The biological activity of curcumin

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The spice turmeric is a component of Indian curry mixtures and enjoys great esteem among practitioners of the traditional Indian Health System, the Ayurveda. The described fields of application are very versatile and reach from antibacterial effects, relief from feelings of fullness, strengthening of the liver functions, antioxidative qualities and cell structure protection up to the inhibition of inflammation in arthritic conditions.

If so many different qualities are awarded to a natural substance, scepticism is generally appropriate. Nevertheless, more and more serious studies and scientific articles are published in renowned journals confirming the effects of the spice's key ingredient, curcumin (and another two curcuminoids) in rheumatoid arthritis (RA) and other diseases with an inflammatory background. Can the molecular structure of curcumin help to explain the diverse biological activities of turmeric?

The molecular structure of curcumin > Although the structure of curcumin is in no way particularly complex, it has some unusual biochemical features. These make reactions and interactions possible with biologically relevant substances, particularly proteins and metal ions. The main features of curcumin are the two conjugated, unsaturated, α, β-diketo groups which play an important role in reactions with proteins, and the

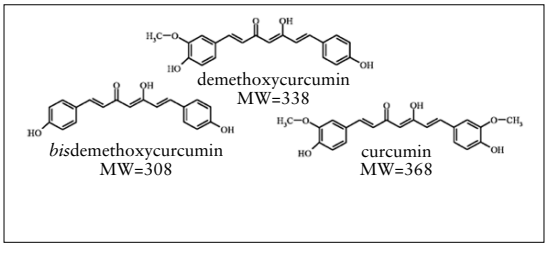

Figure 1: Structural formulae of curcumin and the two main curcuminoids demethoxycurcumin and *bis*demethoxycurcumin.

two phenolic hydroxyl groups which convey the antioxidative properties to curcumin. The conjugated position of the functional groups increases the stability as well as the reactivity of the molecule.

Interestingly curcumin, but not the two curcuminoids demethoxy curcumin and *bis*-demethoxycurcumin, disposes of two methoxy groups. At first glance, these are labelled as not functional as they are believed to be non-reactive; nonetheless they seem to be important for the biological activity of curcumin since this molecule is fundamentally more reactive than dimethoxycurcumin and *bis*-demethoxycurcumin which lack one or both of the two methoxy groups, but are otherwise identical (see Figure 1). After this little excurse on the structure of curcumin it might be a bit easier to understand the effects created by the structural characteristics of the molecule… we hope.

Curcumin, curcuminoids and inflammatory responses > Thanks to the described structural characteristics of the molecule, curcumin is capable to combine antioxidative with anti-inflammatory properties. The two modes of action combine in an ideal way, since an increased oxidation load always causes inflammatory responses, too.

Interesting evidence comes from recent Australian studies with Alzheimer models: Alzheimer tissue has a characteristically increased level of ROS (reactive oxygen species) and a significantly high level of pro-inflammatory cytokines (signalling molecules of inflammatory processes). An epidemiological evaluation of the influence of anti-inflammatory active agents, so-called NSAIDs ("non-steroidal anti-inflammatory drugs") on the probability to develop Alzheimer, shows a clear protective capacity of the NSAIDs: Patients on medication with such active ingredients for a period of over two years had a more than 50 % lower of probability of developing symptoms of morbus Alzheimer[i]. Chronic local inflammation of cerebral areas is thought to be an important cause of senile dementia and Alzheimer's.

However, NSAIDs are rather unsuitable to be prescribed "prophylactically", as the worldwide discussion of cyclooxygenase-2 inhibitors (COX-2 inhibitors, e.g. Vioxx™), has demonstrated.

The inhibition of COX-2 was considered an efficient way to block inflammatory responses, by turning off a key element. However, the inhibition of COX-2 does not stop the complete inflammatory response but only the formation of prostaglandin E2, a cytokine important for pain development and processing. The treatment is therefore perceived as a success by the patient (and the physician, too) – the pain will gradually disappear – but actually only symptoms are being treated, not causes.

And the price paid for this pain reduction is high: Studies have shown that COX-2 plays an important role in the resolution phase of the inflammation process, too[ii,iii]. Without COX-2 the inflammation continues, although the pain may not be perceived any longer.

The central problem seems to be a difficult dilemma: Many chronic inflammation diseases are based on a whole number of different causes and factors. However, modern pharmaceutical active ingredients ("API") are conceived to have only one defined target, such as the inhibition of one enzyme. Consequently, whole "cocktails" of different APIs are often used in the treatment of such syndromes with various unwanted side effects.

If conditions, such as diabetes or high blood pressure, join chronic diseases, it is easily imaginable how many single APIs might become necessary to keep the various symptoms at bay.

In a healthy condition our body reaches a kind of homoeostasis, a delicate balance of partly antagonistic forces. Signalling pathways influence, attenuate, increase, or trig-

ger other signals. Under normal conditions these effects are subject to a temporal and local limitation and react to external or endogenous stimuli. The interruption or inhibition of a pathway often has far-reaching, incalculable consequences in this delicately balanced system. Disturbing the balance may then lead to a continuous inflammation, a chronic illness.

Curcumin acts in a fundamentally different way: Rather than inhibiting a single, defined enzyme completely, curcumin interacts with many different signalling molecules (e.g. some interleukins that fulfil important tasks in inflammatory processes). In this context it is of particular importance that signalling pathways are not completely blocked by curcumin, but are regulated down to their basic level – and this in many places simultaneously so that a signal balance can be achieved on lower level. Enzymes and signal molecules can further provide their service; where conditions are out of control and inflammatory cytokines are released in excess, curcumin helps to prevent a smouldering fire (an inflammation that feeds itself continuously) by a locally and temporarily restricted down-regulation of the overproduction.

The problem of bioavailability > While many publications consider curcumin an extremely promising and effective weapon in the fight against the most important morbidity and mortality factors of the western world, almost just as many authors regret the extremely low bioavailability and the usually very short retention time of the molecule in the body.

Clinical studies of phase I with daily doses of up to 8 g were carried out with cancer patients – with absolutely convincing results[iv]. Again, the authors mention the difficulty of administrating greater amounts of curcuma orally – the study was carried out with capsules of 500 mg.

Other studies with daily amounts reaching from 450 mg to 3,600 mg also point to the little systemic absorption of curcumin, while at the same time the high biological activity of the ingredient is highlighted[v].

What all these studies have in common is the understanding that curcumin has not caused any toxic effects in the participating patients; even when high doses of several grams were administered over periods of up to 4 months. One side effect was mentioned by Cheng et al.: The reduced *compliance* of the participants when given daily dosages of more than 8 g. This, however, is understandable when more than 16 capsules have to be swallowed day by day.

Consequently, many attempts have been made to increase curcumin's bioavailability. The approach to formulate curcumin in combination with piperine, an extract of black pepper, seems promising. Based on results of animal studies (and meanwhile human studies with healthy volunteers, too) an increase of plasma curcumin levels of 150 % could be shown by this combination[vi]. Piperine, however, increases the bioavailability of a wide range of substances, so that caution seems appropriate when other pharmaceutical actives are administered at the same time. Furthermore, some reports have been published that link piperine in minor dosages to hepato-toxic reactions of animals in several *in vivo* studies.

Formulations with lecithin (Phosphatidylcholine, PC) are of interest; too: It could be shown that the bioavailability of curcumin could be increased by more than 500 %, when the formulation contained lecithin – at least in an animal model[vii]. But again the realisation is not without difficulties: one molecule curcumin binds to six molecules PC[viii]. Formulations of PC and curcumin therefore had a low content of the active principle and a large part of lecithin.

A most promising approach seems to be a new development of the Indian company Arjuna who patented a method to produce a highly bioavailable extract of curcuma in

2006[ix]. According to their data, meanwhile published in a scientific journal, a turmeric extract has been developed with high contents of curcumin, curcuminoids and other natural compounds, such as oily fractions, sesquiterpenes and others, that are left to a large extent in their natural matrix. This extract not only demonstrated a 700 to 800 % higher bioavailability in a human clinical study compared with a standard 95 % extract; a second most interesting feature of this extract is the longer retention time of the curcuma in the plasma. Normal turmeric extracts can hardly be detected after 2 hours, this newly developed extract was retained in the plasma in significant quantities for more than 8 hours.

Conclusion > Turmeric with its active principles curcumin and curcuminoids seems to be much more than merely a yellow colorant for Indian curries. Due to its extra-ordinary molecular structure it shows strong anti-oxidative, as well as anti-inflammatory properties. These have been and are being tested in numerous studies, *in vitro*, *in vivo* and meanwhile more and more in human clinical trials of phase I and II. The studies mainly target chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis. The efficacy of the molecule seems to come from its simultaneous down-regulation of a plethora of inflammatory mediators and signalling molecules that are not completely inhibited but are rather "balanced" on a lower, healthier level. Due to curcuma's generally poor bioavailability, studies have been carried out with high daily doses that showed the safety of administration of curcuma for long periods with high dosages.

The problem of poor bioavailability could meanwhile be solved in so far, as a new, patented turmeric extract has become available that leaves the natural components of the rhizome in their natural matrix. The bioavailability of this extract lays 700 to 800 % higher than comparable highly concentrated turmeric extracts and has a significantly longer retention time in plasma.

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