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From virus deactivation *in-vitro* to clinical relevance: a glycerol and cod trypsin-containing mouth spray in the common cold

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Trypsin combined with glycerol caused the deactivation of common cold viruses in vitro. A pilot study and a comparative multicentre study investigated the in vivo reduction in viral load and the improvement in quality of life after use of the active substances as a throat spray by subjects suffering from the common cold. The results showed a decrease in viral load, a shortening of the duration of the cold and an improvement in the quality of life.

With the beginning of autumn, the common cold season starts – runny and stuffy nose, dry and chesty cough, sometimes accompanied by fever, headache or body pain – a daily routine in pharmacies. As causal treatments are missing, recommendation follows individual symptom relief. All symptoms are a sign for an activated immune system with a clear objective – fighting against the common cold virus. Means in turn, less virus – less symptoms. One approach pays to this goal: support the immune system by getting rid of the virus as source of the problem.

Virus deactivation – interesting approach in common cold treatment

Cod trypsin is a serine protease from cold water fish with anti-inflammatory properties [1]. The enzyme combined with glycerol has shown a deactivation of several common cold viruses in-vitro (**table**) [2, 3]. Due to the broad variety of vulnerable viruses it became an interesting candidate for the early treatment of common cold, considering that over 200 serologically different viral types are responsible for human URTIs, with the rhinoviruses being the most common cause [4]. For this reason, it leads to 2–4 common cold episode per

Table: The virus deactivating ability of the mouth spray is shown as mean of Log_{10} reduction and percent deactivation of the individual virus strain [2, 3].

VIRUS	LOG 10 REDUCTION (MEAN)	PERCENT DEACTIVATION
Rhinovirus type IA	1.08 log_{10}	91.7 %
Rhinovirus type 42	1.14 log_{10}	92.8 %
Human Influenza A virus	1.51 log_{10}	96.9 %
RSV	2.94 log_{10}	99.9 %
Adenovirus type 2	0.45 log_{10}	64.5 %
Human coronavirus*	2.88 log_{10}	99.9 %

* Common human coronaviruses, including types 229E, NL63, OC43, and HKU1, usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. This information applies to common human coronaviruses and should **not** be confused with SARS-CoV-2 or Covid 19 [6].

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year in adults and even 6–8 episode per year in children [5].

From in vitro to in vivo: Application via mouth spray – 6 times daily

Although Rhinovirus is described to replicate best at 33 °C [7], it has been found in the lower respiratory tract [7]. This might be the byproduct of fast muco-ciliary transport and cleaning of the nose before virus inoculation and the increase of mouth breathing after virus inoculation due to a stuffy nose. The oropharynx as gate to the lower respiratory tract seems to be a zone where everything comes together and where a protective, virus trapping layer of Cod trypsin and glycerol would make a lot of sense. The physiological "washing" is the application frequency-defining-step, because the half-life activity of cod trypsin is quite long at human body temperature of about 0.7 days [8].

Clinical relevance in common cold: Rhinoviral load reduction in the oropharynx by more than 99% accompanied by significant reduction of symptom severity, halving the duration of a common cold and increase of quality of life of common cold patients.

Successful pilot study in 46 adult healthy volunteer's received rhinovirus-16 and an infection rate of 76% was achieved. Treatment with the mouth spray 6 times daily for 10 days led to a significantly reduced total viral load (median of 7.4×10^3 copies/mL) in the oropharynx compared to the placebo group (6.3×10^{11} copies/mL; $p = 0.023$), which corresponds to a viral load reduction by more than 99% [8]. Furthermore, the number of days with common cold symptoms has been significantly reduced by the mouth spray from 6.5 to 3.0 days ($p = 0.014$) [9].

Confirmatory prospective, randomized parallel group study in 267 subjects with naturally acquired colds. The efficacy of the mouth spray was evaluated for quality of life by the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21 Quality of life scale), the Jackson score (a scoring system which assesses individuals' subjective ratings of 8 respiratory symptoms), and for the Quality of Life (QoL) component [10]. All three symptom scales showed statistically significant improvement. Quality of life parameters were: "think clearly, sleep well, breathe easily, walk, climb stairs, exercise, accomplish daily activities, work outside and inside the home, interact with others, live your personal life." Interestingly, the need for complementary use of symptom-relieving medication for colds was reduced [10].

Real world evidence: surveys revealed reduced number of sick days in different groups like competitive and endurance athletes, elderly care personnel or pre-school-staff. A common cold is not life threatening but sometimes it feels exactly like that because for sure the quality of life is dramatically impacted which goes hand in hand with absence from work and inability to make the day. Surveys of different designs revealed constantly a reduced number of sick days when the mouth spray has been applied early in the course of a common cold. Investigated groups were competitive athletes [11], endurance athletes [12, 13], pre-school staff [14] and elderly care personnel [15].

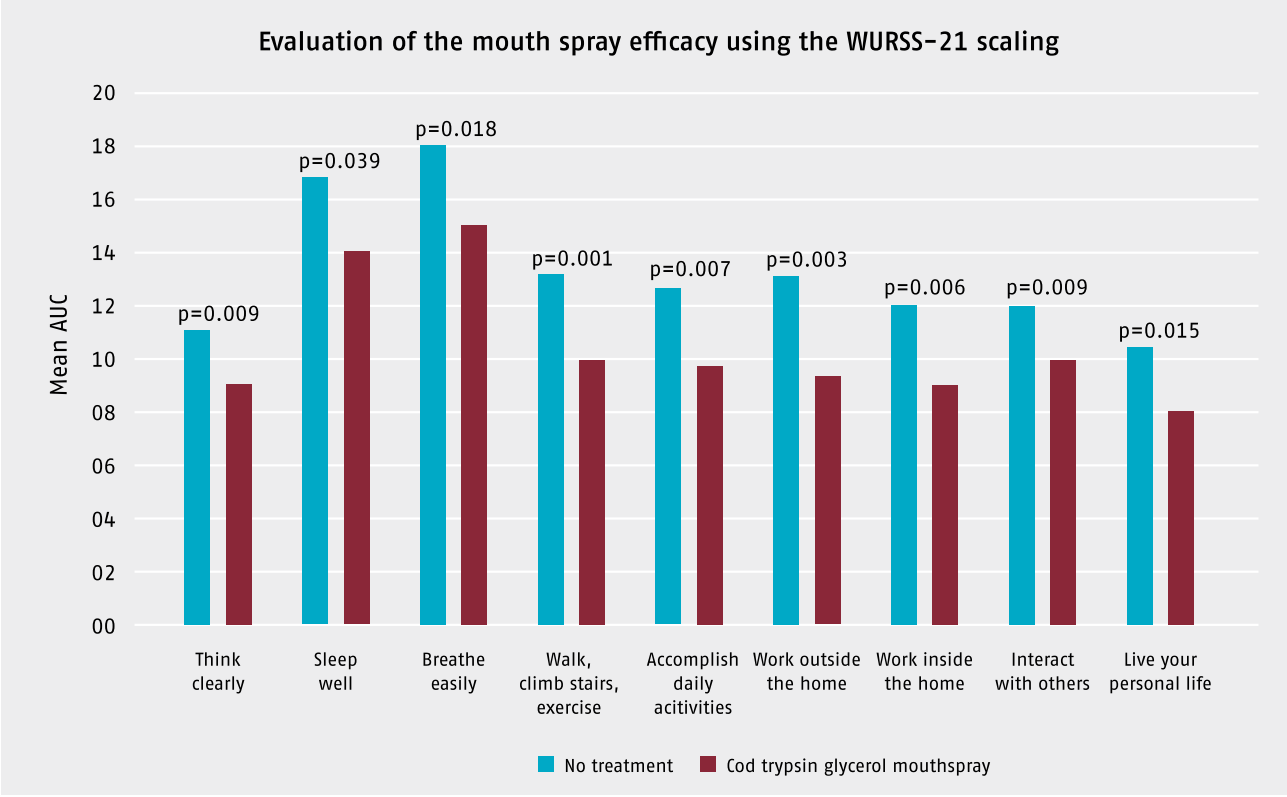

Figure: Evaluation of the mouth spray efficacy using the WURSS-21 scaling. Quality of Life has been scored and shown as a mean AUC of subscore single items of day 1–7. The higher score, the more negative impact on Quality of Life [10].

Conclusion

Cod trypsin / glycerol deactivated several common cold viruses in vitro which makes it to a promising candidate in the treatment of common cold. Applied as mouth-spray in vivo it reduced the Rhinovirus load in the oropharynx by more than 99%. Clinical trials brought the proof of concept and showed a significant reduction of common cold symptom severity with halving of the duration of a common cold accompanied by a significant increase of quality of life in several parameters. The convenient application via mouth spray offers an easy and hygienic common cold treatment even when suffering from a runny or stuffy nose, and even complementary to other symptomatic treatment. According to the positive outcomes of several real-world-survey's different patient groups perceived a clear benefit. This leads inevitably to the question: Who is very often exposed to common cold viruses? Parents with smaller children, pharmacy staff… the list seems endless.

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