

Characterisation of the lipolytic enzymatic activities of fungal rizoenzymes from *Rhizopus oryzae* in comparison to pancreatin from pigs

Research paper

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Abstract **Aim:** In case of exocrine pancreatic insufficiency (EPI), the replacement of digestive enzymes with, for example porcine pancreatin or fungal rizoenzymes, is unavoidable under certain conditions. Current guidelines indicate that preparations from porcine pancreas have more advantageous physicochemical properties compared to those from fungi, especially at high bile salt concentrations, and that the latter can, therefore, only be used clinically to a limited extent. Since rizoenzymes are increasingly used in clinical practice, the present *in vitro* study investigated efficiency of enzymatic activity of rizoenzymes in comparison to pancreatin under various physiological and partly extreme environmental conditions. **Materials and Methods:** The lipolytic properties of two typical preparations containing digestive enzymes from porcine pancreatin and rizoenzymes were compared (same dosage of activity units) at different pH values (pH 3–9), with the addition of different bile salt concentrations (0–15 mmol/L sodium taurocholate). Lipolytic activity was measured by quantifying the fatty acids released from olive oil substrate by liquid chromatography–tandem mass spectrometry after enzymatic digestion. **Results:** For both enzyme preparations, the lipolytic activity maximum was reached at pH 7 with comparable fatty acid conversion rates (57% pancreatin, 58% rizoenzymes). However, in contrast to pancreatin, rizoenzymes were already active for certain fatty acids from pH 3 to 4. At a bile salt concentration up to 10 mmol/L taurocholate, there was an increase in activity of both enzyme preparations (rizoenzymes 69% vs. pancreatin 58% enzymatic conversion). Only at rather unphysiological concentration of 15 mmol/L during EPI, there was a slight decrease in activity (to 56%) for the rizoenzymes. **Conclusions:** Rizoenzymes are an alternative therapeutic option for EPI. Relevant differences between rizoenzymes and pancreatin with regard to lipolytic activity under different physicochemical conditions could not be demonstrated in this study, whereas a potential advantage in favor of rizoenzymes activity at already low pH values was observed.

Keywords Rizoenzymes – pancreatin – exocrine pancreatic insufficiency

INTRODUCTION

Food sources contain fatty acids predominantly esterified in the form of triglycerides, cholesterol esters, and phospholipids, which need to be split before being absorbed in the intestine. Various steps are necessary for this process: physical disintegration/suspension begin in the mouth and stomach, and later on, enzymatic breakdown occurs primarily in the small intestine. Release of the digestive enzymes and bile acids occurs through the release of the hormone cholecystokinin (CCK), which is produced particularly by the mucosal cells of the duodenum [Rehner et al., 1999; Löffler et al., 2007].

CCK causes the gallbladder to empty and stimulates the pancreas to secrete the digestive enzymes into the duodenum. In particular, pancreatic lipase is responsible for the hydrolysis

of dietary fats [Löffler et al., 2007]. Glycerol esters of short- and medium-chain fatty acids are completely broken down into glycerol and fatty acids. Fats with long-chain fatty acids are, however, not completely hydrolysed, and bile acids play an important role in their further absorption [Rehner et al., 1999]. In case of exocrine pancreatic insufficiency (EPI), the pancreas produces only limited amounts of digestive enzymes, causing a disturbance in fat digestion and consequently resulting in fat excretion in the stool (steatorrhea with oily, shiny stools). Due to lack of specific symptoms, EPI is often diagnosed late in time. In addition, a wide variety of other diseases are affected, such as cystic fibrosis, coeliac disease, type I and type II diabetes, as well as the risk factors such as obesity, nicotine, alcohol abuse and age play a role [Capurso et al., 2019]. In EPI/chronic pancreatitis, it is recommended to take enzyme supplements with meals.

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According to the S3-guidelines on pancreatitis of the German Society for Gastroenterology, Digestive and Metabolic Diseases (S3-Leitlinie Pankreatitis der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS [Beyer et al., 2021, Hoffmeister et al., 2012]), a replacement with digestive enzymes is recommended in case of steatorrhoea with faecal fat excretion of more than 15 g/d. Since a quantitative measurement of stool fats is often no longer performed, replacement therapy is also indicated in the case of pathological pancreatic function test in combination with clinical signs of malabsorption. These include weight loss and abdominal complaints with dyspepsia, severe meteorism or diarrhoea. Conversely, digestive enzymes should also be supplemented if the faecal fat excretion is pathological (>7 g/day) without reaching the threshold of 15 g/day, but, at the same time, the above-mentioned clinical signs of malabsorption are present [Beyer et al., 2021; Hoffmeister et al., 2012].

There are various options for enzyme replacement. In addition to the widely used enzyme substitutes like pancreatin (made from porcine pancreas), fungal enzymes (such as enzymes from e.g. *Rhizopus oryzae*, *Aspergillus oryzae*) are also used. Both enzyme preparations include amylase, protease as well as lipase to enzymatically digest all nutrients, differing, however, in their physicochemical properties.

The S3-guidelines on pancreatitis postulate that rapid inactivation occurs for rizoenzymes in the presence of low bile acid concentrations [Beyer et al., 2021; Hoffmeister et al., 2012]. This goes back to studies by Moreau et al. 1988. However, since in clinical practice, rizoenzymes represent an efficient alternative to pancreatin, in this study, the efficiency in enzymatic activity of rizoenzymes was compared to that of pancreatin under diverse physiological and partly extreme environmental conditions. Their lipolytic properties with regard to fatty acid release at different pH values were specifically investigated under the influence of bile salts.

The method which quantifies the lipolytic activity according to the European Pharmacopoeia (Ph. Eur. 11.0/0350) as part of the value determination has proven to be the standard method for the activity of pancreas powder. In this, the rate at which a suspension of the substance hydrolyses an olive oil emulsion serving as a substrate is compared to with the rate at which a suspension of pancreas reference preparation hydrolyses the same substrate under identical conditions. It is an unspecific methodology in which the hydronium ions generated from released fatty acids are titrated with 0.1 mol/L of sodium hydroxide solution. During this procedure, the pH is kept constant at 9.0 and the consumption of the titration solution is measured for time intervals of exactly 1 min.

Since the focus of this work was the comparison of lipolytic activity measurement of pancreas preparations and rizoenzymes under variable conditions, the standard method could not be used in this work. For quantification of fatty acids, different techniques are available, that is, gas

chromatography or liquid chromatography–tandem mass spectrometry (LC–MS/MS). Gas chromatographic methods are usually used to determine fatty acids. However, these require the synthesis of the methyl esters, either of the free fatty acid or by transesterification of the fatty acid bound in the lipids.

Therefore, we chose a validated (LC–MS/MS) method to be able to directly observe the release of the individual fatty acids. This method allows free fatty acids to be distinguished from fatty acids bound in the lipid matrix without prior complex sample preparation.

MATERIALS AND METHODS

Enzyme preparations

The pancreatin enzymes preparation used was Pangrol 10000 (Berlin-Chemie AG, Berlin, Germany), while the rizoenzymes preparation was Nortase® (Repha GmbH Biologische Arzneimittel, Langenhagen,

Germany). Pangrol is porcine pancreatic powder 75.6–137.4 mg per capsule with triacylglycerol lipase (10,000 PhEur units), amylase (at least 9000 PhEur units) and proteases (at least 500 PhEur units) per capsule and is in the form of enteric-coated pellets (from now on named pancreatin enzymes).

Nortase is an enzyme mixture with *R. oryzae* rizolipase (7000 Fédération Internationale Pharmaceutique (FIP) units), *A. oryzae* protease (at least 54 FIP units) and *A. oryzae* amylase (at least 700 FIP units) per capsule (from now on named rizoenzymes).

Four hundred and fifty-three units of enzyme (9.3 mg Pangrol, 10.5 mg Nortase) was added to 15 mL of 1% sodium chloride (Th. Geyer, Renningen, Germany) in water. The solution was shaken for 1 h and then centrifuged (3500 rpm, 10 min, 7 °C). The clear supernatant was used for the enzyme reaction.

Sample preparation with olive oil to investigate the pH dependence of the lipolytic properties of the two enzyme systems

Olive oil (LIDL Primadonna Extra Virgin Olive Oil) was used as the fat source in accordance with the European Pharmacopoeia (Ph. Eur. 11.0/0350). An emulsion was prepared with oil, gum arabicum (from acacia tree; Sigma-Aldrich, Taufkirchen, Germany), CaCl₂ (EMSURE; Supelco, Darmstadt, Germany) and Milli-Q water according to the Food Chemical Codex (FCC-8). The pH was adjusted with phosphate buffer (1.6 mol/L, prepared from disodium hydrogen phosphate, potassium dihydrogen phosphate and phosphoric acid; Th. Geyer, Renningen, Germany) to obtain values from 3 to 9. The buffer capacity was chosen such that the released fatty acids did not change the pH over the measurement period. Sodium taurocholate (0.5%; Acros Organics, Geel, Belgium) and 3.9 U enzymes were added to the emulsion tempered at 37 °C, thereby starting the reaction.

After 15 min incubation at 37 °C with continuous shaking, the reaction was stopped by adding isopropanol.

Sample preparation with olive oil to investigate the influence of bile acids on lipolytic activity

The quantitative determination of lipase activity was carried out by preparing the fat source under identical conditions as described above, but keeping a constant pH 7. In contrast, the taurocholate concentration in the substrate emulsion was varied between 0 and 15 mmol/L sodium taurocholate in eight concentration steps.

Measurement of fatty acid concentrations

Two aliquots were taken from the sample. One aliquot was used for determination of the released fatty acids. It was diluted and mixed with internal standard (deuterated fatty acids, 1 µg/mL each). Sodium hydroxide and butylated hydroxytoluene (BHT) were added to the second aliquot for total hydrolysis and incubated at 80 °C for 2 h. After hydrolysis, acetic acid was added, diluted and internal standard (deuterated fatty acids 1 µg/mL each) was added. The analysis was carried out by LC–MS/MS as applied elsewhere [Gollasch et al, 2020; Liu et al. 2022].

In brief, an Agilent 1290/6470 system was used with a Phenomenex Kinetex-C18, 150 × 2.1 mm, 2.6 µm as the stationary phase and a gradient of 0.05% acetic acid and acetonitrile as the mobile phase. Ionisation was performed by electrospray. Data were recorded in negative Multiple Reaction Monitoring (MRM) mode, see supplementary file Table S1. Each fatty acid was individually quantified using authentic standards. Details of the LC–MS/MS method settings and a validation overview are given in the supplementary file, see Table S2 and Tables S3, and an example chromatogram is presented in Fig. 1. As presented in the supplementary file Table S4, method standard deviation coefficient of variation (CV)% of 3.2%–7.6% and day-to-day stability of 87.1%–95.0% were calculated.

The percentage degree of conversion was determined for each fatty acid contained in the substrate fat in such a way that its content was related to the content that could be completely hydrolysed from the same sample. All measurements were performed as duplicate determinations.

Statistical analysis

Samples were measured in duplicate for the free fatty acids as well as after total hydrolysis. For each detectable fatty acid, a conversion rate was calculated as a percentage of the maximum hydrolysable proportion (total hydrolysis) under the investigated conditions. The data were evaluated descriptively with mean and standard deviation (GraphPad Prism, Version 5.04; GraphPad, La Jolla, San Diego, CA, USA).

RESULTS

Characterisation of olive oil used as substrate

Commercial olive oil was used as a substrate for the experiments.

Fig. 1 shows the composition of the olive oil used in the experimental set-up for the investigation of pH dependence. This corresponds to a typical olive oil composition (see Table 1). Stearic acid was not considered in further experiments, as the value is often disturbed by contamination.

Table 1. Composition of the olive oil used after total hydrolysis.

Fatty acid	Olive oil ^a (%)	Analysed values ^b (%)
14:0	≤0.05–0.5	
16:0	7.5–20.0	13.3
16:1	0.3–3.5	1.3
17:0	≤0.05–0.3	
17:1	≤0.05–0.3	
18:0	0.5–5.0	Not considered
18:1	55.0–83.0	73.2
18:2	3.5–21.0	10.8
18:3	≤0.05–1.0	1.0
20:0	≤0.05–0.6	
20:1	≤0.05–0.4	0.4
20:2	≤0.05	
22:0	≤0.05–0.2	
22:1	≤0.05	
22:2	≤0.05	
24:0	≤0.05–0.2	
24:1	≤0.05	

^aThe values correspond to the trade standard applying to olive oil and olive pomace oil of the International Olive Oil Council (Madrid) COI/T.15/NC no. 3/Rev. 2; 24 November 2006.

^bCalculated from the total release at pH 7 with pancreatin and rizoenzymes.

As shown in Fig. 2, each sample was measured twice for quantification of free fatty acids after enzyme reaction and after total hydrolysis. The percentage degree of conversion was calculated for each fatty acid.

Dependence on the pH value

Both enzyme preparations showed similar fats digestion patterns, but the activity differed in acidic pH at pH 3–4. While rizoenzymes already showed hydrolytic activity in this acidic pH range, pancreatin, with the exception of C16:1, was only lipolytically active starting from pH 5 (see Fig. 3).

Both enzyme preparations showed their maximum lipolytic activities at pH 7 in the neutral range. The release rate by rizoenzymes in the lower pH range of pH 3–4 could be shown particularly for the fatty acids oleic acid (C18:1), palmitoleic acid (C16:1) and linoleic acid (C18:2). However, in contrast, none of the preparations in the lower pH values (pH 3–4) showed conversion of the fatty acids C16:0, C18:3 and C20:1

(see Fig. 4). These fatty acids were only released by both enzymes from pH 5 to 6. The main fatty acid in olive oil, C18:1, showed the highest conversion rate, followed by the fatty acids C16:0, C16:1 and C20:1. The lowest conversion rates were found for C18:2 and C18:3 (comparison, e.g. oleic acid C18:1 at pH 7: pancreatin 62%, rizoenzymes 63%; linoleic acid C18:2 at pH 7: pancreatin 31%, rizoenzymes 37%).

Fatty acid profile of olive oil at pH 7

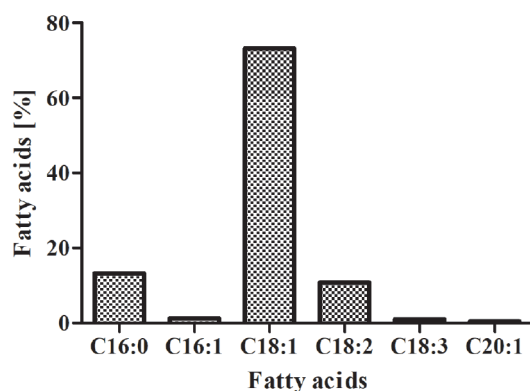


Figure 1. Fatty acids profile of the olive oil used after total hydrolysis.

Dependence on bile salt concentration

For each detectable fatty acid, a conversion ratio in per cent to the maximum hydrolysable fraction (total hydrolysis) was calculated. The measured concentrations were added to all fatty acids with the aim to obtain the total conversion of fatty acids for a given taurocholate concentration.

As shown in Fig. 5, the activity curve as a function of the taurocholate concentration was similar for both enzyme preparations. The lipase activity increased with increasing bile salt taurocholate concentration for both preparations. The rate of increase compared to the maximum activity was a factor of 2 for pancreatin (0 mmol/L taurocholate: 38%, 15 mmol/L taurocholate: 76%) and a factor of 2.9 for rizoenzymes (0 mmol/L taurocholate: 24%; 10 mmol/L taurocholate: 69%). For both enzyme preparations, the increase in lipolytic activity was observed at taurocholate concentrations of

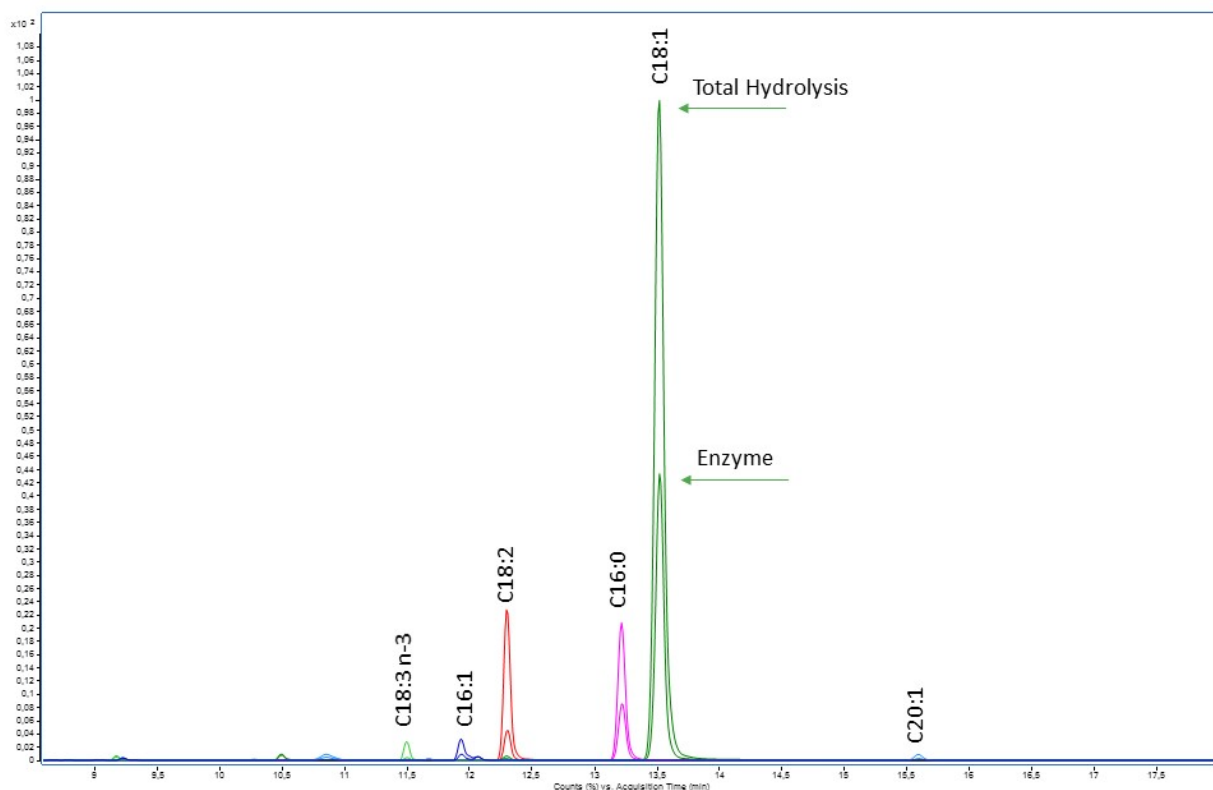


Figure 2. LC–MS/MS chromatogram of olive oil after Pangrol enzyme reaction at pH = 7 overlaid by a total hydrolysis chromatogram of the same sample.

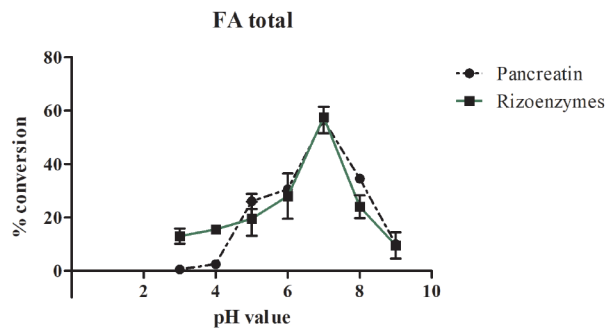


Figure 3. Total fatty acids conversion rate (sum of overall fatty acids) as a function of pH for both enzyme preparations.

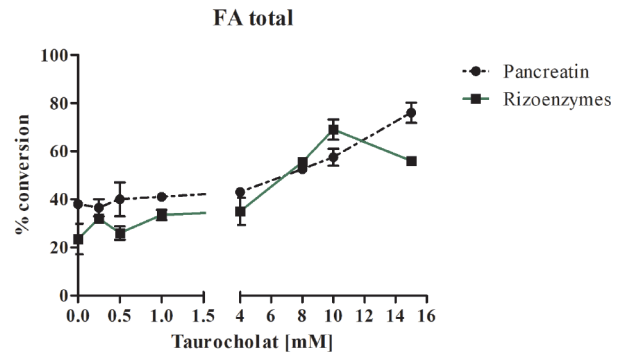


Figure 5. Total fatty acids conversion rate (sum of overall fatty acids) as a function of taurocholate concentration (mmol/L) for both enzyme preparations.

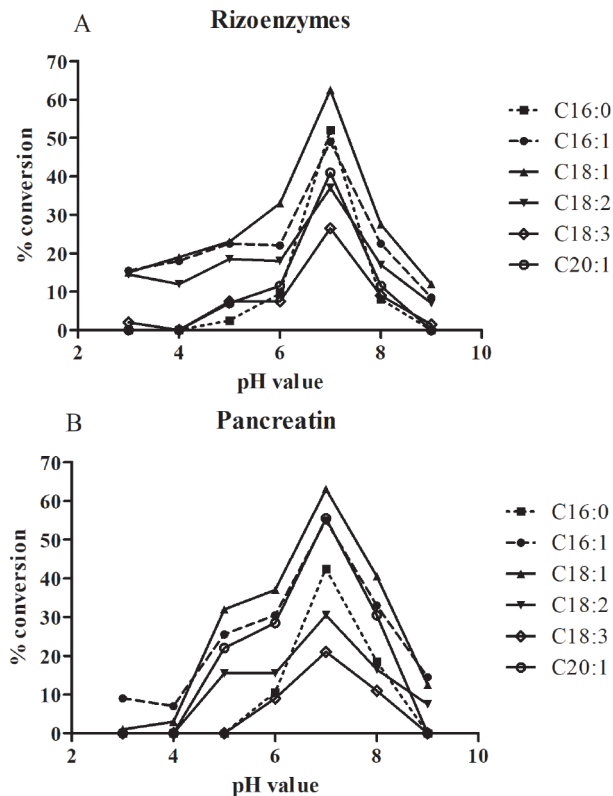


Figure 4. Conversion rate of single fatty acids as a function of pH for both enzyme preparations (rizoenzymes (A) and pancreatin (B)).

8–10 mmol/L. Only the rizoenzymes showed a reduction at a taurocholate concentration of 15 mmol/L compared to the preparation with 10 mmol/L taurocholate. However, the lipase activity was still significantly higher than at low taurocholate concentrations (15 mmol/L taurocholate: 56%; 0–4 mmol/L taurocholate: 30%).

At a taurocholate concentration of 15 mmol/L, the release rate among the rizoenzymes decreased for all considered individual fatty acids of olive oil, compared to 10 mmol/L taurocholate. This was in contrast with the release rate

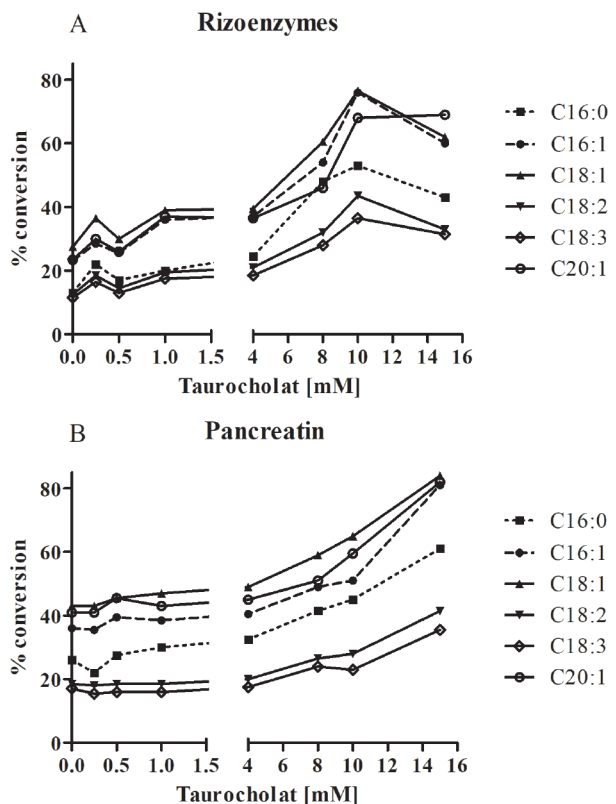


Figure 6. Conversion rate of the single fatty acids as a function of the taurocholate concentration (mM) for both enzyme preparations (rizoenzymes (A) and pancreatin (B)).

of pancreatin enzymes. The release rate for rizoenzymes was, however, higher with 10 mmol/L taurocholate than with pancreatin (see Fig. 5). The clear increase in activity of the rizoenzymes at 10 mmol/L taurocholate compared to pancreatin was particularly evident not only for the fatty acids C16:1, C18:2 and C18:3 (see Fig. 6), but also for the other analysed fatty acids, a similar trend was observed for the rizoenzymes compared to pancreatin.

DISCUSSION

Currently available *in vitro* investigations show comparable lipolytic properties for rizoenzymes and pancreatin in the optimum pH 7. It is, however, noticeable that the investigated rizoenzymes are active already in the acidic pH range of 3–4. Rizoenzymes are naturally stable in acid environments [Fieker et al., 2011]. For this reason, they do not require any galenic acid protection for the gastric tract passage and can exert their enzymatic activity directly after release from the capsule in the postprandially filled stomach (pH 3–5) and continue the breakdown of nutrients in the duodenum [Ogawa, 1998]. Most of the animal enzymes used for replacement therapy are active mainly in the pH range 5–7 [Osterwald, 1977], and therefore need a galenic coating protection from inactivation by gastric acid, as it was the case for pancreatin preparation in this experimental set-up. Their enzymatic activity is, therefore, limited to the small intestine. In physiological metabolism, the pancreatic secretion includes bicarbonate, which raises the pH value from the stomach environment to 6–7 and dissolves the galenic coating protection of pancreatin preparations. Therefore, the released enzymes find their pH optimum in the neutral pH environment of the duodenum.

With increasing severity of EPI, not only enzymes but also bicarbonate production in the pancreas are reduced. The acid load in the duodenum increases postprandially, and the pH value falls below pH 5 (physiologically pH 6–7) [Geus et al., 1999; Ovesen et al., 1986; Regan et al., 1979; Nakamura et al., 1998]. Especially, in severe EPI, the acidic chyme can no longer be neutralised. This condition is particularly challenging for enzyme replacement preparations of animal origin with an effective range of pH 5–7. Due to the high acid load, their enzymatic activity is significantly reduced [Geus et al., 1999; Ovesen et al., 1986].

Moreover, in the case of pyloric defects, spontaneous gastric emptying or short gastric transit times, co-diseases of EPI (such as diabetes mellitus, cystic fibrosis), carcinomas of the digestive tract, pancreas operations or polypharmacy may lead to a non-physiological excessive acidification in the duodenum. For this reason, concomitant therapy with, for example, proton pump inhibitors is administered. The increase of intraluminal pH value increases the enzymatic activity by causing a faster release of encapsulated enzymes and protecting the acid-sensitive lipase (of animal origin) from denaturation.

A proper mixing of the enzyme powders with the chyme is, therefore, crucial for an optimal effect. Complete homogenisation was ensured in the experimental batch by using an extruder. Homogenisation by means of an extruder also explains why pancreatin was already active at pH 5 in the tested batch. In a physiological environment, it is only released from the galenic coating at pH 6.

The particle size of the enzyme pellets is also crucial for the efficiency of the enzyme activity. In the literature, several pancreatin preparations were compared to each other

[Shrikhande et al., 2021; Maev et al., 2020; Löhr et al., 2009]. Clear differences regarding particle size and release kinetics were observed in the determination of lipase activity according to the European Pharmacopoeia (Ph. Eur.), in which the use of olive oil as a substrate is described (Ph. Eur. 11.0/0350). To justify comparability, a similar methodological approach was, therefore, applied in this study by using olive oil as a substrate by, however, adapting it to the current research question. Here, the study endpoint was the amount of fatty acids released from the substrate. For this purpose, a validated LC–MS/MS technology was used, allowing the analysis of free fatty acids after enzyme reaction as well as after total hydrolysis. In contrast to the non-specific measurement of the pH value change, measuring the released fatty acids enables statements to be made about the substrate specificity of the enzymes.

The rizoenzymes tested in this study were available as a powder with a particle size of less than 0.1 mm. Being naturally stable in an acid environment, they were active immediately following their release from the capsule. In the experimental set-up, it could be confirmed that rizolipase, in contrast to porcine pancreatic lipase, already showed lipolytic activity from pH 3 and could thus start fat digestion already in the stomach and then extend it to the duodenum. The longer action time achieved for the hydrolysis of nutrients compared to pancreatin allows the use of comparatively lower active substance concentrations in the treatment of EPI.

Hydrolysis in the low pH range was, however, not identical for all fatty acids. This could be explained by the fatty acids ratio present in olive oil, their particular steric forms, their degree of saturation as well as their particular affinity for enzymes. These factors seemed to be partly responsible for the differences observed in the maximum conversion rate of different fatty acids under selected conditions.

Under physiological conditions, gastric lipase plays a decisive role, particularly in the newborn. Together with the tongue base lipase, it contributes significantly to fat digestion already in the stomach (pre-pyloric lipolysis). As long as the secretion of pancreatic lipase is not yet fully developed, 30%–50% of the dietary fats are lipolysed pre-pylorically in infants [Rehner et al., 1999].

In adults, gastric lipase plays a subordinate role and pancreatic lipase is primarily active in the upper small intestine. However, bile acids and co-lipases are required for an optimal effect of pancreatic lipase. The stimulation of secretion of exocrine pancreatic cells occurs via different mechanisms. In the intestinal phase, it is triggered among others by the passage of acid gastric contents, fats and protein breakdown products in the duodenum.

If the rizoenzymes already split fats and proteins in the stomach, their breakdown products may trigger the I and S cells in the duodenum to release CCK, secretin and gastrin. In EPI, the early secretion of these gastrointestinal signalling molecules and thus the early release of pancreatic enzymes as well as bicarbonate may be beneficial, provided there

is still residual pancreatic function. This may be particularly advantageous in the stage after, for example, a Whipple operation, in which the head of the pancreas, duodenum and gall bladder as well as parts of the bile duct and, sometimes, parts of the stomach also were removed.

In the digestion of fats, bile acids play a decisive role by enabling the enzymes (lipases) to bind a larger surface by emulsifying fats. For hydrolysis by lipases, aggregation of triglycerides as a substrate in the form of an oil–water emulsion is advantageous. In the human body, the full activity of pancreatic lipase is dependent on co-lipase. Only the presence of co-lipase enables efficient lipase binding to emulsified fats and, thus, optimal hydrolysis. With rizoenzymes, however, such a co-lipase function is not known or necessary.

In the currently in force S3-guidelines on pancreatitis of DGVS (Beyer et al., 2021), it is postulated that rapid inactivation occurs with rizoenzymes in the presence of low bile acid concentrations [Rehner et al., 1999]. The physiological bile salt concentration is about 8–10 mmol/L [Rehner et al., 1999]. Both pancreatic and rizoenzymes showed a marked increase in activity in this range, compared to lower bile salt concentrations. This is in contrast to earlier studies with an isolated fungal lipase, in which an inhibition of 25% was observed at a bile acid concentration of 10 mmol/L. In the present study, the maximum conversion with 10 mmol/L bile acids was even higher (69%) for the rizoenzymes than for porcine pancreatic lipases (58%). Only at more unphysiologically high bile acid concentrations of 15 mmol/L a minor reduction in the conversion rate to a value of approx. 56% was observed (comparable to a conversion rate which was also observed at 8 mmol/L). In contrast, at 15 mmol/L, the hydrolysis rate of pancreatic lipase could still be increased (76%) and was thus approx. 8% above the maximum of rizolipase. However, these high bile acid concentrations are not to be expected in an EPI state. The statement that rizoenzymes are already inactivated at low bile acid concentrations could not be confirmed. Probably, earlier data were due to the fact that an isolated fungal lipase from specific *Rhizopus arrhizus* strain was used, but not an enzyme mixture with lipase from *R. oryzae* (Nortase).

CONCLUSIONS

This study shows for the first time deep fatty acid analysis of rizoenzymes versus pancreatin and demonstrates that rizoenzymes from a medicinal product on the market have comparable lipolytic activities to pancreatin at the pH optimum, but also advantageous lipolytic properties even at low pH values of 3–4. Bile acids support these properties, both for porcine pancreatic lipase and rizoenzymes. Up to a physiological concentration range of 10 mmol/L, there is no evidence of an inhibitory effect. This supports the effectiveness of rizoenzymes as an alternative therapeutic option for EPI. It is also known that enzyme substitution with pancreatin does not always lead to symptom reduction. This may be due to various patient-specific factors, such as the acidic environment of the small intestine, which does not provide optimal conditions for pancreatin galenics. It, therefore, makes sense to continue investigating these results of the comparison in the clinical setting. Which therapy option is appropriate for the individual patient depends, however, on many factors and must always be clinically evaluated on an individual basis. From our point of view at least, alternatives to porcine pancreatic enzymes are becoming increasingly important these days. Products containing rizoenzymes are not only important for vegan or vegetarian patients, but also for patients who are not allowed to take porcine medicines for religious reasons.

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CONFLICTS OF INTEREST

The authors of BioTeSys (CS and RW) and Lipidomix (MR) declare no conflicts of interest. AI and BL are employees of Repha GmbH.

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