Journal of Inflammation Research

Dovepress
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REVIEW

Impact of polyphenols in phagocyte functions

This article was published in the following Dove Press journal:
Journal of Inflammation Research

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Abstract: Polyphenols are a broad group of substances with potential health benefits found in plant species. Several of these compounds are capable of influencing the activation of intracellular signaling pathways, such as NF-kB, MAPK and JAK-STAT, responsible for the production of various inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin 1 beta (IL-1β) and 12 (IL-12), enzymes involved in the production of reactive species such as inducible nitric oxide synthase (iNOS) and superoxide dehydrogenase (SOD), as well as enzymes involved in the production of eicosanoids, such as cyclooxygenase (COX) and lipoxygenase (LO). There is increased interest in the use of polyphenol-rich foods because of their immunomodulatory effect; however, the mechanisms used during macrophage responses are extremely complex and little is known about the effects of polyphenols on these cells. As such, this review summarizes the current view of polyphenol influences on macrophages.

Keywords: polyphenols, inflammation, macrophage activation, cytokine modulation

Introduction

Polyphenols are the largest group of phytochemicals present in fruits and beverages, such as tea and red wine. Certain polyphenols, such as quercetin, are found in all plant-derived products, while others are specific in certain foods (flavanones in citrus fruits, isoflavones in soy and phlorizin in apples). In most cases, foods contain complex mixtures of polyphenols.[1] In plants, they are secondary metabolites and are generally involved in protection against a variety of physical, chemical or biological stress, including ultraviolet radiation and pathogens.[2]

In recent years, scientific interest has increased regarding potential health benefits from polyphenol consumption because of their anti-inflammatory properties. Most polyphenol actions occur by interfering in the enzymatic reactions of tyrosine and serine-threonine kinases, which are involved in cellular activation and cytokine production.[3] For instance, Dugo et al (2017), evaluating TPH-1 cells in vitro treated with cocoa polyphenolic extract, demonstrated reduction of inflammatory response in pro-inflammatory macrophages (M1 macrophages), promoting the secretion of anti-inflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin 12 (IL-12)inducing a phenotypic switch to alternative anti-inflammatory state M2.[4] Another study has shown that pomegranate has dose-dependent anti-inflammatory properties, decreasing TNF-α and interleukin 6 (IL-6) production by macrophages in response to interferon gamma (IFN-γ) and lipopolysaccharide (LPS) stimulation; this same study showed that mice, supplemented with dietary pomegranate juice, which are rich in ellagic acid and gallic acid substantially inhibited the M2 to M1 macrophage phenotypic shift favoring anti-inflammatory M2 phenotype.[5] The polyphenols found in plum suppress in vitro nitric oxide (NO)

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DovePress
http://doi.org/10.2147/JIR.S193749

and cyclooxygenase-2 (COX-2) production in RAW 264.7 macrophages, as well as, malondialdehyde in lypho-stimulated macrophages.[6,7] Polyphenols metabolites, such as 3-glucoside/arabinoside/galactoside-based polymers, consisting of delphinidin, petunidine, peonidine, malvidin, cyanidine extracted from blueberries can inhibit the expression of IL-1, IL-6 and IL-12 in LPS-induced RAW 264.7 macrophages, modulating important anti-inflammatory responses.[8]

The mechanisms behind the immunomodulatory properties of polyphenol-rich foods have been the subject of several studies. These mechanisms might alter innate immune functions that are important to initiate anti-pathogen defense and stimulate the subsequent specific adaptive immune response. Macrophages have the ability to clear pathogens and apoptotic cells by recognizing antigens or damage-associated molecular patterns, producing chemical mediators in response and instructing other immune cells. However, they are also involved in inflammatory processes and degenerative diseases where their normal response becomes hyperactive or when they are continuously stimulated. The mechanisms used during macrophage responses are complex and little is known about the effects of polyphenols on these cells. This article presents a current view of the influence of polyphenols on macrophage functions.

Impact on pathogen-associated molecular pattern (PAMP) receptors

Inflammation is triggered when innate immune cells detect infection or tissue damage. Surveillance mechanisms involve pattern recognition receptors (PRRs) on the cell surface and in the cytoplasm of the macrophages. Most PRRs respond to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering the activation of intracellular transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), activator protein 1 (AP-1), cAMP response-element binding protein (CREB), CCAAT-enhancer-binding proteins (c/EBP) and interferon regulatory factors (IRF). PAMPs are molecular structures derived from carbohydrates, lipids or proteins present in bacteria, viruses, fungi or other parasites, which, though they can be common to more than one pathogen, they are not found in normal human cells.[9] There are a variety of PAMPs receptors, including the toll family (TLRs) that recognize both molecular structures of bacteria, including teichoic acid from gram-positive, and LPS from gram-negative bacteria, as they can recognize fungal mannose or viral nucleic acid.

Several studies support the hypothesis that polyphenols might regulate immune responses by suppressing toll-like receptor signaling. Epigallocatechin gallate-3, a polyphenol found in green tea, was shown to reduce in vitro TLR4 expression, after treatment with lipopolysaccharide, on the surface of murine macrophages and bone marrow dendritic cells.[10,11] In addition, Byun et al (2012) showed that the 67 laminin receptor protein (67LR) acts as a cell surface receptor for gallate-3 epigallocatechin, playing a vital role in mediating inflammation by positively regulating the expression of toll-interacting protein (Tollip), a regulator of TLR4 signaling through 67LR. Green tea polyphenols may also decrease in vitro TLR4 protein expression levels in LPS-activated melanoma murine cells, inhibiting proliferation, migration, and invasion of melanoma cells.[12]

Trans-3,5,4-trihydroxystilbene (resveratrol), a polyphenol found in red grapes and other plant sources, has potent anti-inflammatory properties through negatively controlling in vitro microglial inflammation triggered by LPS stimulation.[13] A study with microglial BV2-cells showed that resveratrol interfered in the oligomerization of TLR4 and, consequently, downregulated signaling cascades triggered by NF-kB and members of the signal transducer and activator of transcription (STAT) protein family, which are involved in pro-inflammatory mediator production.[14]

The polyphenol curcumin, widely used in Indian food, also suppresses the expression of inflammatory mediators by inhibiting the NF-kB pathway. Primary rat vascular smooth muscle cells stimulated with LPS (1 μg/L) and curcumin (5, 10 or 30 μmol/L) have shown reduced neuronal apoptosis through a mechanism related to the TLR4/myeloid differentiation primary response 88 (MyD88)/NF-kB pathway[15] Mice receiving 200 mg/kg body weight of curcumin dissolved in pyrogen-free phosphate-buffered saline (PBS) showed hepatic protection by decreasing intrahepatic expression of genes encoding pro-inflammatory molecules, such as, TNF-α and IFN-γ, and by inhibiting pro-inflammatory intracellular signaling initiated by TLR2, TLR4 and TLR-9.[16]

Polyphenols also influence initial signaling steps conducted by other recognition receptors. For example, curcumin and parthenolide alter the oligomerization of nucleotide-binding oligomerization domain containing protein 2 (NOD2), which detects a portion of a bacterial peptide, downregulating NF-kB proinflammatory

signaling.[17] In addition, acting on nucleotide fragments such as poly (dA:dT), quercetin (2, 5 and 10 μM) decreased IL-18 secretion in human primary epidermal keratinocytes from neonatal foreskin, HEKn, e human keratinocyte cell line HaCaT, as it inhibits caspase 1-dependent-activation by interfering with interferon inducible protein AIM2 (absent in melanoma 2) signals and pro-IL-18 gene transcription by Janus kinase 2 (JAK2)/STAT1.[18]

However, if these effects described could be applicable for humans, should be better evaluated, because, the polyphenols concentration used in the in vitro tests and metabolites taken into consideration in these reports are not that normally used by humans.

Impact on adhesion mechanism

Leukocyte trafficking to lymphoid organs or other tissues is initiated by chemoattractant stimuli and an adhesion step.[19] These mechanisms are particularly important when the immune system is responding to a pathogen in an injured tissue. Monocyte recruitment to inflammatory sites involves chemokines, adhesins and their receptors on the endothelium and leukocytes. Normally, early tethering and rolling interactions between endothelium and monocytes are mediated by proteins from the selectin ligands family and their receptors.[20] Mediators such as platelet-activating factor (PAF), thrombin, histamine, TNF-α and IL-1β stimulate the expression of selectins on the endothelial cell membrane.[21] Meanwhile, chemokines, produced at the injured site enter blood vessels associated with proteoglycans and are deposited at high concentrations on the endothelial cell surface. The chemokines activate the monocyte membrane and stimulate stable adhesion by interacting with integrins, such as intercellular cell adhesion molecules (ICAMs). Finally, transmigration and migration to inter-endothelial spaces occur based on the chemokine concentration gradient, which is more abundant at injured or inflamed sites.[22] There are few studies describing the effect of polyphenols on chemokine regulatory functions, but it was observed accelerated wound closure in rats by local treatment with verbascoside. In addition, in vitro treatment with quercetin and verbascoside of human keratinocytes obtained from skin biopsies of healthy volunteers decreased the chemokines IL-8, monocyte chemoattractant protein 1 (MCP-1) and IP-10 in supernatant of the cultures.[23] In another study carried out in HaCaT cells, a keratinocyte cell line from adult human skin, downregulation of chemokines IL-8 and interferon gamma-induced protein 10 (IP-10) was observed in the presence of verbascoside (10 and 50 μmol/L).[24]

In pathogenic conditions, proinflammatory cytokines stimulate the increase of adhesin expression and often this promotes an exacerbated response in the endothelium and in the adjacent tissue.[25] This response promotes monocyte/macrophage adhesion and activation on the microvasculature, which is an important pathogenic mechanism during atherosclerosis. Soluble forms of ICAM-1 are related to the pathogenesis of ischemic stroke[26] and inflammatory events in the cardiac vascular endothelium.[27,28] A randomized clinical trial study demonstrated that red wine, that is rich in phenolic compounds including resveratrol, reduced serum ICAM-I and IL-6 concentrations and negatively regulated vascular cell adhesion protein 1 (VCAM-1) and E-selectin expression on leukocyte cell surfaces;[29] resveratrol metabolites including trans-3,5,4-trimethoxystilbene (TMS) inhibits human acute monocytic leukemia TPH-1 cells adhesion to TNF-α-activated human umbilical vein endothelial cells (HU-V-E12) in vitro. These cells pretreated with resveratrol and TMS showed reduced TNF-α induced ICAM expression. In addition, it was shown that TMS can act by inhibiting the NF-kB pathway on HUVECs.[30] It was emphasized that cardiovascular risk might be prevented by following a Mediterranean-style diet rich in polyphenols present in red wine, nuts and olive oil because they decreased serum VCAM-1, ICAM-1 and IL-6 observed in a randomized trial.[31]

The isolated polyphenols present in apples suppress the reactive oxygen species (ROS)/mitogen-activated protein kinase (MAPK)/NF-kB signaling pathway, and consequently, downregulate chemokine (C-C motif) ligand 2 (CCL-2), ICAM-1 and VCAM-1 expression, important molecules related to atheroma plaque formation on rat aortic endothelial cells.[32] Further human randomized clinical trial suggests that polyphenolic compounds found in tea, red wine cocoa, olive oil and blueberries improve cardiovascular protection by disrupting TNF-α signaling in the vascular wall.[29]

Impact on the production of reactive species of nitrogen and oxygen

After phagocytosis, pathogens within the phagolysosomes are degraded to epitopes by lysosomal enzymes and by the action of reactive oxygen and nitrogen species produced at

this site. The production of reactive species is particularly important in eliminating or controlling intracellular infections, such as those caused by mycobacteria or leishmaniasis.[33] The release of reactive oxygen and nitric species, such as hydrogen peroxide (H_2O_2) and NO, to the extracellular fluid stimulates paracrine production of inflammatory mediators, local neuronal transmission and vasodilatation.[34] If overproduced, these reactive species become involved in necrosis, apoptosis and tissue aggression. On the other hand, low NO bioavailability alters neuron signaling and endothelial relaxation.

Polyphenols influence the production of reactive species in different ways. Studies prove the importance of tannic acid as a chelating antioxidant and free radical scavenger. Tannic acid, the simplest form of hydrolysable tannin found in various foods such as grapes, lentils, chocolate, red wine, beer, coffee, black tea and green tea[35,36] complexes with metal ions and these act as free radical scavengers.[37] Green tea and tannic acid polyphenols were effective in inhibiting NO generation induced by 12-O-tetradecanoyl phorbol 13-acetate (TPA) in rat hepatocytes.[38]

Quercetin and resveratrol inhibited inducible nitric oxide synthase (iNOS) in murine macrophages in a dose-dependent manner and consequently decreased NO production;[39] while epigallocatechin gallate (EGCG) present in green tea eliminated NO in murine tumor cell lines.[40] In addition, increased plasma NO levels have been associated with a reduction in systolic and diastolic blood pressure levels, adding to the evidence that polyphenols might protect the cardiovascular system because they improve endothelial function by increasing NO production, resulting in vasodilation.[41,42]

The antioxidant effect of polyphenols on the protection of cell integrity and ROS suppression is well documented in the literature.[43] Polyphenols might decrease endothelial lesions via the MAPK/extracellular signal-regulated kinase (ERK) pathway, an important intracellular signaling pathway that promotes cell growth and proliferation in many mammalian cell types.[44] For example, quercetin and myricetin have been demonstrated to have antioxidant properties that protect against DNA injury. This process might provide for improved cancer coadjutant treatment.[45,46]

High concentrations of resveratrol decreased NO production without influencing iNOS expression in LPS-activated RAW 264.7 cells;[39] however, higher plasma concentration of resveratrol is required to increase iNOS expression and to negatively regulate NF-kB.[4] Furthermore, resveratrol and curcumin, at final concentration ranging from 10^{-4} to 10^{-6} M, increased the expression of endothelial nitric oxide synthase (eNOS) and NO production on equine neutrophils by inhibiting the expression of NADPH oxidase.[48] Other polyphenols, such as epigallocatechin-3-gallate (EGCG), the major constituent of green tea, also caused an increase in the activity of eNOS in bovine aortic endothelial cells.[41] In addition, rats fed with diets rich in either dealcoholated red wine, quercetin or catechin induced endothelium-dependent vasorelaxation in rat aorta in a resting state through the enhancement of nitric oxide production.[47]

In humans, a meta-analysis of 13 randomized controlled trials showed that the regular green tea consumption reduces blood pressure.[49] Similarly, in rats treated with curcumin at a dose of 50 or 100 mg/kg/day, there was an increased eNOS expression in the vascular tissue[50] and also reduced oxidative DNA damage in rats treated therapeutically with 100 mg/kg curcumin by gavage.[51]

Intracellular mechanisms to protect cell organelles from damage by the excessive formation of free radicals include neutralization by antioxidants (glutathione, carotenoids) and enzymes, such as superoxide dismutase, glutathione peroxidase and catalase.[52] In a study with diabetic subjects, the serum activity of glutathione peroxidase and superoxide dismutase increased significantly in the group that was given polyphenol supplements from *Sambucus nigra*.[53] Uto-Kondo et al showed that tea polyphenols might provide anti-atherosclerotic effects by inhibiting the oxidation of LDL, by increasing the endothelium-bound superoxide dismutase.[54]

In summary, polyphenols can protect against oxidation by a combination of several mechanisms involving their structure, phenolic ring characteristics, acidity of the medium, nature of the oxidizable substrate, the physical state of the system and the presence of pro-oxidants and synergists. The effectiveness of antioxidants also depends strongly on their concentrations at the reaction site, emphasizing that they act in different regions of the body depending on availability and demand. All these parameters need to be evaluated to better understanding of the efficacy of polyphenols as antioxidant agents.[55]

Impact on production of cytokines

The response of phagocytes after pathogen recognition or any tissue change requires a series of communications between these cells and the external environment in order to stimulate subsequent cellular responses and present an efficient adaptive response.[56] For example, local actions

include: a) the attraction of neutrophils to response sites by IL-8;[57] b) expression of adhesins, reduction of tight-junctions on endothelial cells and vasodilation of vascular endothelium promoted by IL-1β and TNF-α;[58] c) IL-12 enhancement of Natural Killer cells cytotoxicity and T cell activation during antigen recognition;[59] d) induction of new macrophage phenotypes, changing to the M1 form by INF-γ or to M2 by IL-10;[60] and e) expression of costimulatory and major histocompatibility complex (MHC) molecules for induction of the adaptive response.[61]

There are several reports showing the modulation of cytokine production by polyphenols. For example, in human whole blood cultures stimulated with concanavalin A and treated with kaempferol, the IFN-gamma concentration was significantly lower than in cultures stimulated but not treated.[63] Other in vitro studies showed that curcumin reduced IL-8, macrophage inflammatory protein 1 α (MIP-1α), MCP-1, IL-1β and TNF-α production in monocytes and human alveolar macrophages[64] or IL-18 production in LPS-stimulated murine macrophage cell line RAW264.[65]

Luteolin is a polyphenolic flavonoid present in celery, green peppers, broccoli, carrots, olive oil and several other food sources.[62] Funaro et al (2016) evaluated the influence of luteolin and tangeretin in LPS-stimulated RAW 264.7 macrophages, and these compounds suppressed the overexpression of proinflammatory mediators, such as IL-1β, IL-6 and prostaglandin E2 (PGE_2), synergistically decreasing mRNA expression of iNOS and COX-2.[66] In LPS-stimulated murine microglial cells, luteolin downregulates NO, PGE_2, TNF-α and IL-1β.[67]

The anti-inflammatory effects are potentiated when polyphenols are associated with other bioactive compounds. For example, chicory acid found in basil can enhance the anti-inflammatory effect of luteolin by enhancing Akt phosphorylation and decreasing the production of reactive species that activate the NF-kB pathway.[68] The association of chlorogenic acid and luteolin has a significant effect on the reduction of IL-1β-induced RSC-364 cell apoptosis. In addition, in a study using human keratinocytes, luteolin was able to inhibit the production of inflammatory mediators such as IL-6, IL-8 and TNFα. This mechanism possibly occurred by the inhibitory action of luteolin on the activation of NF-kB.[69]

Other polyphenols appear to have beneficial effects in in vitro and in vivo models. A study in rats has shown that quercetin and resveratrol decrease the expression of IL-1α and TNF-α in LPS-treated microglia,[70] and protect glial cells against the action of ROS.[71] Another study examined the anti-inflammatory properties of quercetin in human fetal brain cultures, where quercetin inhibited IL-1β, IL-6, IL-8, IFN-γ and free radical production in astrocyte cultures.[72] The polyphenols present in blueberry have anti-inflammatory activity modulating the proinflammatory cytokines IL-1β, IL-6 and IL-12 on LPS-induced RAW264.7 macrophages.[8]

IL-1β is released in response to cell injury, pathogen antigens and other inflammatory cytokines. In the central nervous system (CNS), IL-1β is responsible for increasing the production of PGE_2 and COX-2 in neuronal and glial cells[73] and stimulates the production of TNF-α and IL-6 by microglia and astrocytes.[74] Systemically, IL-1β induces fever, suppresses appetite and stimulates muscle proteolysis.[75] It is also associated with a decrease in NK cells and the release of IL-6 to the bloodstream.[76] EGCG from green tea is a potent inhibitor of IL-1β signal transduction in vitro.[77,78] Polyphenols might interfere in cytokine production of human aortic endothelial cells by altering NF-kB signaling, as observed with avenanthramide present in oats.[79]

IL-6 is synthesized by mononuclear phagocytes in response to many DAMPs released during tissue aggression, trauma and burns,[80,81] and also in response to IL-1β and TNF-α. Some neurological and psychiatric reports have described its elevation in pathological conditions, such as autistic spectrum,[82] Alzheimer's disease[83] and depression.[84] The use of polyphenols might attenuate these conditions by decreasing IL-6 production from microglial cells. Consistent with this hypothesis, luteolin and tangeretin decreased the synthesis of IL-1β and IL-6 by RAW 264.7 macrophages, previously stimulated with LPS.[66] Similarly, Weng et al observed IL-6 decreased in cultures of keratinocytes seeded and treated with TNF-α and luteolin.[69] Other polyphenolic compounds, such as apigenin and quercetin have positive anti-inflammatory activity in human macrophages by suppressing IL-6 expression.[85] However, its effect on the disease should be better evaluated in randomized trials.

IL-12 is an important cytokine released by monocytes and macrophages. It plays an important role in cell-mediated immunity, especially in response to intracellular infections, acting on T cells.[86] Its main actions are to stimulate type 1 T helper (TH1) cell responses and CD8 T cell cytotoxicity.[87] Once activated, TH1 cells are potent producers of IFN-γ. In turn, IFN-γ stimulates the response of phagocytes, including macrophages, by increasing the

production of lysosomal enzymes and microbicidal reactive species, such as NO and H_2O_2 and by increasing antigen presentation.[88] Some studies demonstrate that polyphenols might impair inflammation by interfering in IL-12 production. For instance, topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin by showing protective effects against UVB-induced immunosuppression via IL-12 production.[89] In a human study, serum levels of IL-12 decreased in patients with controlled blueberry consumption. In fact, polyphenols might act by balancing the immune response by controlling the exacerbated cytokine response and by stimulating the appropriate immune response. Different polyphenols from green tea and red wine modulate the immune system by releasing IL-12 and consequently promoting macrophage, NK and cytotoxic cell responses toward various pathogens, such as bacteria, viruses and parasites.[90] Besides, few clinical trials showed changes on inflammatory response, such as, by evaluating biomarkers, as IL-6, after regular consumption of red wine by healthy human.[29,91]

Impact on NF-kB and other signaling pathways

Many intracellular pathways are activated in macrophages during an immune response. These pathways are mainly regulated by the NF-kB, STAT, MAPK families, and any intervention in one of the proteins involved in the signaling cascades interferes significantly with the cellular activation state, or its mechanism of action, or cytokine production, or induces cell apoptosis. Considering that proinflammatory actions of macrophages are under transcriptional control of these signaling pathways, the role of polyphenols on macrophage intracellular activation has been extensively studied.

Many genes that encode proinflammatory mediators and proteins involved in the cell cycle, cell differentiation, apoptosis and oncogenesis are under NF-kB regulation. The NF-kB family has 5 members – RelA or p65, RelB or p68, cRel, NF-kB1 or p100 and NF-kB2 or p105. These factors form homo or heterodimers that share a Rel homology domain (RHD) necessary to bind the kB elements to DNA. In basal state, NF-kB signaling pathways are blocked by a family of inhibitors of NF-kB (IkB). A wide range of stimuli, including proinflammatory cytokines IL-1β and TNF-α, bacterial LPS, carcinogens, tumor promoters and UV radiation stimulate NF-kB activation by promoting IkB proteasomal degradation or proteolytically processing of p105–p52.[92] This allows the release and dimerization of NF-kB proteins in the cytoplasm and permits nuclear translocation of the dimers.[93]

Considering that proinflammatory actions of macrophages are under transcriptional control of NF-kB, the role of polyphenols in this pathway has been extensively studied. Some polyphenols might exert their anti-inflammatory effect by interfering in the phosphatidylinositide 3-kinase (PI3K)/Akt signaling pathway. Akt activates inhibitory-kB kinase alpha (IKKα) that phosphorylates IkB proteins, resulting in NF-kB dimerization.[94] Other polyphenols, such as curcumin negatively regulate NF-kB and inhibit IkB kinase, thereby suppressing proliferation and inducing apoptosis of these cells.[95]

The MAPK subfamily consists of serine/threonine-specific protein kinases that respond to extracellular stimuli and regulate various cellular activities, such as gene expression, mitosis, differentiation, cell survival and apoptosis. The starting point for this pathway is the binding of a ligand to a transmembrane protein, a tyrosine kinase receptor (TKR). The resulting signaling cascade culminates with ERK translocation to the nucleus, where it activates Elk, Ets and Myc transcription factors.[96] JNK is a member of the MAPK family and controls essential processes such as inflammation, cell differentiation and apoptosis.[97,98] Mature macrophages have a selective requirement of JNK for their survival, proliferation and differentiation.[99,100] Polyphenols might influence such mechanisms, as some studies have shown that myricetin acts in suppressing the phosphorylation of MAPK family members, p38 and JNK, preventing apoptosis in human astrocytoma U373MG cells.[101] In rats, curcumin also blocks JNK-related signaling and reduces activation of MAPK p38 on a chronic experimental colitis model.[102]

Activation of NF-kB is essential for the survival of macrophages. Blocking the intracellular activation of NF-kB induces IkBα-induced apoptosis independent of caspase 3 by reducing mitochondrial function. Thus, activation of NF-kB preserves the viability of macrophages, maintaining mitochondrial homeostasis.[103] Mice bone marrow-derived macrophages pretreated in vitro with tannic acid blocked the cleavage of caspase-1 and inhibited IL-1β secretion, suppressing the activation of NF-kB signaling by inhibiting nuclear localization of NF-kB/P65, suggesting that tannic acid inhibited the activation of the inflammasome NLRP3.[104]

EGCG inhibited the $CoCl_2$-induced apoptosis of PC12 cells through the mitochondria-mediated apoptosis pathway involved in modulating the Bcl-2 family.[105]

In vitro treatment with epicatechin or kaempferol acted in protecting mouse striatal neurons from LDL-oxidation by inhibiting the activation of c-Jun N-terminal kinases (JNK), c-Jun and caspase-3.[106] Another known anti-inflammatory activity related to inhibiting the expression of caspase-3 induced by resveratrol-promoted IL-1β was demonstrated in an in vitro model conducted in human articular chondrocytes.[107]

Other polyphenols found in *Lonicera japonica*, a native plant of Asia, alter these signaling pathways by inhibiting eicosanoids and free radical species production in RAW 264.7 macrophages as they downregulate COX-2 and iNOS activities or negatively interfering in the production of cytokines such as TNF-α, IL-1β and IL-6.[108] This study also demonstrated that in vitro treatment with polyphenol components isolated from Korea *L. japonica* inhibited the expression of p38 protein, but not JNK and ERK, in LPS-stimulated RAW 264.7 mouse macrophages.

Another important signaling pathway, IKK-NF-kB regulates the activity of important transcription factors such as NF-kB (p50/p65) and AP-1 (c-Fos/c-Jun), which after activation can induce the expression of numerous genes encoding inflammatory mediators in macrophages.[109,110] Polyphenols found in ethanol extract from Chinese propolis, containing abundant flavonoids, including rutin, myricetin, quercetin, kaempferol, apigenin, pinocembrin, chrysin and galangin are able to inhibit the phosphorylation of IkBα and AP-1 in LPS-stimulated RAW 264.7 by regulating the expression of the iNOS, IL-1β and IL-6 mRNA in a time- and dose-dependent manner.[111] In the same way, resveratrol in LPS-treated human intestinal cells can block the phosphorylation of the p65 subunit of NF-kB, inhibiting its translocation to the nucleus and its action on genes by inhibition of phosphorylation and degradation of IkB.[112] In general, polyphenols reduce the degradation of IKK by promoting retention of the p65 subunit in the cytosol.[112]

Atopic dermatitis-like skin lesions were induced in NC/Nga mice using cream containing *Dermatophagoides farinae* extract and oral treatment with tannic acid inhibited serum IL-4 and IF-γ, while TNFα, high mobility group (HMG), B1 protein, receptor of advanced glycation end product (RAGE), extracellular signal-regulated kinase (ERK)1/2, NF-kB, cyclooxygenase (COX) 2, IL-1β, and increased the protein expression of peroxisome proliferator-activated receptor (PPARγ) in skin sample showed by western blot. These results suggest that skin inflammation can be mediated by NF-kB signaling and tannic acid might be a potential therapeutic agent for skin dermatitis treatment, which may possibly act by induction of the PPARγ protein.[113]

The effect of polyphenols on the intracellular pathways of macrophages is still controversial. In fact, considering the complexity of intracellular networks that control functions of the cells, it is expected that the diversity of polyphenols found in nature will have distinct effects especially concerning the dose and the metabolite used. Furthermore, the way these observations were done, by in vitro assays or by ingestion of in nature, the polyphenols may determine different results. In addition, they can also act differently on different cells and organs or tissues. Overall, the actions of polyphenols on intracellular mechanisms need further studies, mainly to be able to use this knowledge to improve human health.

Impact on the phenotypes of macrophages

Macrophages have the ability to assume inflammatory or suppressive states and have repairing properties during resolution phases of inflammation.[114] This differentiation allows the organism to effectively combat antigens and re-establish itself after infection. In experimental systems, the classical phenotype of inflammatory macrophages is called M1 and is often induced by IFN-γ.[115] M1 acts in the first phase of the response to tissue injury and in the inflammatory response against pathogens. This subtype is able to recognize pathogens and DAMPs efficiently, either eliminating them or stimulating a specific adaptive response by releasing cytokines, such as TNF-α, IL1β and IL-12 and IL-23.[116]

The M2 phenotype can be induced by IL-4 and IL-13. This macrophage blocks M1 response and induces pro-resolution molecule production, such as IL-10 and TGF-β that suppress inflammation and contribute to tissue repair, remodeling, angiogenesis and homeostasis recover.[117,118]

It is considered that due to their anti-inflammatory action, polyphenols might alter the phenotype of macrophages, favoring an M2 anti-inflammatory state. For example, a polyphenolic extract of cocoa suppresses inflammation on THP1 cell line macrophages and stimulates their polarization to activated M2 macrophages.[4] A study of ellagic and gallic acids, polyphenols found on pomegranate, demonstrated, that these bioactive

compounds directly suppress the inflammatory responses of murine peritoneal macrophages and promote macrophage phenotype switching from M1 to M2.[5] Resveratrol also stimulates phenotype switching to M2 in human monocyte cell culture and neutralize pro-atherogenic signaling in the subgroups of M1 macrophages within atherosclerotic plaques.[118] Finally, in vitro treatment with EGCG regulates immune system cells, especially promoting the M2 polarization of macrophages in cartilage and bone tissue.[119]

Impact on mechanisms of autophagy and apoptosis

The elimination of apoptotic cells is driven by a phagocyte mechanism.[120] Cell death by apoptosis contributes to cell turnover in most tissues. Removal of apoptotic cells maintains tissue integrity under healthy conditions and contributes to maintaining an anti-inflammatory state.[121] Apoptotic cells might also release IL-10[122] that acts simultaneously with TGF-β to induce a suppressive immune response by promoting regulatory T cell formation.[123]

Polyphenols found in foods have the ability to inhibit genes involved in cell proliferation and inducing apoptosis.[68] Evidence suggests that cellular and molecular mechanisms responsible for the induction of apoptosis by polyphenols depend on the concentration of polyphenols, cell type, cell age and stage of the degenerative process.[124]

Studies have shown that plant extracts rich in polyphenols, and isolated polyphenols as single compounds and combinations might exert pro-apoptotic effects by selectively attacking cancer cells. For example, in vitro treatment of breast cancer cells with different concentrations of pomegranate extract induced cell death by apoptosis through activation of the caspase-3 pathway. Polyphenolic extract prepared from a pomegranate juice extract containing the ellagitannins punicalagin A, punicalagin B, anthocyanins delphinidin 3-glucoside and cyanidin-3-glucoside was shown in human mammary carcinoma cell lines to induce suppression of mRNA and specific protein transcription factors Sp1, Sp3 and Sp4, which are involved in cell cancer apoptosis.[125] It is important to emphasize that the predominant and therapeutically relevant compounds of pomegranate extract are ellagic acid and ellagitannins; both ellagic acid and ellagitannins are produced after microbiotal metabolization leading to dibenzopyranones known as urolithin A (3,8-dihydroxy-6H-dibenzopyran-6-one) and its monohydroxylated analog known as urolithin B.[126] All these urolithin phenotypes could show differences in the human gut microbiota and should be considered in intervention trials dealing with health benefits of ellagitannins or ellagic acid.

Hsieh and Wu (2009) have shown that the combination of EGCG, quercetin and genistein decreased expression of the androgen receptor, tumor suppressor p53 and quinone reductase type 1 detoxification enzyme in human prostate cancer cells.[127] In vivo, tumors from nude mice injected with pancreatic cancer cells and treated with curcumin (1 g/kg) showed significant reductions in volume by inhibition of NF-kB-regulated gene products, such as cyclin D1, c-Myc, Bcl-2, Bcl-xL, COX-2, matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF).[128]

Quercetin is present in high concentrations in fruits and vegetables, such as apples, strawberries, onions, potatoes, broccoli, soybeans, peanuts and red wine.[129] This polyphenol showed antioxidant and cytoprotective effects that prevented endothelial apoptosis caused by oxidizing agents in primary hippocampal cultures, significantly attenuating β-amyloid peptide-induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis.[130] Flow cytometry analyses demonstrate tannic acid increased the rate of early apoptosis both in in vitro prostate cancer PC-3 cells by 25.8% and in LNCaP cells by 20.9%, suggesting that tannic acid may be a promising candidate for combined therapy with great effectiveness to reduce the occurrence of prostate cancer.[131]

Conclusion

Polyphenols found in a wide variety of foods such as fruits, vegetables, teas, olive oil and nuts showed anti-inflammatory and antioxidant properties that interfere at several steps during intracellular signaling, mainly in NF-kB inflammatory pathways. Some dietary polyphenols also induce apoptosis promoting cell renewal and suppressing the growth of cancer cells. All these effects reported in this review have been extensively studied and data show that polyphenols may have the potential to ameliorate inflammatory and degenerative diseases. However, it is important to note that these beneficial properties depend on the amount consumed and their bioavailability and those observations in vitro could not to be the same that will be observed in vivo. Further, bioavailability, formulation and doses are crucial points to be made clear previously if we will be able to use these bioactive plants compounds in the clinical practice to improve human health.

To date, most research has been conducted in vitro or in animal models, and other clinical trials are necessary since in vitro results do not often coincide with the findings of in vivo studies. However, in vitro studies are necessary for the better understanding of the mechanism of action of these compounds that are not possible to know by only in vivo studies.

To the better understanding of the mechanisms of action of polyphenols, it is still necessary to establish daily consumption recommendations considering that a sufficient dose for its effect, it is necessary these foods to be ingested every day and that, unlike minerals and vitamins, the active component is not stored or temporarily retained in the body.

In addition, even though much research was already done about polyphenols present in each food, guidelines and daily recommendation are missing, furthermore, it is necessary to determine whether these compounds can exert their effects complexed in food.

Studies in vitro and in animals have used levels of the polyphenols to a much higher value than those commonly found in human diets. The safety and benefits therefore should be evaluated by quantitative research to extend the benefits of polyphenols described in this review to human health and to prevent pathology.

Disclosure

The authors report no conflicts of interest in this work.

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