRef] [PubMed]
109. Welton, A.F.; Tobias, L.D.; Fiedler-Nagy, C.; Anderson, W.; Hope, W.; Meyers, K.; Coffey, J.W. Effect of Flavonoids on Arachidonic Acid Metabolism. *Prog. Clin. Biol. Res.* 1986, 213, 231–242. [PubMed]
110. Laughton, M.; Evans, P.; Moroney, M.; Hoult, J.; Halliwell, B. Inhibition of Mammalian 5-Lipoxygenase and Cyclo-Oxygenase by Flavonoids and Phenolic Dietary Additives. Relationship to Antioxidant Activity and to Iron Ion-Reducing Ability. *Biochem. Pharmacol.* 1991, 42, 1673–1681. [CrossRef]
111. Aviram, M.; Fuhrman, B. Polyphenolic Flavonoids Inhibit Macrophage-Mediated Oxidation of LDL and Attenuate Atherogenesis. *Atherosclerosis* 1998, 137, 9694541. [CrossRef]
112. Ferrandiz, M.L.; Alcaraz, M.J. Ferrandiz 1991-Anti-Inflammatory Activity and Inhibition of Arachidonic Acid Metabolism by Flavonoids. *Agent Action* 1991, 32, 283–288. [CrossRef]
113. Kim, H.; Mani, I.; Iversen, L.; Ziboh, V. Effects of Naturally-Occurring Flavonoids and Biflavonoids on Epidermal Cyclooxygenase and Lipoxygenase from Guinea-Pigs. *Prostaglandin Leuk. Essent. Fat. Acid.* 1998, 58, 17–24. [CrossRef]
114. Luceri, C.; Caderni, G.; Sanna, A.; Dolara, P. Red Wine and Black Tea Polyphenols Modulate the Expression of Cyclooxygenase-2, Inducible Nitric Oxide Synthase and Glutathione-Related Enzymes in Azoxymethane-Induced F344 Rat Colon Tumors. *J. Nutr.* 2002, 132, 1376–1379. [CrossRef] [PubMed]
115. Hou, D.X.; Luo, D.; Tanigawa, S.; Hashimoto, F.; Uto, T.; Masuzaki, S.; Fujii, M.; Sakata, Y. Prodelphinidin B-4 3′-O-Gallate, a Tea Polyphenol, Is Involved in the Inhibition of COX-2 and INOS via the Downregulation of TAK1-NF-KB Pathway. *Biochem. Pharmacol.* 2007, 74, 742–751. [CrossRef] [PubMed]
116. Hou, D.; Masuzaki, S.; Hashimoto, F.; Uto, T.; Tanigawa, S.; Fujii, M.; Sakata, Y. Green Tea Proanthocyanidins Inhibit Cyclooxygenase-2 Expression in LPS-Activated Mouse Macrophages: Molecular Mechanisms and Structure? Activity Relationship. *Arch. Biochem. Biophys.* 2007, 460, 67–74. [CrossRef] [PubMed]
117. Miles, E.A.; Zouboulil, P.; Calder, P.C. Differential Anti-Inflammatory Effects of Phenolic Compounds from Extra Virgin Olive Oil Identified in Human Whole Blood Cultures. *Nutrition* 2005, 21, 389–394. [CrossRef] [PubMed]
118. Tuck, K.L.; Hayball, P.J. Major Phenolic Compounds in Olive Oil: Metabolism and Health Effects. *J. Nutr. Biochem.* 2002, 13, 636–644. [CrossRef]
119. De la Puerta, R.; Gutierrez, V.R.; Hoult, J. Inhibition of Leukocyte 5 Lipoxygenase by Phenolics from Virgin Olive Oil. *Biochem. Pharmacol.* 1999, 57, 445–449. [CrossRef]
120. Beauchamp, G.K.; Keast, R.S.J.; Morel, D.; Lin, J.; Pika, J.; Han, Q.; Lee, C.H.; Smith, A.B.; Breslin, P.A.S. Ibuprofen-like Activity in Extra-Virgin Olive OIl. *Nature* 1995, 377, 437, 45–46. [CrossRef] [PubMed]
121. Berlett, B.S.; Stadtman, E.R.; Berlett, B.S.; Stadtman, E.R. Protein Oxidation in Aging, Disease, and Oxidative Stress. *J. Biol. Chem.* 1997, 272, 20315–20316. [CrossRef] [PubMed]
122. Coppo, L.; Sacre, S.; et al. Linkage of Inflammation and Oxidative Stress via Release of Glutathionylated Peroxiredoxin-2, Which Acts as a Danger Signal. *Proc. Natl. Acad. Sci. USA* 2014, 111, 12157–12162. [CrossRef] [PubMed]
123. Willcox, J.K.; Ash, S.L.; Catignani, G.L. Antioxidants and Prevention of Chronic Disease. *Crit. Rev. Food Sci. Nutr.* 2004, 44, 275–295. [CrossRef] [PubMed]
124. Bryan, N.; Ahswin, H.; Smart, N.; Bayon, Y.; Wohler, S.; Hunt, J.A. Reactive Oxygen Species (ROS)-A Family of Fate Deciding Molecules Pivotal in Constructive Inflammation and Wound Healing. *Eur. Cells Mater.* 2012, 24, 249–265. [CrossRef]
125. Naik, E.; Dixit, V.M. Mitochondrial Reactive Oxygen Species Drive Proinflammatory Cytokine Production: Figure 1. *J. Exp. Med.* 2011, 208, 417–420. [CrossRef] [PubMed]
126. Clark, R.A.; Valente, A.J. Nuclear Factor Kappa B Activation by NADPH Oxidases. *Mech. Ageing Dev.* 2004, 125, 799–810. [CrossRef] [PubMed]
127. Geiszt, M.; Leto, T.L. The Nox Family of NAD(P)H Oxidases: Host Defense and Beyond. *J. Biol. Chem.* 2004, 279, 51715–51718. [CrossRef] [PubMed]
128. Heim, K.E.; Tagliaferro, A.R.; Bobiaya, D.J. Flavonoid Antioxidants: Chemistry, Metabolism and Structure-Activity Relationships. *J. Nutr. Biochem.* 2002, 13, 572–584. [CrossRef] [PubMed]
129. Mishra, A.; Sharma, A.K.; Kumar, S.; Saxena, A.K.; Pandey, A.K. Bauhinia Variegata Leaf Extracts Exhibit Considerable Antibacterial, Antioxidant, and Anticancer Activities. *Biomed. Res. Int.* 2013, 2013, 915436. [CrossRef] [PubMed]
130. Mishra, A.; Kumar, S.; Pandey, A.K. Scientific Validation of the Medicinal Efficacy of Tinospora Cordifolia. *Sci. World J.* 2013, 2013, 292934. [CrossRef] [PubMed]

131. Marnett, L.J.; Riggins, J.N.; West, J.D. Endogenous Generation of Reactive Oxidants and Electrophiles and Their Reactions with DNA and Protein. *J. Clin. Investig.* 2003, 111, 583–593. [CrossRef] [PubMed]

132. Prousek, J. Fenton Chemistry in Biology and Medicine. *Pure Appl. Chem.* 2007, 79, 2007–2010. [CrossRef]

133. Deby-Dupont, G.; Mouithys-Mickalad, A.; Serteyn, D.; Lamy, M.; Deby, C. Resveratrol and Curcumin Reduce the Respiratory Burst of Chlamydia-Primed TH-1 Cells. *Biochem. Biophys. Res. Commun.* 2005, 333, 21–27. [CrossRef] [PubMed]

134. Chow, S.E.; Hshu, Y.C.; Wang, J.S.; Chen, J.K. Resveratrol Attenuates OxLDL-Stimulated NADPH Oxidase Activity and Protects Endothelial Cells from Oxidative Functional Damages. *J. Appl. Physiol.* 2007, 102, 1520–1527. [CrossRef] [PubMed]

135. Petrò, M.S.; Zeraik, M.L.; Da Fonseca, L.M.; Ximenes, V.F. Apocynin: Chemical and Biophysical Properties of a NADPH Oxidase Inhibitor. *Molecules* 2013, 18, 2821–2839. [CrossRef] [PubMed]

136. Shen, L.; Ji, H.F. Insights into the Inhibition of Xanthine Oxidase by Curcumin. *Bioorg. Med. Chem. Lett.* 2009, 19, 5990–5993. [CrossRef] [PubMed]

137. Aucamp, J. Inhibition of Xanthine Oxidase by Tea Catechins (Camellia Sinensis). *Method Mol. Biol.* 1997, 702, 47–60.

138. Schmidt, A.; Böhmer, A.E.; Antunes, C.; Schallenberger, C.; Porciuncula, L.; Elisabetsky, E.; Lara, D.; Souza, D. Anti-Noceiceptive Properties of the Xanthine Oxidase Inhibitor Allopurinol in Mice: Role of A1 Adenosine Receptors. *Br. J. Pharmacol.* 2009, 156, 163–172. [CrossRef] [PubMed]

139. Nguyen, M.T.T.; Nguyen, N.T. Xanthine Oxidase Inhibitors from Vietnamese *Blume balsamifer* L. *Phyther. Res.* 2012, 26, 1178–1181. [CrossRef] [PubMed]

140. Bräunlich, M.; Slimestad, R.; Wangensteen, H.; Brede, C.; Malterud, K.E.; Barsett, H. Extracts, Anthocyanins and Procyanidins from Aronia Melanocarpa as Radical Scavengers and Enzyme Inhibitors. *Nutrients* 2013, 5, 663–678. [CrossRef] [PubMed]

141. Huang, X.F.; Li, H.Q.; Shi, L.; Xue, J.Y.; Ruan, B.F.; Zhu, H.L. Synthesis of Resveratrol Analogues, and Evaluation of Their Cytotoxic and Xanthine Oxidase Inhibitory Activities. *Chem. Biodivers.* 2008, 5, 636–642. [CrossRef] [PubMed]

142. Cheon, B.S.; Kim, Y.H.; Son, K.S.; Chang, H.W.; Kang, S.S.; Kim, H.P. Effects of Prenylated Flavonoids and Biflavonoids on Lipopolysaccharide-Induced Nitric Oxide Production from the Mouse Macrophage Cell Line RAW 264.7. *Planta Med.* 2000, 66, 596–600. [CrossRef] [PubMed]

143. Sarkar, A.; Bhaduri, A. Black Tea Is a Powerful Chemopreventor of Reactive Oxygen and Nitrogen Species: Comparison with Its Individual Catechin Constituents and Green Tea. *Biochem. Biophys. Res. Commun.* 2001, 284, 173–178. [CrossRef] [PubMed]

144. Sporn, M.B.; Liby, K.T. NRF2 and Cancer: The Good, the Bad and the Importance of Context. *Nat. Rev. Cancer* 2012, 12, 564–571. [CrossRef] [PubMed]

145. Chu, A. Antagonism by Bioactive Polyphenols Against Inflammation: A Systematic View. *Inflamm. Allergy Drug Targets* 2014, 13, 34–64. [CrossRef] [PubMed]

146. Meydani, M.; Hasan, S.T. Dietary Polyphenols and Obesity. *Nutrients* 2010, 2, 737–751. [CrossRef] [PubMed]

147. Yahfoufi, N.; Mallet, J.F.; Graham, E.; Matar, C. Role of Probiotics and Prebiotics in Immunomodulation. *Curr. Opin. Food Sci.* 2018, 20, 82–91. [CrossRef]

148. Roy, D.; Perreault, M.; Mareotte, A. Insulin Stimulation of Glucose Uptake in Skeletal Muscles and Adipose Tissues in Vivo Is NO Dependent. *Am. J. Physiol. Endocrinol. Metab.* 1998, 274, E692–E699. [CrossRef]

149. Fryer, L.G.; Hajduch, E.; Rencurel, F.; Salt, I.P.; Hundal, H.S.; Hardie, D.G.; Carling, D. Activation of Glucose Transport by AMP-Activated Protein Kinase via Stimulation of Nitric Oxide Synthase. *Diabetes* 2000, 49, 1978–1985. [CrossRef] [PubMed]

150. Roberts, C.K.; Barnard, R.J.; Scheck, S.H.; Balon, T.W. Exercise-Stimulated Glucose Transport in Skeletal Muscle Is Nitric Oxide Dependent. *Am. J. Physiol.* 1997, 273, E220–E225. [PubMed]

151. Peters, U.; Poole, C.; Arab, L. Does Tea Affect Cardiovascular Disease? A Meta-Analysis. *Am. J. Epidemiol.* 2001, 154, 495–503. [CrossRef] [PubMed]

152. Lindsay, J.; Laurin, D.; Verreault, R.; Hebert, R.; Helliwell, B.; Hill, G.; McDowell, I. Risk Factors for Alzheimer’s Disease: A Prospective Analysis from the Canadian Study of Health and Aging. *Am. J. Epidemiol.* 2002, 156, 445–453. [CrossRef] [PubMed]
153. Truelsen, T.; Thudium, D.; Gronbaek, M.; Copenhagen City Heart Study. Amount and Type of Alcohol and Risk of Dementia: The Copenhagen City Heart Study. *Neurology* 2002, 59, 1313–1319. [CrossRef] [PubMed]

154. Hadi, S.M.; Asad, S.F.; Singh, S.; Ahmad, A. Putative Mechanism for Anticancer and Apoptosis-Inducing Properties of Plant-Derived Polyphenolic Compounds. *IUBMB Life* 2000, 50, 167–171. [PubMed]

155. Park, S.; Ahmad, F.; Philip, A.; Baar, K.; William, T.; Luo, H.; Ke, H.; Rehmhan, H.; Taussing, R.; Brown, A.; et al. Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting CAMP Phosphodiesterases. *Cell* 2012, 148, 421–433. [CrossRef] [PubMed]

156. Wallerath, T.; Deckert, G.; Ternes, T.; Anderson, H.; Li, H.; Witte, K.; Forstermann, U. Resveratrol, a Polyphenolic Phytoalexin Present in Red Wine, Enhances Expression and Activity of Endothelial Nitric Oxide Synthase. *Circulation* 2002, 106, 1652–1658. [CrossRef] [PubMed]

157. Kumar, S.; Narwal, S.; Kumar, V.; Prakash, O. Advanced Glycation End Products and Cardiovascular Disease. *Arch. Biochem. Biophys.* 2009, 58, 64–70. [CrossRef] [PubMed]

158. Di Castelnuovo, A.; Ronotto, S.; Iacoviello, L.; Donati, M.B.; De Gaetano, G. Meta-Analysis of Wine and Beer Consumption in Relation to Vascular Risk. *Circulation* 2002, 105, 2836–2844. [CrossRef] [PubMed]

159. Hooper, L.; Kroon, P.A.; Rimm, E.B.; Cohn, J.S.; Harvey, I.; Cornu, K.A.; Le Ryder, J.J.; Hall, W.L.; Cassidy, A. Flavonoids, Flavonoid-Rich Foods, and Cardiovascular Risk: A Meta-Analysis of Randomized Controlled Trials 1, 2. *Am. J. Clin. Nutr.* 2008, 88, 38–50. [CrossRef] [PubMed]

160. Shen, M.; Zhao, L.; Wu, R.X.; Yue, S.Q.; Pei, J.M. The Vasorelaxing Effect of Resveratrol on Abdominal Aorta from Rats and Its Underlying Mechanisms. *Vasc. Pharmacol.* 2013, 58, 64–70. [CrossRef] [PubMed]

161. Peppa, M.; Raptis, S.A. Advanced Glycation End Products and Cardiovascular Disease. *Curr. Diabete Rev.* 2008, 4, 92–100. [CrossRef]

162. Huang, S.M.; Wu, C.H.; Yen, G.C. Effects of Flavonoids on the Expression of the Pro-Inflammatory Response in Human Monocytes Induced by Ligation of the Receptor for AGEs. *Mol. Nutr. Food Res.* 2006, 50, 1129–1139. [CrossRef] [PubMed]

163. Kim, J.M.; Lee, E.K.; Kim, D.H.; Yu, B.P.; Chung, H.Y. Kaempferol Modulates Pro-Inflammatory NF-KB Activation by Suppressing Advanced Glycation Endproducts-Induced NADPH Oxidase. *Age* 2010, 32, 197–208. [CrossRef] [PubMed]

164. Wilkinson-Berka, J.L.; Rana, I.; Armani, R.; Agrotis, A. Reactive Oxygen Species, Nox and Angiotensin II in Angiogenesis: Implications for Retinopathy. *Clin. Sci.* 2013, 124, 597–615. [CrossRef] [PubMed]

165. Thomasset, S.; Teller, N.; Cai, H.; Marko, D.; Berry, D.; Steward, W.; Gescher, A. Do Anthocyanins and Anthocyanidins, Cancer Chemopreventive Pigments in the Diet, Merit Development as Potential Drugs? *Cancer Chemother. Pharmacol.* 2009, 64, 201–211. [CrossRef] [PubMed]

166. Aviram, M.; Fuhrman, B. Wine Flavonoids Protect against LDL Oxidation and Atherosclerosis. *Ann. N. Y. Acad. Sci.* 2002, 957, 146–161. [CrossRef] [PubMed]

167. Commenges, D.; Scotet, V.; Renaud, S.; Jaquemin-Gadda, H.; Barberger-Gateau, P.; Dartigues, J.F. Intake of Flavonoids and Risk of Dementia. *Eur. J. Epidemiol.* 2000, 16, 357–363. [CrossRef] [PubMed]

168. Dai, Q.; Borenstein, A.R.; Wu, Y.; Jackson, J.C.; Larson, E.B. Fruit and Vegetable Juices and Alzheimer’s Disease: The Kame Project. *Am. J. Med.* 2006, 119, 751–759. [CrossRef] [PubMed]

169. Morris, M.C.; Evans, D.A.; Tangney, C.C.; Bienias, J.L.; Wilson, R.S. Associations of Vegetable and Fruit Consumption with Age-Related Cognitive Change. *Neurology* 2006, 67, 1370–1376. [CrossRef] [PubMed]

170. Checkoway, H.; Powers, K.; Smith-Weller, T.; Franklin, G.M.; Longstreth, W.T.; Swanson, P.D. Parkinson’s Disease Risks Associated with Cigarette Smoking, Alcohol Consumption, and Caffeine Intake. *Am. J. Epidemiol.* 2002, 155, 732–738. [CrossRef] [PubMed]

171. Shehzad, A.; Lee, Y.S. Molecular Mechanisms of Curcumin Action: Signal Transduction. *Biofactors* 2013, 39, 27–36. [CrossRef] [PubMed]

172. Gomez-Pinilla, F.; Nguyen, T.T.J. Natural Mood Foods: The Actions of Polyphenols against Psychiatric and Cognitive Disorders. *Nutr. Neurosci.* 2012, 15, 127–133. [CrossRef] [PubMed]

173. Vauzour, D.; Vafeiadou, K.; Rice-Evans, C.; Williams, R.J.; Spencer, J.P.E. Activation of Pro-Survival Akt and ERK1/2 Signalling Pathways Underlie the Anti-Apoptotic Effects of Flavanones in Cortical Neurons. *J. Neurochem.* 2007, 103, 1355–1367. [CrossRef] [PubMed]

174. Vafeiadou, K.; Vauzour, D.; Lee, H.Y.; Rodriguez-Mateos, A.; Williams, R.J.; Spencer, J.P.E. The Citrus Flavanone Naringenin Inhibits Inflammatory Signalling in Glial Cells and Protects against Neuroinflammatory Injury. *Arch. Biochem. Biophys.* 2009, 484, 100–109. [CrossRef] [PubMed]
175. Wang, X.; Chen, S.; Ma, G.; Ye, M.; Lu, G. Genistein Protects Dopaminergic Neurons by Inhibiting Microglial Activation. *Neuroreport* 2005, 16, 267–270. [CrossRef] [PubMed]

176. Bhat, N.R.; Feinstein, D.L.; Shen, Q.; Bhat, A.N. P38 MAPK-Mediated Transcriptional Activation of Inducible Nitric-Oxide Synthase in Glial Cells: Roles of Nuclear Factors, Nuclear Factor KB, CAMP Response Element-Binding Protein, CCAAT/Enhancer-Binding Protein-β, and Activating Transcription Factor-2. *J. Biol. Chem.* 2002, 277, 29584–29592. [CrossRef] [PubMed]

177. Whiting, S.; Derbyshire, E.; Tiwari, B.K. Capsaicinoids and Capsinoids. A Potential Role for Weight Management? A Systematic Review of the Evidence. *Appetite* 2012, 59, 341–348. [CrossRef] [PubMed]

178. Saito, M.; Yoneshiro, T. Capsinoids and Related Food Ingredients Activating Brown Fat Thermogenesis and Inducing Hepatic Hyperplasia, Inflammation, Cellular Gene Products and Cell-Cycle-Related Proteins in Rats. *Cancer Res.* 2005, 63, 6295–6304. [CrossRef] [PubMed]

179. Panahi, Y.; Hosseini, M.S.; Khalili, N.; Naimi, E.; Soflaei, S.S.; Majeed, M.; Sahebkar, A. Effects of Supplementation with Curcumin on Serum Adipokine Concentrations: A Randomized Controlled Trial. *Nutrition* 2016, 32, 1116–1122. [CrossRef] [PubMed]

180. Okamoto, M.; Irii, H.; Tahara, Y.; Ishii, H.; Hirao, A.; Udagawa, H.; Hiramoto, M.; Yasuda, K.; Takanishi, A.; Shibata, S.; et al. Synthesis of a New [6]-Gingerol Analogue and Its Protective Effect with Respect to the Development of Metabolic Syndrome in Mice Fed a High-Fat Diet. *J. Med. Chem.* 2011, 54, 6295–6304. [CrossRef] [PubMed]

181. Liou, G.-Y.; Storz, P. Reactive Oxygen Species in Cancer. *Free Radic. Res.* 2010, 44, 479–496. [CrossRef] [PubMed]

182. Wang, C.; Schuller Levis, G.B.; Lee, E.B.; Levis, W.R.; Lee, D.W.; Kim, B.S.; Park, S.Y.; Park, E. Platycodin D and D3 Isolated from the Root of Platycodon Grandiflorum Modulate the Production of Nitrile Oxide and Secretion of TNF-Alpha in Activated RAW 264.7 Cells. *Int. Immunopharmacol.* 2004, 4, 1039–1049. [CrossRef] [PubMed]

183. Amararathna, M.; Johnston, M.R.; Rupasinghe, H.P.V. Plant Polyphenols as Chemopreventive Agents for Lung Cancer. *Int. J. Mol. Sci.* 2016, 17, 1352. [CrossRef] [PubMed]

184. Tsuji, P.A.; Walle, T. Inhibition of Benzo[a]Pyrene-Activating Enzymes and DNA Binding in Human Bronchial Epithelial BEAS-2B Cells by Methoxylated Flavonoids. *Carcinogenesis* 2006, 27, 1579–1585. [CrossRef] [PubMed]
Zhai, X.; Lin, M.; Zhang, F.; Hu, Y.; Xu, X.; Li, Y.; Liu, K.; Ma, X.; Tian, X.; Yao, J. Dietary Flavonoid Genistein Induces Nrf2 and Phase II Detoxification Gene Expression via ERKs and PKC Pathways and Protects against Oxidative Stress in Caco-2 Cells. *Mol. Nutr. Food Res.* **2013**, *57*, 249–259. [CrossRef] [PubMed]

Lambert, J.D.; Elias, R.J. The Antioxidant and Pro-Oxidant Activities of Green Tea Polyphenols: A Role in Cancer Prevention. *Arch. Biochem. Biophys.* **2010**, *501*, 65–72. [CrossRef] [PubMed]

Nakazato, T.; Ito, K.; Ikeda, Y.; Kizaki, M. Green Tea Component, Catechin, Induces Apoptosis of Human Malignant B Cells via Production of Reactive Oxygen Species. *Clin. Cancer Res.* **2005**, *11*, 6040–6049. [CrossRef] [PubMed]

Howells, L.M.; Mitra, A.; Manson, M.M. Comparison of Oxaliplatin- and Curcumin-Mediated Antiroliferative Effects in Colorectal Cell Lines. *Int. J. Cancer* **2007**, *121*, 175–183. [CrossRef] [PubMed]

Balasubramanian, S.; Efimova, T.; Eckert, R.L. Green Tea Polyphenol Stimulates a Ras, MEKK1, MEK3, and PI3-K Cascade to Increase Activator Protein 1 Factor-Dependent Involutin Gene Expression in Normal Human Keratinocytes. *J. Biol. Chem.* **2002**, *277*, 1828–1836. [CrossRef] [PubMed]

Kao, Y.-L.; Kuo, Y.-M.; Lee, Y.-R.; Yang, S.-F.; Chen, W.-R.; Lee, H.-J. Apple Polyphenol Induces Cell Apoptosis, Cell Cycle Arrest at G2/M Phase, and Mitotic Catastrophe in Human Bladder Transitional Carcinoma Cells. *J. Funct. Food* **2015**, *14*, 384–394. [CrossRef]

Singh, M.; Singh, R.; Bhu, K.; Tyagi, S.; Mahmood, Z.; Shukla, Y. Tea Polyphenols Induce Apoptosis through Mitochondrial Pathway and by Inhibiting Nuclear Factor-KappaB and Akt Activation in Human Cervical Cancer Cells. *Oncol. Res.* **2011**, *19*, 245–257. [CrossRef] [PubMed]

Monasterio, A.; Urdaci, M.C.; Pinchuk, I.V.; López-Moratalla, N.; Martínez-Irujo, J.J. Flavonoids Induce Apoptosis in Human Leukemia U937 Cells through Caspase- and Caspase-Calpain-Dependent Pathways. *Nutr. Cancer* **2004**, *50*, 90–100. [CrossRef] [PubMed]

Castillo-Pichardo, L.; Dharmawardhane, S.F. Grape Polyphenols Inhibit Akt/Mammalian Target of Rapamycin Signaling and Potentiate the Effects of Gefitinib in Breast Cancer. *Nutr. Cancer* **2012**, *64*, 1058–1069. [CrossRef] [PubMed]

Sepporta, M.V.; Fuccelli, R.; Rosignoli, P.; Ricci, G.; Servilli, M.; Morozzi, G.; Fabiani, R. Oleuropein Inhibits Tumour Growth and Metastases Dissemination in Ovariectomised Nude Mice with MCF-7 Human Breast Tumour Xenografts. *J. Funct. Food* **2014**, *8*, 269–273. [CrossRef]

Rivera, A.R.; Castillo-Pichardo, L.; Gerena, Y.; Dharmawardhane, S. Anti-Breast Cancer Potential of Quercetin via the Akt/AMPK/Mammalian Target of Rapamycin (MTOR) Signaling Cascade. *PLoS ONE* **2016**, *11*, e0157251. [CrossRef] [PubMed]

Xia, Y.; Shen, S.; Verma, I.M. NF-KB, an Active Player in Human Cancers. *Cancer Immunol. Res.* **2014**, *2*, 823–830. [CrossRef] [PubMed]

Kim, J.-M.; Noh, E.-M.; Kwon, K.-B.; Kim, J.-S.; You, Y.-O.; Hwang, J.-K.; Hwang, B.-M.; Kim, B.-S.; Lee, S.-H.; Lee, S.J.; et al. Curcumin Suppresses the TPA-Induced Invasion through Inhibition of PKCα-Dependent MMP-Expression in MCF-7 Human Breast Cancer Cells. *Phytomed. Int. J. Phyther. Phytopharm.* **2012**, *19*, 1085–1092. [CrossRef] [PubMed]

Sarkar, F.H.; Li, Y.; Wang, Z.; Kong, D. The Role of Nutraceuticals in the Regulation of Wnt and Hedgehog Signaling in Cancer. *Cancer Metastasis Rev.* **2010**, *29*, 383–394. [CrossRef] [PubMed]

Aggarwal, B.B. Nuclear Factor-KappaB: The Enemy Within. *Cancer Cell* **2004**, *6*, 203–208. [CrossRef] [PubMed]

Bachmeier, B.; Nerlich, A.G.; Iancu, C.M.; Cilli, M.; Schleicher, E.; Vené, R.; Dell’Eva, R.; Jochem, M.; Albini, A.; Pfeffer, U. The Chemopreventive Polyphenol Curcumin Prevents Hematogenous Breast Cancer Metastases in Immunodeficient Mice. *Cell. Physiol. Biochem.* **2007**, *19*, 137–152. [CrossRef] [PubMed]

Farhangi, B.; Alizadeh, A.M.; Khodayari, H.; Khodayari, S.; Dehghan, M.J.; Khor, V.; Heidarzadeh, A.; Khaniki, M.; Sadeghiezadeh, M.; Najafi, F. Protective Effects of Dendrosomal Curcumin on an Animal Metastatic Breast Tumor. *Eur. J. Pharmacol.* **2015**, *758*, 188–196. [CrossRef] [PubMed]
214. Tsai, J.H.; Yang, J. Epithelial–Mesenchymal Plasticity in Carcinoma Metastasis. *Gene Dev.* 2013, 27, 2192–2206. [CrossRef] [PubMed]

215. Kang, J.; Kim, E.; Kim, W.; Seong, K.M.; Youn, H.; Kim, J.W.; Kim, J.; Youn, B. Rhamnetin and Cirsiliol Induce Radiosensitization and Inhibition of Epithelial-Mesenchymal Transition (EMT) by MiR-34a-Mediated Suppression of Notch-1 Expression in Non-Small Cell Lung Cancer Cell Lines. *J. Biol. Chem.* 2013, 288, 27343–27357. [CrossRef] [PubMed]

216. Lin, C.-H.; Shen, Y.-A.; Hung, P.-H.; Yu, Y.-B.; Chen, Y.-J. Epigallocatechin Gallate, Polyphenol Present in Green Tea, Inhibits Stem-like Characteristics and Epithelial-Mesenchymal Transition in Nasopharyngeal Cancer Cell Lines. *BMC Complement. Altern. Med.* 2012, 12, 201. [CrossRef] [PubMed]

217. Lin, Y.-S.; Tsai, P.-H.; Kandaswami, C.C.; Cheng, C.-H.; Ke, F.-C.; Lee, P.-P.; Hwang, J.-J.; Lee, M.-T. Effects of Dietary Flavonoids, Luteolin, and Quercetin on the Reversal of Epithelial-Mesenchymal Transition in A431 Epidermal Cancer Cells. *Cancer Sci.* 2011, 102, 1829–1839. [CrossRef] [PubMed]

218. Hara, Y. Tea Catechins and Their Applications as Supplements and Pharmaceutics. *Pharmacol. Res.* 2011, 64, 100–104. [CrossRef] [PubMed]