Antioxidant and antiproteolytic: synergistic cell protection in inflammatory processes

PADMA 28

PADMA –

For the benefit

of our health.

Publication
I. Ginsburg et. al., Inflammopharmacology 1999;7/1:47-62.

A study on the mechanism of action

The antioxidative and antiproteolytic effects of PADMA 28 have been demonstrated in vitro in various different systems [1]. Extracts of PADMA 28 inhibit four cytotoxic processes that occur in inflammation and which, if they become chronic, can lead to damage to endogenous cells.

This potential explains the success obtained in the treatment of intermittent claudication. In several controlled double-blind studies PADMA 28 has been shown to significantly increase the distance walked by patients with intermittent claudication [2], [3], [4]. In vitro and ex vivo, PADMA 28 reduced the inflammatory stress reaction of macrophages [5], [6].

From the results of the present in vitro study of Ginsburg et al. it can be assumed that PADMA 28 is also effective in other chronic inflammatory diseases. This hypothesis is substantiated by various pilot studies and clinical case reports [7], [8], [9].

Results

1.

Inhibition of cytolysis

In the inflammatory reaction, a «cocktail» of free radicals, membrane-perforating substances (lysins) and proteases is activated. PADMA 28 inhibits these three cytotoxic-acting substance groups simultaneously.

In cell cultures (BGM epithelial cells), aqueous and methanolic extracts of PADMA 28 reduced the cytotoxic effect of such a mixture, whereby the apolar methanol fraction showed an activity at least greater by the factor of 10 than that of the polar, aqueous extract (which indicates the presence of liposoluble active components). The inhibition was dose-dependent.

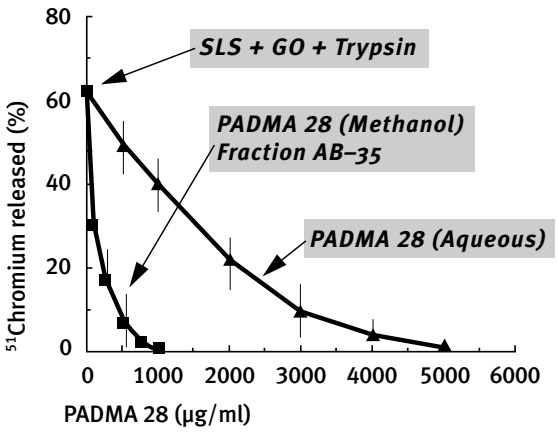

Fig.1: *Inhibition of cytolysis. The aqueous whole extract and a methanolic partial extract of PADMA 28 inhibit, in a dose-dependent manner, the destruction of cells (measured on the release of 51Cr from the cells) by a mixture of streptolysin S (SLS), glucose oxidase (GO, a generator of radicals) and the protease, trypsin. The effect of the apolar fraction is distinctly more pronounced. Results from 5 experiments (means ± standard deviation).*

Results

2.

Inhibition of the «oxidative burst» in neutrophils

Inhibition of the oxidative stress reaction of neutrophils stops the overreaction of the inflammation. PADMA 28 extracts displayed this effect both in the present experiment and in earlier studies [5], [6].

In this trial, neutrophils were activated by bacterial cells, so that they released oxygen radicals. These oxygen radicals can be measured by means of chemiluminescence. An overproduction of oxygen radicals - for example within the framework of a chronic inflammatory process - can have a destructive effect on the adjacent endogenous tissue.

When added before the activation of the neutrophils, PADMA 28 extracts had an inhibitory effect on the production of radicals.

PADMA 28 also reduced the chemiluminescence rapidly and efficiently through binding of the free radicals, when it was added at the peak of the activation of the neutrophils. Some methanolic fractions of PADMA 28 were even more effective than the whole extracts. These apolar extracts indicate the presence of liposoluble components.

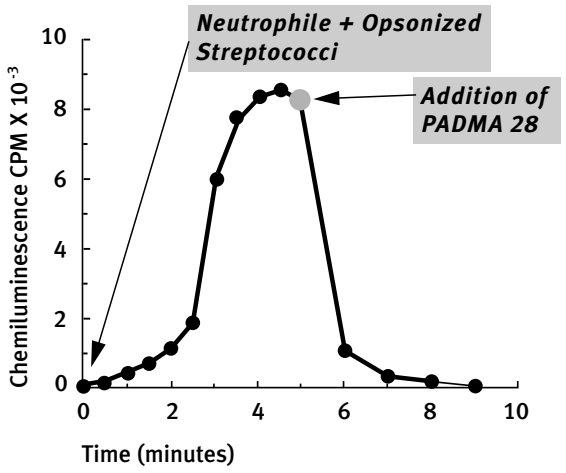

Fig. 2: Inhibition of the oxidative stress reaction in neutrophils. After the addition of aqueous PADMA 28 extract to activated neutrophils, the concentration of free radicals (measured by means of chemiluminescence) decreases rapidly. A typical result from a series of experiments.

3.

Inhibition of lipid peroxidation

Peroxidated lipids play an important role in the formation of arteriosclerotic deposits in the vascular lumen.

PADMA 28 extract inhibited the peroxidation of lipids (here: Intralipid) in a dose-dependent manner. This confirms earlier clinical results [3].

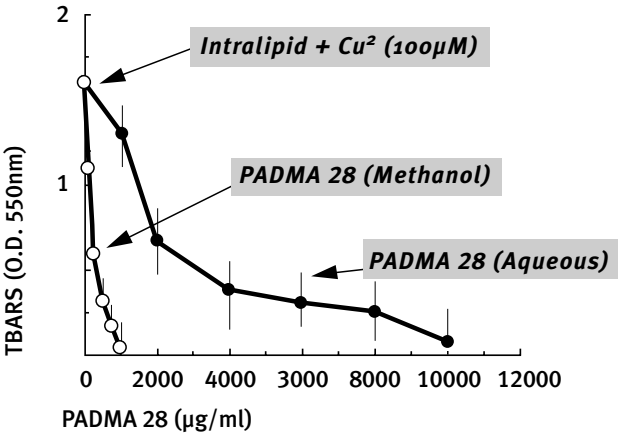

Fig. 3: Inhibition of Intralipid peroxidation in the presence of copper. With increasing concentrations of PADMA 28 (methanolic and aqeous extracts) the proportion of oxidised Intralipid (measured on the thiobarbituric acid concentration, TBARS). The results are presented as means ± standard deviations from three experiments.

4.

Inhibition of proteases

The enzyme elastase is involved in the destruction of tissue at foci of inflammation.

PADMA 28 extracts inhibited the protease activity of elastase and trypsin.

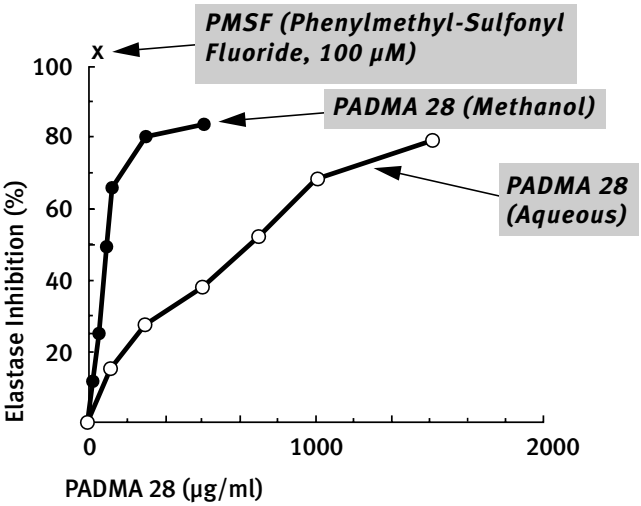

Fig. 4: Dose-dependent inhibition of elastase by extracts of PADMA 28, compared with inhibition by a known elastase inhibitor, PMSF. The cleavage of synthetic substrates was measured. The results are mean values from 3 experiments.

Context

Chronic inflammation, a complex interplay of various amplifying mechanisms

At foci of acute inflammation, large amounts of phagocytes accumulate. Once activated, they release free radicals and other cytotoxic, inflammation-promoting and proteolytic substances.

This synergistically acting cocktail of aggressive substances, however, not only attacks substances that are recognised as foreign, but can also damage endogenous cells and tissue - a veritable «double-edged sword» [10]. Persistent stress of the immune system causes an overreaction of the defence functions, and amplifying mechanisms lead to chronic inflammation, which in the case of arteriosclerosis is localised on the inner wall of the artery.

Widely differing substances therefore have to be available to the body, helping to counteract the immunological overreaction, which occurs in several cascades. In order to achieve this to the optimum, there must be regulating mechanisms at different levels at the same time [11], for example through:

- elimination of oxidative chemical reactions through reduction
- scavenging of free radicals (especially $O_2^{\bullet-}$, $OH^{\bullet}$, $HO_2^{\bullet}$)
- binding of catalytic metal ions (suppression of the Fenton reaction)
- inhibition of proteolytic enzymes
- removal of damaged molecules

The present study shows that PADMA 28 can intervene in these inflammatory processes at several levels.

Treatment and prevention of oxidative stress with PADMA 28 - effective and with few side effects

The oxidation of LDLs (low-density lipoproteins) and the subsequent uptake of the damaged lipids by macrophages contributes to the formation of foam cells and plaques and thus makes a decisive contribution to the development of atherosclerosis [11]. Effective treatment and prevention of oxidative stress, with few side effects, therefore play an important role. On the basis of this and earlier studies it can be assumed that the wide range of plant-based antioxidants contained in PADMA 28 can prevent the progress of the damage due to the atherosclosis successfully and with minimal side effects.

Conclusions

Anti-atherosclerotic effect of PADMA 28

The authors postulate that the synergistic effect of the herbal substances contained in PADMA 28 on the foci of chronic inflammation can provide efficient protection against cell damage and lipid peroxidation. This hypothesis contributes significantly to the understanding of the effect of PADMA 28 in the prevention and treatment of atherosclerosis.

Anti-inflammatory and antioxidative effects

The antioxidative and antiproteolytic effects of PADMA 28 demonstrated in this study by Ginsburg et. al. arouse interest in further investigation of its effect on other diseases associated with chronic inflammation and the effect of free radicals.

Synergism of the active ingredients

In this series of experiments PADMA 28, a multi-compound preparation, proved to be effective against a combination of several cytotoxic substances. The authors speculate that many different active substances in PADMA 28 have a synergistic effect and can thus have a particularly efficient influence on the multiple effects of chronic inflammation.

Literature

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PADMA 28

Composition: Aegle sepiar fructus 20 mg, Amomi fructus 25 mg, Aquilegiae vulgaris herba 15 mg, Calcii sulfas pulv. 20 mg, Calendulae flos 5 mg, Cardamomi fructus 30 mg, Caryophylli flos 12 mg, Costi amari radix 40 mg, Dextrocamphora 4 mg, Hedychii rhizoma 10 mg, Lactucae sativae folium 6 mg, Lichen islandicus 40 mg, Liquiritiae radix 15 mg, Meliae tousend fructus 35 mg, Myrobalani fructus 30 mg, Plantaginis herba 15 mg, Polygoni herba 15 mg, Potentillae aureae herba 15 mg, Santali rubri lignum 30 mg, Sidae cordifoliae herba 10 mg, Aconiti tuber 1 mg, Valerianae radix 10 mg, Excip. pro compr.

Indications: Tingling sensation, formication, heaviness und tenseness in arms and legs, numbness of hands and feet, cramps in the calf.

Administration/Dosage: Initially, ingest 3 x 2 tablets 1/2 – 1 hours before meals. Depending on the patient’s condition, the dosage may subsequently be reduced to 1 – 2 tablets daily.

Side effects: Occasionally gastrointestinal symptoms may occur. Gastric discomfort can be remedied by ingesting plenty of fluid (1 – 2 glasses of fluid) or by taking the tablets during the meals. In a few isolated cases, palpitations and slight restlessness have been observed in predisposed individuals.

Information: Comprehensive information regarding this product can be found in the «Arzneimittelkompendium der Schweiz – Publikumsausgabe».

Production and distribution: PADMA AG, Wiesenstrasse 5, CH-8603 Schwerzenbach, Switzerland, Tel. +41-1-887 00 00, Fax +41-1-887 00 99, mail@padma.ch, www.padma.ch