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Mini Review

Anti-Inflammatory, Anti-Thrombotic and Antiviral Substances from Onions could be an Option for the Treatment of COVID-19: A Hypothesis

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ABSTRACT

Onions could help against the Coronavirus! As shown in numerous scientific studies (*in vivo*, *in vitro*, animal and human studies), onions (*Allium cepa L.*) produce anti-inflammatory, antithrombotic and probably antiviral substances, which should be valuable for the initial treatment of patients with COVID-19. Modes of preparation and application are crucial.

Keywords: Corona virus; COVID-19; *Allium cepa*

INTRODUCTION

Onions (*Allium cepa L.*) have been cultivated since more than 10000 years not only for taste, but also for beneficial health effects, for example in the treatment of parasite infections. In the present pandemic the use of onions might be helpful, too. There are three main arguments for onions or onion-based phytopharmaceutical preparations as candidates for the treatment of COVID-19 patients, namely anti-inflammatory, antithrombotic and, rather speculative, antiviral effects [1].

BACKGROUND

In 1983, we reported to the American Academy of Allergology on inhibitory effects of onions on human allergen-induced late phase inflammatory reactions and bronchial asthma: In double blind studies we observed a marked reduction of extension and thickness especially of the late phase inflammatory response to intradermal injection of anti-human IgE-antibodies by 45% ethanolic onion extracts [2]. These and control solutions have been applied topically one hour prior to the injection under occlusion. In an open study with two patients suffering from allergic bronchial asthma we observed pronounced inhibitory effects after oral ingestion of 200 ml 5% ethanolic extract of 200 g raw onions.

One patient suffering from severe chronic asthma showed a pronounced late bronchial reaction after allergen inhalation [1,3]. Onion treatment abolished especially the inflammatory late bronchial reaction (Figure 1).

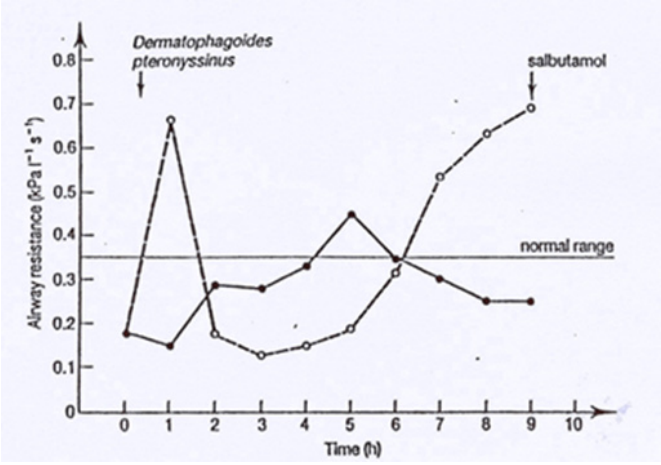

Figure 1: Time course of the bronchial reaction of one adult patient to the inhalation of house dust (dermatophagoides pteronyssinus) after ingestion of 200 ml 05% alcoholic onion extract from 200 g raw onions (solid line) or control (dashed line - - -).

After these initial clinical studies we went back to preclinical investigations. First we identified the active substances and their mechanisms of action in cooperation with other scientists supported by the German Research Foundation, the Federal Ministry of Research and Technology and a pharmaceutical company (Boehringer-Mannheim). We found pharmaceutical activity in our test systems in fractions containing Thiosulfinates (TS) and

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previously unknown compounds (Alpha-Sulfinyldisulfides) named by us Cepaenes" (CS, 4), for example: CS1: Trans-5-ethyl-4,6,7-trithia-2-decen-oxid; CS2A: Trans,trans-5-ethyl-4,6,7-trithia-2,8-decadien-4-oxid; CS2B: Trans,cis-5-ethyl-4,6,7-trithia-2,8-decadien-4-oxid; CS4A (=diasteromer to CS2A) and CS4B (diasteromer to CS2B).

In addition to the naturally occurring active substances, synthetic analogues were produced (e.g.: Dipropyl-TS, Diallyl-TS, Methyl-phenyl TS, Phenyl-Methyl-TS, Diphenyl-TS, Methyl-l-propenyl TS, Propyl-l-propenyl-TS) and tested for their pharmacological effects.

These substances have been found to inhibit the following inflammatory, allergic and thrombogenic reactions [1,3-6]:

- Release of histamine from human peripheral granulocytes,
- Release of histamine from human adenoidal mast cells,
- Leukotriene biosynthesis (LTB4 and LTC4) in human granulocytes,
- Thromboxane biosynthesis in human platelet-rich plasma,
- Binding of Platelet-activating factor (PAF) to human platelets,
- PAF-induced activation of human leukocytes,
- Lipoxygenase activity in pig leukocytes,
- Cyclooxygenase activity in sheep seminal vesicles,
- Chemotaxis of human granulocytes,
- Chemotaxis of human lung fibroblast,
- Zymosan-induced chemiluminescence of human leukocytes,
- Proteinase release from human leukocytes,
- Allergen-induced constriction of guinea pig lung parenchymal strips,
- Allergic bronchial reactions in guinea pigs PAF-induced bronchial obstruction and bronchial hyperreactivity in guinea pigs, while histamine or acetylcholine-induced reactions are not altered,
- PAF-induced lethality in mice, rats and guinea pigs.

Onions have been used in traditional medicine for thousands of years worldwide. The Ebers Papyrus in ancient Egypt mentions the onion as a remedy for a number of infectious and inflammatory processes, including worm disease and diarrhea. Modern studies have shown that onion extracts are effective against worms and microbes such as *Ascarids* (*in vivo*), *Salmonella typhimurium* (*in vitro*), *Streptococcus faecalis* (*in vitro*), *Escherichia coli* (*in vitro*), *Klebsiella pneumoniae* (*in vitro*), *Streptococci* (*in vitro*), *Staphylococci* (*in vitro*), *Mycobacterium tuberculosis* (*in vitro*), *Candida albicans* (*in vitro*), *Aspergillus fumigatus* (*in vitro*). Chemically undefined onion ingredients show positive effects in type II diabetes (clinical study: 50 g onions oral lowers the need for oral antidiabetics), alimentary hyperlipidemia (onion extract lowers the serum levels of cholesterol, betalipoprotein and triglycerides) as well as thromboxane biosynthesis and platelet aggregation (summary in 1 and 3).

With regard to the pathogenesis of COVID-19, anticoagulant effects are particularly interesting. Antiplatelet activities of crude onion extracts are well established. We were particularly interested in the effect of onion extracts and thiosulfinates on PAF-induced lung injury, especially the PAF-induced lethality in experimental animals and the PAF-induced bronchial hyperreactivity to histamine in guinea pigs [5,6]. The effects are convincing (see list above)!

Antiviral effects – of course-would be interesting. As far as we know specific tests on this virus are planned, but not published yet. Computer modelling provided important information on possible anti-covid effects of onion substances [1]. A group of Vietnamese scientists tested 18 different sulfur compounds that also occur in garlic and onions in a computer model [7]. 17 organosulfur compounds, accounting for 99.4% contents of the garlic essential oil, have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2. The strongest anticoronavirus activity is expressed in allyl disulfide and allyl trisulfide, which account for the highest content in the garlic essential oil (51.3%). Similar compounds are present in onion preparations. Iranian veterinary scientists found, that especially aqueous extracts of the red onion can destroy the avian influenza virus subtype H9N2 and may therefor decrease the propagation of the virus in embryo chicken eggs. In 1919 onions were regarded as a prophylactic home remedy against the Spanish influenza (H1N1) in the United States. Americans were informed that it was their patriotic duty to "Eat More Onions!".

COMPLEX ONION CHEMISTRY

It should be kept in mind that the chemistry of onion compounds is highly complex: Depending on the type of production, a wide variety of active ingredients will be found in aqueous or alcoholic onion extracts or essential oils. Most of the active substances are not found in the intact bulb, they are not stored there, as in other plants, they are synthesized newly as a defense weapon against predators as soon as the plant is crushed or otherwise injured. In this process the enzyme alliinase plays a central role as well as the time in which the chemical processes take place. The highly active thiosulfinates and cepaenes are relatively unstable and can only be stored for limited hours or days, as lipophilic substances best in alcohol. Other technologies, such as embedding in cyclodextrin (unpublished data), are too complex and expensive. Many pharmacological effects of thiosulfinates, cepaenes and active fractions of onion juice are obviously inextricably linked to their chemical instability. This was probably an important advantage in evolutionary selection in, as the plant was able to defend itself and the people cultivating them against a wide variety of predators by constantly varying its warfare agents.

The complex onion chemistry cannot be explained here. In order to harvest active substances the preparation method is crucial; boiled or fried onions are poorly effective. We assume that onions were often misused, for example in 1919 during the "Spanish Flu", while the biosynthesis of the active ingredients were not known. Many recipes of today, too, do not pay attention to their biosynthesis, use too high temperatures, the wrong solvent, too short or too long times of incubation, the wrong storage. Thiosulfinates from the allium species are known to decompose upon heating even at temperatures of 85°C [8]. Microwave drying and air drying destroy antimicrobial effects of onions, totally. Heating is in general detrimental for onion *in vitro* antiplatelet activity and thiosulfinate content, extensively cooked onions may stimulate rather than inhibit platelet aggregation.

CONCLUSION WITH RESPECT TO COVID-19-TREATMENT

Taken together there is evidence for at least three possible important effects of onions in the pathophysiology of COVID-19 disease, namely anti-inflammatory, anti-thrombogenic and possibly

antiviral effects. Onion active ingredients are likely to be the more effective the earlier they are used. They belong in the outpatient treatment area, probably that of self-medication, and must not endanger anyone. In view of the high spontaneous healing rate, the proof of a specific effect is difficult, but indispensable. Anosmia could be a useful first leading clinical symptom: It is common, relatively specific and relatively easy to objectify. Three pathophysiological processes in the nose could be the target of onion-derived substances.

The COVID-19 virus attaches to ACE receptors of the olfactory cells. A possible interference should be tested. Severe long lasting anosmia is caused by secondary inflammatory processes in which epithelia and especially endothelia in the sense of foudroyant endotheliitis are involved (similar to the lungs). A massive accumulation and clumping of platelets lead to widespread microangiopathies. Corticosteroids can shorten the duration of illness. The pharmacological potential of onions could be useful here, both through its anti-inflammatory effects (onion active ingredients impair similar mediator systems such as corticosteroids), as well as through their pronounced antithrombotic and platelet activation-hindering properties, which we have found in numerous *in vivo* and *in vitro* models. In the clinical model of anosmia, inhalation or topical application can even be considered besides the oral route (see below). Steam inhalation (by analogy with chamomile steam inhalation, for example) is unlikely to make much sense, since heating has a strong adverse effect on the pharmacology of the onion. Different types of preparation could be tested. Analytical methods are available in our group.

NEXT STEPS-RECOMMENDATIONS

Facing the dramatic development of the pandemic we ask for cooperation: Whether COVID-19 induced lung diseases can be prevented or even treated with onion substances should be the subject of extensive clinical studies. Currently we recommend for clinical trials: Peeling 200 g raw yellow onions room temperature, cutting into small cubes, mixing with 80 g dextrose, squeezing, sieving after two hours, adding alcohol (final 10%), and drinking the daily dose of 100 ml in small portions. Side effects should be tolerable: Onions have been used in traditional medicine over thousands of years worldwide. In 1999 the WHO assessed the use of the onion as harmless, the only contraindication being allergies to the plant [9]. Allergic reactions such as rhinoconjunctivitis and contact dermatitis have been reported. According to this statement, the level of safety of Bulbus Alii cepae is reflected by its worldwide use as a vegetable. No general precautions and no precautions have been reported concerning drug interactions, drug and laboratory test interactions, nursing mothers, pediatric use, or teratogenic or non-teratogenic effects on pregnancy. No warnings have been reported at this time. A daily dosage of 50 g fresh onion or 20 g of the dried drug is considered save [9]. We assume, a daily intake of 200 g for a week, too!

A nasal sniffing therapy could be equally effective with fewer side effects: We recommend for the beginning of clinical studies: Peel 120 g yellow onions ("hot" onions, no shallots), cut 100 g of them into small pieces, pound them with a mortar and incubate them in the absence of air for two hours. During this time, anti-inflammatory and anti-thrombotic substances will be synthetized, the "Tear-producing factor" evaporates. After that, people should inhale every hour for 5 minutes by taking 30 breaths deeply through the nose and exhaling immediately through the mouth.

DECLARATION ON CONFLICTS OF INTERESTS

There are no conflicts and no grants. We would like to thank our colleagues for their cooperation and support, especially Hildebert Wagner, to whom we dedicate this publication.

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