Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols

Viera JANČINOVÁ 1, Tomáš PEREČKO 1, Juraj HARMATHA 2, Radomír NOSÁĽ 1, Katarína DRÁBIKOVÁ 1
1 Institute of Experimental Pharmacology & Toxicology, Slovak Academy of Sciences, SK-84104 Bratislava, Slovakia
2 Institute of Organic Chemistry and Biochemistry, Academy of Sciences, v.v.i., CZ-16610 Prague, Czech Republic

ABSTRACT
Prolonged or excessive formation and liberation of cytotoxic substances from neutrophils intensifies inflammation and the risk of tissue damage. From this perspective, administration of substances which are able to reduce activity of neutrophils and to enhance apoptosis of these cells may improve the therapy of pathological states connected with persistent inflammation. In this short review, neutrophil oxidative burst and apoptosis are presented as potential targets for pharmacological intervention. Effects of natural polyphenols (resveratrol, pterostilbene, pinosylvin, piceatannol, curcumin, N-feruloylserotonin) are summarised, considering the ability of these compounds to affect inflammation and particularly neutrophil activity. The intended neutrophil inhibition is introduced as a part of a new strategy for pharmacological modulation of chronic inflammatory processes, focused on supporting innate anti-inflammatory mechanisms and enhancing resolution of inflammation.

KEY WORDS: neutrophils; oxidative burst; apoptosis; natural polyphenols; resolution of inflammation

New strategy for pharmacological modulation of inflammatory processes

Resolution (i.e. termination of the defense/beneficial inflammation) has historically been viewed as a passive process, occurring as a result of withdrawal of pro-inflammatory signals. Thus most anti-inflammatory drugs in use suppress mechanisms engaged at the onset and progression of inflammation, but they are not targeted to support natural anti-inflammatory reactions. Only recently has the concept been established that resolution is an active process with a distinct set of chemical mediators (lipoxins, resolvins, protectins), involving decrease in activities of neutrophils and eosinophils, programmed death (apoptosis) of these cells, as well as their clearance from the site of inflammation by macrophages (Kohli & Levy, 2009; Serhan et al., 2007, 2008). An abnormal, ineffective or absent regulation of these processes contributes to cellular dysfunction, tissue damage and to persisting inflammation. Moreover, defective regulation is thought to participate in the pathogenesis of chronic inflammatory diseases, such as asthma, rheumatoid arthritis or chronic obstructive pulmonary disease. Therefore the novel strategy of anti-inflammatory therapy is based upon pharmacological agents capable to enhance the resolution of inflammation (Sawatzky et al., 2006; Serhan et al., 2007; Hallett et al., 2008). Several drugs were found to promote pro-resolution pathways, such as aspirin (stimulates formation of lipoxins), glucocorticoids (activate macrophages and accelerate apoptosis of eosinophils), methotrexate (increases synthesis of endogenous anti-inflammatory mediators), as well as substances modulating neutrophil activity and apoptosis (Yasui & Baba, 2006; Rossi et al., 2007; Filep & El Kebir, 2009).

Correspondence address:
PharmDr. Viera Jančínová, PhD.
Institute of Experimental Pharmacology & Toxicology,
Slovak Academy of Sciences
Dúbravská cesta 9, 841 04 Bratislava, Slovak Republic
TEL.: +421-2-59410672 • E-MAIL: viera.jancinova@savba.sk

Pro-inflammatory activity of neutrophils

Neutrophils (neutrophilic polymorphonuclear leukocytes) represent the body’s primary line of defense against invading pathogens. Nevertheless, recently they
have been increasingly studied as active participants in the initiation and progression of many pathological states, such as rheumatoid polyarthritis, carcinoma, allergy or ischaemia-reperfusion. All these conditions are generally accompanied by dysregulated, persistent and excessive activation of neutrophils, resulting in damage of adjacent tissues by neutrophil “destructive hardware” – by reactive oxygen species, cytotoxic proteins and proteolytic enzymes (Cascao et al., 2009, 2010; Fialkow et al., 2007; Wright et al., 2010). In rheumatoid arthritis, neutrophil derived oxidants can induce cartilage degradation, depolymerise hyaluronan and decrease its lubricative properties. Further they can reduce the protective antioxidant and antiproteinase capacity of synovial fluid and thus participate in joint erosion (Cascao et al., 2009; Edwards & Hallett, 1997). Besides, neutrophils are capable to release inflammatory mediators (eicosanoids, chemokines, cytokines), which along with their altered recruitment and delayed apoptosis, have the potential to maintain permanent inflammation (Cascao et al., 2010; Wright et al., 2010). The treatment of diseases associated with chronic inflammation should thus be focused also on neutrophil functions; formation of reactive oxygen intermediates and apoptosis of these cells represent two promising targets for pharmacological intervention.

### Formation of reactive oxygen species

Reactive oxygen species (ROS) are produced in large quantities when neutrophils are stimulated by pro-inflammatory agents or by particles such as bacteria. This process, known as “oxidative burst”, is initiated by the activation of NADPH oxidase (NADPH: nicotine amide adenine dinucleotide phosphate). During this process, the cytosolic phox proteins (phox: phagocyte oxidase) p47phox, p67phox, p40phox and Rac2 translocate to the plasma membrane or to membranes of specific granules, where they associate with the membrane-bound components (p22phox, gp91phox) to assemble the catalytically active oxidase (El-Benna et al., 2010; Ambruso et al., 2004). A partial association of NADPH oxidase components was observed in neutrophils primed with TNFα, GM-CSF or LPS. This configuration, not sufficient for ROS generation, amplifies the oxidative burst initiated by subsequent stimulation of neutrophils (Sheppard et al., 2005).

Activated NADPH oxidase transfers an electron from NADPH to molecular oxygen, generating superoxide anion. This precursor of other ROS is immediately transformed into hydrogen peroxide (H₂O₂), spontaneously or through enzymatic dismutation by superoxide dismutase. Interaction between H₂O₂ and superoxide anion can give rise to the hydroxyl radical, one of the most powerful oxidants. Moreover, hydrogen peroxide is a substrate of myeloperoxidase, which catalyses its transformation into highly toxic molecules such as hypochlorous acid, chloramines and tyrosyl radicals (El-Benna et al., 2010; Robinson, 2009). The percentage of particular oxygen metabolites was found to be dependent on the mechanism of neutrophil activation (Takahashi et al., 1991).

Activated neutrophils form and liberate reactive oxygen species both extra- and intracellularly (El-Benna et al., 2010; Karlsson & Dahlen, 2002). Oxidative burst arising inside neutrophils is much less pronounced and reaches maximum values later than the external ROS formation. The intracellular oxidants fulfill a regulatory role and participate in the initiation of neutrophil apoptosis (Luo & Loison, 2008; Witko-Sarsat et al., 2011). The substantial part of reactive oxygen species is formed at neutrophil plasma membranes and is liberated extracellularly or into phagosomes. These radicals are involved in the elimination of pathogens, however their overproduction may result in damage of surrounding tissues. Confirmation of the destructive role of radicals in pathological states associated with persistent inflammation (Halliwell & Whiteman, 2004; Lonkar & Dedon, 2011) initiated an

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**Box 1. Factors regulating neutrophil apoptosis.**

**Pro-apoptotic factors**
- Bcl-2 (B-cell lymphoma-2) proteins Bak, Bax, Bid control integrity of mitochondrial membrane
- Bcl-2 proteins Bad, Bim activate Bak/Bax and inhibit anti-apoptotic Bcl-2 proteins
- Cytochrome c, APAF1 (apoptotic protease-activating factor-1) activate caspase-9
- Caspases (cystein-dependent aspartate-directed proteases); initiate caspases-8 and -9 activate the executioner caspase-3, responsible for cytomorphological alterations
- TNFα (tumour necrosis factor-a, high concentrations) activates caspase-8
- Reactive oxygen intermediates cause DNA damage, upregulate death receptor clustering and activation of caspase-8
- Cathepsin D activates caspase-8 and Bid
- Calpain 1 regulates Bax and caspase-3 activation
- Inhibitors of CDK (cycline-dependent kinase), e.g. R-roscovitine, reduce Mcl-1 level

**Anti-apoptotic factors**
- Bcl-2 (B-cell lymphoma-2) proteins Mcl-1, Bel-XL, A1 control integrity of mitochondrial membrane
- XIAP (X-linked inhibitor of apoptosis protein) inhibits activity of caspases -3 and -9
- cAMP/protein kinase A inhibits caspase-8
- NF-κB (nuclear factor-κB) increases transcription of survival proteins Mcl-1 and A1
- p38MAPK (mitogen-activated protein kinase) inhibits caspases -8 and -3
- PI3K (phosphoinositide-3-kinase) inhibits Bad and Bax activation
- TNFα (tumour necrosis factor-α, lower concentrations) stimulates expression of A1
- GM-CSF (granulocyte macrophage-colony stimulating factor) upregulates ant apoptotic pathways such as PI3K, blocks Bid/Bax redistribution
- LPS (lipopolysaccharide) upregulates pro-survival factors Mcl-1 and A1
intensive search for substances with antioxidant activity. Since the optimum therapy is expected to minimise tissue damage without reduction of the physiological function of neutrophils, separate analysis of extra- and intracellular effects of antioxidants is of particular importance. The chemiluminescence method, based on different abilities of luminol and isoluminol to cross biological membranes and to interact with radicals inside cells, represents an effective tool for such differentiation (Drábiková et al., 2006; 2009).

**Neutrophil apoptosis**

Apoptosis is a complex physiological mechanism in which a cell undergoes programmed death as a result of withdrawal of survival factors and/or of exposure to pro-apoptotic signals. It represents a sensitive and highly regulated process (Box 1), which includes mitochondrial membrane permeabilisation, followed by the release of cytochrome c and other pro-apoptotic proteins into the cytosol, gradual activation of caspases, DNA fragmentation, chromatin condensation, loss of membrane asymmetry and formation of apoptotic bodies. In contrast to necrosis, apoptosis saves the integrity of neutrophil membranes and prevents the discharge of cytotoxic and proteolytic contents into the surrounding tissues (Luo & Loison, 2008; Witko-Sarsat et al., 2011; Hallett et al., 2008). Alterations in plasma membrane (e.g. externalisation of phosphatidylserine) facilitate the recognition and clearance of apoptotic neutrophils by macrophages, resulting in safe removal of these cells from the site of inflammation. Moreover, on recognising apoptotic neutrophils, macrophages are programmed to upregulate the production of anti-inflammatory mediators such as transforming growth factor (TGF)-β and interleukin (IL)-10, resulting in reduction of the inflammatory process (Duffin et al., 2010; Nussbaum & Shapira, 2011). Due to these facts, better comprehension of neutrophil apoptosis might lead to novel therapeutic strategies designed to enhance resolution of inflammation without tissue damage (Witko-Sarsat et al., 2011). At present, a great deal of substances directing neutrophils to apoptosis are tested in vitro as well as under conditions of experimental inflammation (Hallett et al., 2008; Hu et al., 2005; Sawatzky et al., 2006; Derouet et al., 2006; Serhan et al., 2007; Jagetia & Aggarwal, 2007). The most intensively examined substances have been inhibitors of nuclear factor-κB, compounds modifying the expression of pro- and anti-apoptotic Bcl-2 (B-cell lymphoma-2) proteins or PI3K (phosphoinositide-3-kinase) and CDK (cycline-dependent kinase) inhibitors.

**Neutrophils as potential targets for pharmacological intervention**

Prolonged or excessive formation and liberation of cytotoxic substances from neutrophils, accompanied by delayed apoptosis of these cells, intensify inflammation and the risk of tissue damage (Figure 1). From this...
Table 1. Mechanisms of the anti-inflammatory activity of natural polyphenols.

| Compound                  | References                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| Resveratrol               | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |
| Pterostilbene             | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |
| Pinosyvin                 | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |
| Piceatannol               | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |
| Curcumin                  | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |
| N-feruloyl serotonin     | Decreased activity and accelerated apoptosis of neutrophils in the presence of natural polyphenols could provide appropriate candidates for such a combined therapy. |

Abbreviations used: AKT: kinase B; Bcl-2: B-cell lymphoma 2; Bcl-Xl: B-cell lymphoma-extra large; COX: cyclooxygenase; CRP: C-reactive protein; GM-CSF: granulocytemacrophage colony-stimulating factor; ICAM: intracellular adhesion molecule; IL-8: interleukin 8; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; LDL: low density lipoprotein; LOX: lipoxigenase; MAC-1: macrophage-1 antigen; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; MPO: myeloperoxidase; NF-kB: nuclear factor kappa B; NO: nitric oxide; PGE2: prostaglandin E2; PISK: phospholipidase-A2; ROS: reactive oxygen species; Src: non-receptor tyrosine kinases; Syk: spleen tyrosine kinase; TNFα: tumour necrosis factor alpha; TXB2: thromboxane B2; VCAM-1: vascular cell adhesion protein; VEGF: vascular endothelial growth factor; XIAP: X-linked inhibitor of apoptosis protein.

Table 2. Effects of natural polyphenols on neutrophils.

| Compound                  | References                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| Resveratrol               | Effects of natural polyphenols on neutrophils.                            |
| Pterostilbene             | Effects of natural polyphenols on neutrophils.                            |
| Pinosyvin                 | Effects of natural polyphenols on neutrophils.                            |
| Piceatannol               | Effects of natural polyphenols on neutrophils.                            |
| Curcumin                  | Effects of natural polyphenols on neutrophils.                            |
| N-feruloyl serotonin     | Effects of natural polyphenols on neutrophils.                            |

Abbreviations used: see Table 1.
**Natural polyphenols and their effects on neutrophils**

Phenolic compounds of plant origin integrate a large group of plant secondary metabolites with remarkably rich structural variations. They are generally characterised as aromatic compounds, possessing one or more hydroxyls attached directly to the aromatic (phenolic) moiety of the molecule. The most common types of plant phenols involve phenolic acids, coumarins, stilbenes, flavonoids, lignans, condensed tannins and lignins (Harmatha et al., 2011). In this review, effects of two derivatives of ferulic acid (curcumin, N-feruloylsperotonin) and four stilbenes (resveratrol, pterostilbene, pinosylvin, piceatannol) are summarised, considering the ability of these compounds to affect inflammation and particularly neutrophil activity.

Besides their broad structural variability, natural polyphenols are characterised by a great variety of biological effects. Beneficial anti-inflammatory activities, most completely examined for resveratrol and curcumin (Table 1), have been attributed to the capacity of plant phenols to prevent activation of nuclear factor-kappa B and the subsequent overexpression of pro-inflammatory mediators — cytokines, adhesion molecules, cyclooxygenase-2, 5-lipoxygenase, myeloperoxidase or inducible nitric oxide synthase. Minor attention has been concentrated on the effect of polyphenols on the activity of neutrophils (Table 2). The existing results suggest that plant polyphenols can control neutrophil activity by multiple mechanisms and therefore may be more efficient than synthetic inhibitors directed against one particular enzyme or receptor (Burgos et al., 2009).

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