ABSTRACT

Polymorphonuclear neutrophils (PMNs) play a major role in inflammatory diseases. They act as a first line of defense against invading infectious microorganisms. For this purpose, PMNs contain granules filled with proteolytic and other cytotoxic enzymes. Besides releasing enzymes, PMNs are also able to phagocytose and to convert oxygen into highly reactive oxygen species (ROS). Following phagocytosis, ingested microorganisms may be killed inside the phagosome by a combined action of enzyme activity and ROS production. Although the formation of ROS by stimulated PMNs is a physiological response which is advantageous to the host, it can also be detrimental in many inflammatory states in which these radicals give rise to excessive tissue damage. Therefore, there is an ongoing search for anti-inflammatory compounds which are able to prevent this damaging ROS production without affecting the other killing capacities of the PMN.

In 1971, the isolation of apocynin from the roots of *Picrorhiza kurroa* Royle ex Benth. was reported. *Picrorhiza kurroa* is a small, perennial plant growing at high altitudes in the western Himalayas and which has been used extensively for ages and is still in use in the Ayurvedic system of medicine in India and Sri Lanka. Following experiments showed that apocynin was a potent anti-inflammatory agent, based on the selective inhibition of the production of ROS by activated human PMNs. Although proven to be an active anti-inflammatory compound in several experimental animal models, the exact mechanism of action of apocynin was still not fully understood.

In this thesis, experiments are described that have led to a better understanding of the mode of action by which apocynin inhibits the ROS production by activated human PMNs. One of the conclusions is that apocynin itself is not active, but that it is converted into an active dimer inside the phagosomes of activated PMNs.