

Natural Products, Especially Fruits and Vegetables are an Excellent Source of Chemical Structures with a Wide Variety of Biological Activity, Including Inhibition of Nitric Oxide Production

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Editorial

Nitric oxide (NO) is an important signalling molecule that acts in many tissues to regulate a diverse range of physiological and cellular processes. Its role was first discovered by several groups who were attempting to identify the agent responsible for promoting blood vessel relaxation and regulating vascular tone. This agent was termed endothelium-derived relaxing factor (EDRF), and was initially assumed to be a protein like most other signalling molecules. The discovery that EDRF was in fact nitric oxide - a highly reactive gas - has led to an explosion of interest in this field resulted in over 60,000 papers published in the last ten years and won the Nobel Prize in 1998. Nitric oxide has now been demonstrated to play a role in a variety of biological processes including neurotransmission, immune defence, the regulation of cell death (apoptosis) and cell motility. Since it is such a small molecule NO is able to diffuse rapidly across cell membranes and, depending on the conditions, is able to diffuse distances of more than several hundred microns. The biological effects of NO are mediated through the reaction of NO with a number of targets such as haem groups, cysteine residues and iron and zinc clusters. Such a diverse range of targets for NO helps explain the wide range of roles that it plays. Due to the importance of NO, abnormal regulation or control of NO synthesis is capable of affecting a number of important biological processes and has been implicated in a variety of diseases. Nitric oxide in brain is involved in neurotransmission and regulation of cerebral blood flow (CBF). Although, numerous studies have described the pathophysiology of NO during ischemic/hypoxic states; the role of NO in ischemic brain injury is not fully elucidated yet [1]. Most information comes from animal models reflecting rather stroke than hypoxia/ischemia as seen in perinatal asphyxia (PA) and only limited literature on NO in the neonatal/perinatal period is available. No direct evidence for a pathophysiological role and/or generation of NO in PA has been provided; while studies have focussed on indirect methods as e.g., evaluation of nitric oxide synthase (NOS) or on the effect of NOS inhibition. Groenendaal et al. [2] studied cytosolic and membrane-bound cerebral NOS activity during hypoxia in cortical tissue of two- to four-day-old piglets. They found that both forms of NOS remained unaffected following 60 min of hypoxia. In a comparable model Jiang and co-workers confirmed their findings of unchanged NOS in cortical tissue, but reported significantly reduced NOS activity in striatum, hippocampus, cerebellum and other areas [3]. The free radical nitric oxide is formed by the catalysis of L-arginine by the enzyme NO synthase (NOS) [4]. Three isoforms of NOS have been identified. Brain NOS (bNOS) and endothelial cell NOS (ecNOS) exist constitutively and are calcium-dependent. ecNOS is found in the vascular endothelium and plays an important role in the regulation of vasomotor tone. Tonic production of NO by ecNOS provides for the baseline, physiological blood flow to most organs, including the brain, heart, lung and kidneys. The third isoform, inducible NOS (iNOS), is induced by proinflammatory stimuli such as endotoxin (bacterial lipopolysaccharide; LPS) and interferon gamma. Unlike bNOS and ecNOS, iNOS in rodents is calcium-independent; iNOS has

been found in a variety of mammalian cells, including macrophages, hepatocytes, vascular smooth muscle cells and respiratory epithelial cells. NO produced by iNOS plays a key role in the bactericidal effects of macrophages. The sustained overproduction of NO by iNOS in the vasculature plays an important role in the circulatory collapse seen with endotoxemia. Moreover, high local concentrations of NO are cytotoxic and cause cell lysis and organ dysfunction [5].

Foods of plant origin, especially fruits and vegetables, draw increased attention because of their potential benefits to human health. For decades, most of the attention of nutritionists and health professionals has focused on the impact of the major dietary components, such as the amounts and types of fats, proteins, carbohydrates and fibers, on human health. However, interest in the role of minor components is rapidly growing. Many constituents of plants are non-nutritional compounds that play key roles in plant physiology and interactions with the environment.

The interest of the research is motivated by the current need to find new substances of natural origin which have demonstrated effectiveness in the described fields of application and low degree of toxicity for humans. Natural products provide a vast pool of NO inhibitors that can possibly be developed into clinical products. A wide variety of dietary plants including grains, legumes, fruits, vegetables, tea, wine, etc. contain polyphenols [6]. The disease preventive abilities of fruit and vegetables have been attributed to the antioxidants/polyphenols present in these dietary sources [7]. It is noteworthy that most reports on the beneficial effects of polyphenols have been obtained from *in vitro* studies and more detailed investigations are required to extrapolate these results to *in vivo* situations. Polyphenols, with over 8000 structural variants, are secondary metabolites of plants and denote a huge gamut of substances having aromatic ring(s) bearing one or more hydroxyl moieties. The structure of natural polyphenols varies from simple molecules, such as phenolic acids, to highly polymerized compounds, such as condensed tannins. The most widely distributed group of plant phenolics are flavonoids. Their common structure is that of diphenylpropanes (C6-C3-C6) and consists of two aromatic rings linked through three carbons that usually form an oxygenated heterocycle [8]. Natural products provide a vast pool of NO inhibitors

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that can possibly be developed into clinical products. Garlic (*Allium sativum* L.) is one of the basic components of Mediterranean cooking and it has long been used as a folk medicine. It is now accepted that allicin, the main biologically active compound in garlic, inhibit nitric oxide (NO) production by cytokine-induced NO synthase (iNOS) [9]. Mandarin oranges (*Citrus reticulata* L.), with their glossy dark green leaves, fragrant springtime blossoms and bright orange fruits, are beautiful little specimen trees in the home landscape. The citrus peel extract inhibition of iNOS gene expression was the major NO-suppressing mechanism [10]. *Oryza sativa* L. (rice) is one of the most important crops in the world and it provides the main resource of energy for more than half of the world population and is the major food crop in China. The rice showed inhibition of nitric oxide synthase [11]. It is well established that natural products are an excellent source of chemical structures with a wide variety of biological activity, including inhibition of nitric oxide production. The large number of compounds derived from natural sources, that are currently undergoing evaluation in clinical trials, is another positive indicator that natural product discovery provides good value for human medicine.

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