

The “multi-target“ approach of Tibetan remedies

Mechanisms of action of Padma 28 in inflammation, with the example of atherosclerosis

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Summary

Chronic inflammation poses high demands on modern medicine. Multifactorial chronic diseases require multilevel therapies that work on different pathogenic processes and at the same time have few side effects. Due to their multicomponent composition and their high tolerability Tibetan medicines offer valuable therapeutic approaches. Tibetan formulas are multicomponents containing different, mostly herbal raw material. Their composition is based on the principles of Tibetan medicine. Therapeutically cooling or warming formulas are used to counterbalance the disturbed equilibrium of bodily energies. Because of the complex pharmacological activity profile of Tibetan remedies they act as “multi-target drugs”. The concept of multi-target drugs comprises partial effects at multiple sites of action simultaneously. Such a profile of activity is not limited to a strong effect at only one site of action as it occurs in the case of single-target drugs. This multi-target approach seems especially appropriate in multifactorial, chronic diseases.

The multicomponent formula Padma 28 is based on Tibetan medicine. In clinical, in-vitro und ex-vivo studies it showed promising effects on atherosclerotic changes. The comparison of these scientific results and the processes in atherogenesis clearly proves the character of Padma 28 as a multi-target drug. The multicomponent interacts with the pathogenic processes simultaneously at different sites of the artery wall and in different stages of the disease. The example of Padma 28 in atherosclerotic changes shows that Tibetan medicines act as multi-target drugs and offer promising therapeutic approaches, especially in chronic diseases with complex etiology. The subject of multi-target drugs represents an important contribution to the modern understanding of Tibetan medicines and complementary practice in general.

Keywords

Tibetan Medicine - atherosclerosis - multi-target drug - multicomponent - Padma 28

Inflammation is a defence mechanism of the immune system and is necessary for survival against infections with pathogens such as bacteria, viruses, parasites and fungi. Inflammatory conditions also play an important role in the control and repair of other lesions, e.g. tissue damage caused by thermal or mechanical influences. Here activated macrophages release an “inflammatory cocktail“ of proteolytic, cytotoxic and membrane-perforating substances as well as free radicals. This cocktail destroys bacteria and damaged cells, which is a prerequisite for the healing and regeneration of healthy tissue.

As an integral component of the healing process, inflammatory reactions in the body must be strictly regulated. Pro-inflammatory and anti-inflammatory mechanisms act in concert with one another, with the aim to eliminate

the cause of the inflammation, to remove damaged cells and to repair tissue lesions. If these mechanisms work together optimally, the inflammation-free state, based on a labile equilibrium, is reached.

With chronic inflammation the situation presents itself in a different way: once the inflammatory processes have flared up the complex regulatory mechanisms can no longer stop them. This can happen due to a disturbance of the regulatory systems or due to a persistent inflammatory stimulus, which leads to continuous stimulation of the body cells, especially the immune cells.

In this way a pathological picture often develops, where it is no longer possible to differentiate between the damage that occurred due to the original cause of the inflammation and the damage that was caused by the in-

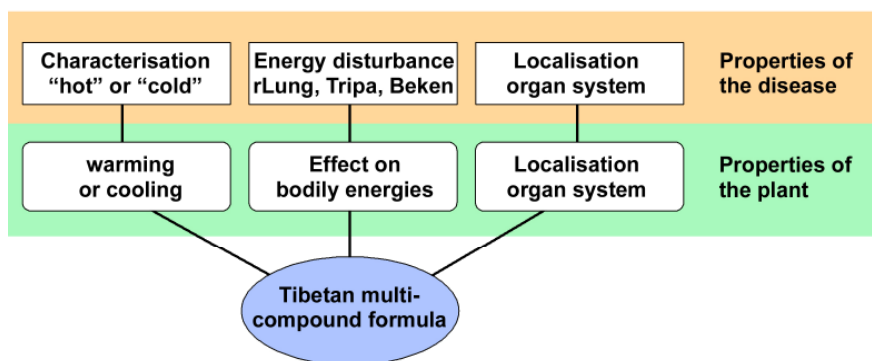
flammatory process which started in the course of the healing process. Here the inflammatory processes become responsible for most of the pathological changes and they determine the clinical picture. This is the case, for example, with atherosclerosis, Type I diabetes mellitus and liver cirrhosis, whether caused by alcohol abuse or by viral infection, as in the case of chronic hepatitis C.

Such diseases with complex etiology and chronic course confront modern medicine with ever greater challenges. They require therapies which act at different levels and on different processes in the pathogenesis, and which at the same time have few side effects. On account of their multicomponent composition and their good tolerability, Tibetan remedies offer valuable treatment alternatives.

Figure 1: Myrobalan (*Terminalia chebula*) and Tibetan formula as a multicomponent preparation: raw drugs contained in Padma 28.



Figure 2: Criteria for the combination of herbs in a Tibetan drug. (after Nikolayev [2]).



Tibetan remedies as multi-target drugs

Tibetan remedies are multicomponents containing from 3 to 20 components, or even more. The Tibetan “materia medica” consists of a large number of plant-based active substances, such as leaves, bark, roots, flowers and resins (Fig. 1). To a lesser extent, minerals are also used and, in rare cases animal-based substances. All these substances are classified on the basis of the effects observed and the sensory properties such as taste, texture and colour [1]. The untreated raw materials, mostly in dried, powdered form are mixed together according to the different recipes. The drugs resulting from this process are applied mainly

in the form of powders, pills, tablets and decoctions.

The composition of the components in the different remedies is in accordance with the principles of Tibetan medicine. Primarily, diseases are divided into cold and hot disorders and are defined as a shift in the individual equilibrium of the 3 bodily energies rLung, Tripa and Beken – roughly translated as wind, bile and phlegm. Different drug components are then combined in a formula that compensates the disturbance of the energy balance. The components are selected on the basis of their characterisation according to three different aspects: 1) hot or cold, 2) effect on the bodily energies and 3) their organotropic properties (Fig. 2) [2].

Accordingly the characteristic feature of Tibetan remedies is their complex composition of raw materials left in their natural state. The individual components are present in very small amounts – if used alone such small dosages would in fact have no effect. It is the combination that ensures the efficacy of the Tibetan remedies, in that the various ingredients mutually complement one another and at the same time are effective at different sites of action. The ingredients contribute synergistically to the main effect and some of them also act as antagonists, in that they mutually eliminate certain effects. Such drugs can also be described as multi-target drugs (in contrast to single-target drugs) [3].

Multi-target drugs of this type have only a relatively low binding affinity which, together with principle of synergism, explains that these multicomponents have only very few adverse effects.

The partial inhibition and/or the partial activation of metabolic processes resulting from this could, overall, be more effective and more useful than the total inhibition or activation of a single target [4]. This is of particular importance in multi-causal and multi-factorial diseases such as atherosclerosis, where chronic inflammatory processes are causative in the pathogenesis.

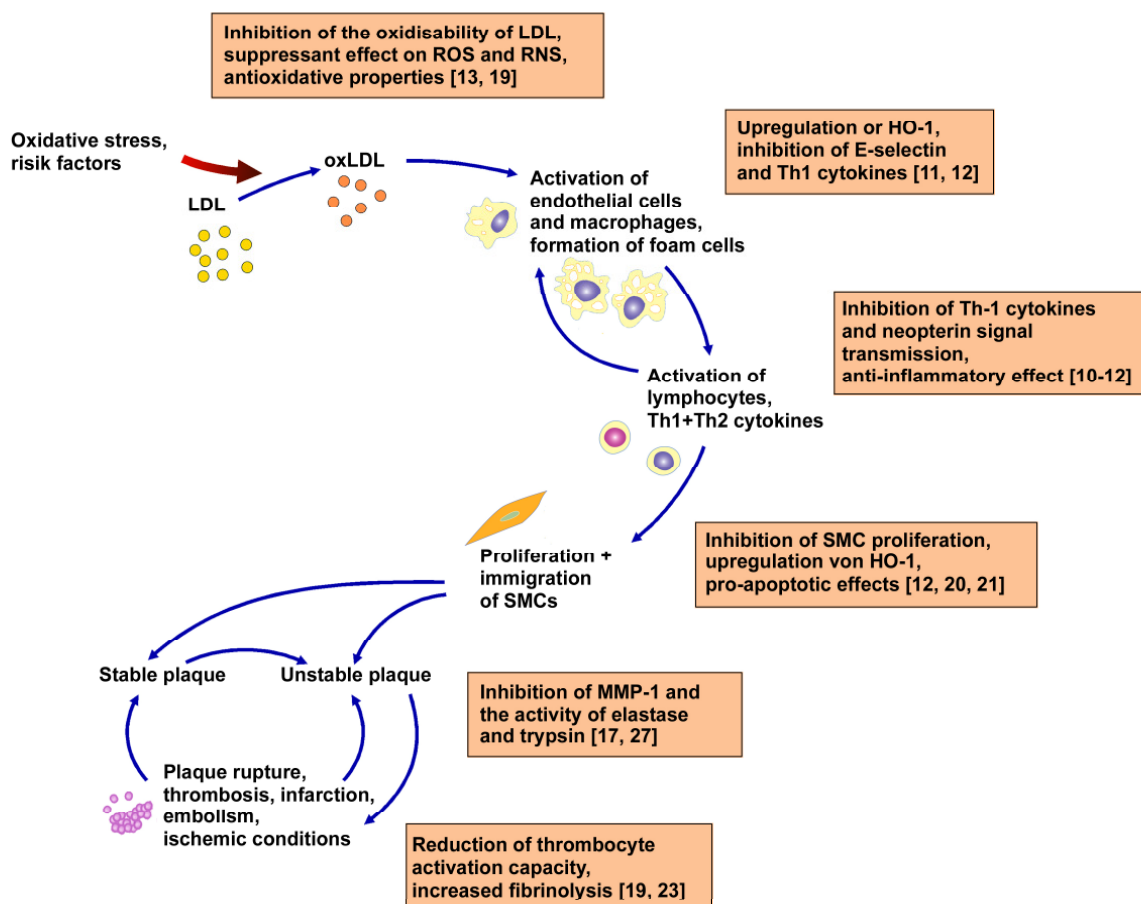
Arteriosclerosis as a chronic inflammatory process

Atherosclerosis and the many secondary complications are among the most widespread chronic diseases in the Western industrial societies. With the globalisation of consumers’ behaviour and ways of life, they are constantly on the increase also in other parts of the world.

Atherosclerosis is a multifactorial, inflammatory disease with complex etiology and chronic course. Various different pathogenic processes are involved in the development of atheromatous changes and have a decisive influence on the course of the disease. Oxidative stress, the status of the immune system and hemodynamic factors, for example, play a role here.

Figure 3: Processes in the development of atherosclerotic lesions.

Results from *in vitro* and *ex vivo* studies on Padma 28 are summarised and related to the different stages of atherogenesis. (oxLDL: Oxidised low-density lipoprotein; ROS/RNS: Reactive oxygen and nitrogen species; HO-1: Hemoxygenase 1; SMCs: Smooth muscle cells; MMPs: Matrix metalloproteinases).



However, the pathogenesis of the disease also has a strong autoimmune component, and other possible causes such as bacterial infections are discussed.

Atherogenesis involves a series of steps, whereby the inflammatory processes continually build up in a cascade-like manner (Fig. 3).

Oxidised cholesterol (oxLDL) as primary triggering factor:

Cholesterol, more concretely the low-density lipoprotein (LDL) cholesterol in its oxidatively modified form (oxLDL), plays a central role in the triggering and maintenance of the inflammatory processes. LDL diffuses passively through the endothelium and into the tunica intima of the vessel wall.

Under elevated oxidative stress the oxidative and enzymatic modification

of LDL molecules increases. OxLDL can no longer diffuse freely out of the tunica intima, leading thus to a retention of this blood lipid in the vessel wall. Here, oxLDL acts as an auto-antigen and triggers an inflammatory reaction [5].

Activation of endothelial cells, immigration of macrophages:

The thus initiated inflammatory reaction activates endothelial cells, which express adhesive molecules. Immune cells increasingly release cytokines and chemotactic factors, which lead to the immigration of monocytes into the tunica intima. These change into macrophages, which take up oxLDL in large amounts. The activated macrophages release pro-inflammatory cytokines and reactive nitrogen and oxygen species (RNS and ROS), which in turn

oxidise LDL and thus strengthen the local inflammatory response.

Deposit of the foam cells:

The cholesterol that is taken up is deposited, in the form of lipid drops, in the immune cells and these then become foam cells. The accumulation of such foam cells forms the basis for the first macroscopically visible atherosclerotic changes, the so-called fatty streaks. Initially the fatty streak is still reversible, but over years and decades it can develop into a fully formed atherosclerotic plaque.

Formation of the plaque:

The plaque consists of a necrotic lipid nucleus of dead foam and immune cells and secreted free cholesterol and cholesterol crystals. The atheromatous nucleus is covered by a fibrous cap consisting of immigrated vascular

smooth-muscle cells (SMCs) of the tunica media and of its extracellular matrix. The activity of inflammatory processes in the nucleus and the cap, the extent of the cell death, the necrosis of the SMCs, macrophages and the degradation of the extracellular matrix, for example due to matrix-metalloproteinases (MMPs), determine the stability of the plaque. Stable plaques with a thick fibrous cap, strengthened by collagen and elastin, and a small lipid nucleus can change into unstable plaques.

Further complication due to pro-inflammatory stimuli:

Factors that contribute to the formation of unstable plaques are pro-inflammatory mediators, which inhibit the synthesis of components of the extracellular matrix. Matrix-degrading factors such as matrix-metalloproteinases, break down collagen and elastin by proteolysis.

In the formation of the plaque a thickening of the arterial wall first takes place. Until this stage the lumen of the vessel is largely unchanged and the disease is initially asymptomatic. In the case of unstable (vulnerable) plaques, the fibrous cap can rupture. The contact of the contents of the plaque with the blood triggers platelet aggregation and a thrombus forms. Large thrombi may cause sudden arterial occlusions which lead to ischemic infarctions. The rupture of a thrombus can have dramatic consequences, such as myocardial or cerebral infarction. Small thrombi can be resorbed to a large extent with thrombolytics. However, also in this situation a wound-healing cascade is triggered.

Wound healing or a further inflammatory cycle:

Due to the "scarring" at the site of the wound there is also a reduction in the diameter of the vessel which can, especially in states of stress, lead to ischemic conditions such as intermittent claudication or angina pectoris. The effects of various different factors determine whether there is a further cycle of plaque rupture and scarring or whether the course of the disease stagnates. Persisting pro-inflammatory stimuli, the continuing influence of risk factors and a "pro-atherogenic" life style all make a decisive contribution to the pro-atheroge-

nic milieu and thus to exacerbation of the disease.

If the risk factors persist, these processes can continue for many years. In the chronic situation the course of the disease shows different degrees of intensity and frequency, which is explained by the multicausal, cascade-like pathological process. This course of the disease requires a multifocal basic therapy, which simultaneously affects the various different processes that are involved, and which also has a preventive effect.

Multi-target approach with Padma 28 in the chronic inflammatory processes of arteriosclerosis

As multi-target drugs the Tibetan multicomponents have the potential to meet the requirements of such a basic multifocal therapy. The Padma 28 formula, a complex multicomponent of 20 plants, camphor and calcium carbonate, is a mixture of polyphenols, flavonoids and tannins [6]. (PADMA AG, Schwerzenbach, Switzerland; Swissmedic Nr. 41125). In the case of atherosclerotic changes it has shown very promising effects, both in clinical studies and also in-vitro and ex-vivo studies.

In different systematic reviews this plant-based product has been shown to be effective in intermittent claudication [7, 8], which is a consequence of atherosclerotic changes in the peripheral arteries of the legs. A number of research groups have investigated various aspects of the mode of action of Padma 28, which can be classified very well into the cascade of the development of atherosclerotic lesions (Fig. 3). The synopsis of the results shows a whole spectrum of anti-atherogenic modes of action [9]. In various experiments for example, the anti-inflammatory effect [10-12] and strong antioxidative and cell-protecting properties, as well as a pro-oxidative potential, have been established [13-19]. Also, antiproliferative, pro-apoptotic and anti-microbial effects, as well as an effect on blood coagulation and platelet aggregation, have been observed [12, 19-23].

These biochemical effects complement the clinical findings. They show an overall inhibitory effect on the formation of atheromas, which can be

described as low-level inflammation. The low-level activity of chronic inflammation is always accompanied by increasing episodic processes. This is the case in the processes that take place when a stable atheromatous plaque changes into an unstable, susceptible, so-called "vulnerable" plaque. Here, the inflammatory processes in the fibrous cap and in the atheromatous nucleus are more active and are perpetually reigniting themselves.

They can be demonstrated as an increase in the peripheral inflammation markers such as C-reactive protein (CRP) and can in fact be confirmed by thermographically measured plaque temperatures [24, 25]. These temperature measurements show an analogy to the heat character, which according to the Tibetan view is typical for this disease. With such unstable, thrombogenic plaques, components of the plaques, such as tissue factor or atherosclerotic debris, come into contact with the blood stream and trigger the coagulation cascade. The resulting formation of thrombi can lead to vascular stenosis or even to complete obliteration and, in the case of dislodgement of a thrombus, to embolism and infarction.

Factors that contribute to the vulnerability of atherosclerotic plaques and promote the formation of thrombi are a disturbed endothelial function over the plaque, the infiltration of the fibrous cap by macrophages and matrix-degrading factors such as certain matrix-metalloproteinases which break down collagen and elastin by proteolysis. In cell cultures of human dermal fibroblasts, Padma 28 inhibited the production of the MMP-1 [26] associated with plaque instability, but not that of MMP-2 [27], associated with stable plaques [28]. This was confirmed in organ cultures of skin biopsies, in which an increase of Type I procollagen, a stabilising factor of the extracellular matrix, was also observed. The histological picture of the culture remained unchanged.

Padma 28 also inhibits the protease activity of elastase, cathepsin G and trypsin [17] and impedes the release of lysozymes from activated human neutrophils [18].

The complex composition and the carefully harmonised components act at different levels of the development of diseases. This is shown with the example of Padma 28 and its syner-

gistic profile of action in arteriosclerosis. The complexity of the effects concerns both the sites of action (endothelium, tunica intima, tunica media) and also the course of atherogenesis in terms of time. Here, on the one hand the early changes, such as the adhesion of monocytes to the endothelium and the oxidative modification of LDL-cholesterol, are inhibited. On the other hand the results indicate an inhibitory effect on the development of the fully formed plaque, especially on the mechanisms of the formation of vulnerable plaques.

Conclusions

The multi-substance composition and the principle of the synergistic action of Tibetan remedies make them particularly suitable for the treatment of chronic diseases where inflammatory processes are causative.

While acute inflammations can be treated very successfully in Western medicine, chronic inflammatory diseases such as atherosclerosis pose great demands on the treatment and prevention. It is precisely in the case of diseases with complex etiology which may persist for months or years that, besides a high level of efficacy, good tolerability of the treatment is very important. Here Tibetan medicine with its formulas from carefully balanced natural substances and their favourable side-effects profile, offers promising therapeutic possibilities.

The concept of the multi-target drugs makes it possible to comprehend the complexity of the effects and also to understand the relatively slight binding affinity of these drugs. The example of the inflammatory cascade shows the efficiency of this concept and its ability, to act simultaneously at different sites with only relatively limited strength of action. The subject of the multi-target drugs therefore represents an important contribution towards the modern understanding of Tibetan remedies in particular and of complementary practice and integrative medicine in general.

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