Guanine and Xanthine Phosphoribosyltransfer Activities of Lactobacillus casei and Escherichia coli

THEIR RELATIONSHIP TO HYPOXANTHINE AND ADENINE PHOSPHORIBOSYLTRANSFER ACTIVITIES

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SUMMARY

The specificity and properties of the group of enzymes present in extracts of Lactobacillus casei which catalyzed phosphoribosyltransfer from 5-phosphoribosyl 1-pyrophosphate to purine bases were markedly different from those in extracts of Escherichia coli.

A comparison of the levels of hypoxanthine, guanine, and xanthine phosphoribosyltransfer activities in extracts of a wild strain and a 6-mercaptopurine-resistant strain of L. casei suggested the presence of a xanthine phosphoribosyltransferase which was distinct from the enzyme specific for hypoxanthine and guanine. This suggestion was substantiated by the finding that the activity toward xanthine was less stable at -21° and 60° than the activities toward hypoxanthine and guanine, and by its separation from these activities on Sephadex G-100. The hypoxanthine-guanine phosphoribosyltransferase present in the 6-mercaptopurine-resistant strain differed from that of the wild strain in its lower rate of ribonucleotide synthesis with hypoxanthine relative to that with guanine, and in its somewhat lower affinities for hypoxanthine and 6-mercaptopurine.

When extracts of E. coli were treated at 60°, the phosphoribosyltransfer activities toward guanine and xanthine decreased at the same rate, whereas the activity toward hypoxanthine decreased more rapidly. Chromatography on Sephadex G-100 did not resolve the activities toward hypoxanthine, guanine, and xanthine in extracts of E. coli. However, on Ecteola-cellulose, these activities were separated into two distinct peaks, the relative specificities of which indicated the presence of two different enzymes or enzyme forms. With one, hypoxanthine was the most efficient phosphoribosyl acceptor, whereas with the other, guanine was the most efficient acceptor. No distinct xanthine phosphoribosyltransferase was detected in extracts of E. coli.

In extracts of both L. casei and E. coli, the activity toward adenine was distinct from the activities toward hypoxanthine, guanine, and xanthine. This was shown by separations on Sephadex G-100 columns and by the differences in rates of heat inactivation.

The major metabolic pathway for the conversion of purines to mononucleotides is phosphoribosyltransfer from 5-phosphoribosyl 1-pyrophosphate to the purine base. Two distinct enzymes capable of catalyzing this transfer are known to be present in mammalian tissues. One preferentially acts on 6-aminopterines (adenosine monophosphate:pyrophosphate phosphoribosyltransferase, EC 2.4.2.7) (1) and the other on the 6-oxopurines (inosine monophosphate:pyrophosphate phosphoribosyltransferase, EC 2.4.2.8) (2). Studies with highly purified preparations from brewers' yeast (3, 4) and with less pure preparations from human blood cells (2, 5-7) indicate that a single enzyme catalyzes phosphoribosyltransfer to both hypoxanthine and guanine. However, with enzyme preparations from other sources some differential effects on the activities toward hypoxanthine and guanine have been observed (8-11).

The enzymatic basis for phosphoribosyltransfer to xanthine is likewise somewhat unclear. The hypoxanthine guanine phosphoribosyltransferase from human blood cells has been shown to have low but detectable activity toward xanthine (2, 12). The binding constant and reaction rate of xanthine with this enzyme are poor as compared to those for hypoxanthine or guanine (2).

Studies with microorganisms indicate the existence of a xanthine phosphoribosyltransferase which is distinct from that for hypoxanthine and guanine. The earliest suggestions of the existence of this enzyme came from studies on purine utilization by bacteria which were resistant to 6-mercaptopurine (13, 14). Later, enzyme preparations from purine analogue-resistant strains of Salmonella typhimurium (15) and Streptococcus faecalis (8) were reported to catalyze phosphoribosyltransfer preferentially to xanthine.

Previous studies with Lactobacillus casei have shown that a 6-mercaptopurine-resistant strain was able to utilize guanine, xanthine, and, to a lesser extent, adenine, but not hypoxanthine to support growth (13). The wild strain utilized all four purines equally well. These observations suggested that a study of the phosphoribosyltransfer activities from both a wild and a 6-mercaptopurine-resistant strain of L. casei might help to elucidate the multiplicity and specificity of the purine phosphoribosyltransferases of this organism. To test the generality of the findings with L. casei, similar experimental procedures were applied to extracts of Escherichia coli.

EXPERIMENTAL PROCEDURE

Materials—Hypoxanthine-8-14C, guanine-8-14C, and adenine-8-14C were purchased from Schwarz BioResearch, Inc. Xanthine-8-14C was purchased from Cal Atomic and 6-mercaptopurine-35S...
from the International Chemical and Nuclear Corporation. The dimagnesium salt of 5-phosphoribosyl 1-pyrophosphate was purchased from P.L. Biochemicals. Proteins used to calibrate the Sephadex columns were purchased from Mann. Ecteola-cellulose (capacity 0.34 meq per g) was purchased from Bio-Rad Laboratories, Richmond, California. E. coli B (ATCC 11303), grown in Kornberg medium and harvested in late log phase, was purchased from General Biochemicals, and stored at -21°C. The second subculture (2 liters) was seeded with washed cells harvested from the first subculture. The medium, incubation time, and temperature of each of the sequential subcultures were the same. These parameters are individually specified under "Results." Cells were harvested by centrifugation at 13,000 × g for 20 min. The cell pellet was resuspended in a volume of 0.14 M sodium chloride equal to the original culture volume and centrifuged as above.

### Table I

| Purine | RF values |
|-------|-----------|
|       | Free base | Ribose-1-phosphate | Ribose-5-phosphate |
| Adenine | 0.39 | 0.55 | 0.72 |
| Xanthine | 0.47 | 0.65 | 0.84 |
| Guanine | 0.45 | 0.66 | 0.85 |
| Hypoxanthine | 0.56 | 0.71 | 0.85 |

*0-*Ribosyl derivative of the base.

*5-*Monophosphate derivative of the ribonucleotide.

### Table II

| Culture conditions | Amount of ribonucleotide formed with phosphoribosyl acceptor |
|-------------------|---------------------------------------------------------------|
|                   | Hypoxanthine | Guanine | Xanthine | Adenine |
| Wild strain,a Medium 1,b 21 hours at 38°C | 64 | 68 | 5.7 | 33 |
| Resistant strain,b Medium 1, 21 hours at 38°C | 1.5 | 3.3 | 4.7 | 42 |
| Resistant strain,b Medium 3,a 21 hours at 38°C | 0.74 | 1.7 | 3.9 | 35 |
| Wild strain, Medium 3,a 48 hours at 30°C | 51 | 57 | 14 | 41 |
| Resistant strain, Medium 3, 48 hours at 30°C | 9.7 | 17 | 4.6 | 31 |
| Resistant strain, Medium 3, 32 hours at 30°C | 9.1 | 16 | 5.5 | 41 |
| Resistant strain, Medium 4,a 21 hours at 38°C | 5.4 | 10 | 4.3 | 65 |

*a-*Parent wild strain (ATCC 7469).

*b-*Difco folic acid assay medium (47 g per liter) supplemented with 1 mg per ml of folic acid. This medium contained 27 μg per ml of adenine and 38 μg per ml of guanine.

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*1-*Kornberg medium consists of yeast extract, 1%; dextrose, 1%; dibasic potassium phosphate, 2.18%; and monobasic potassium phosphate, 1.7%.

*2-*When reactions in assay mixtures containing E. coli extracts were stopped by immersion in a boiling water bath for 3 min, the phosphatase activity was found to be appreciably higher than when the reactions were stopped by the addition of EDTA.
Preparation of Cell Extracts—*L. casei* cells harvested from the second subculture were resuspended in a minimal amount (2 to 10 ml) of 0.1 M Tris hydrochloride-0.1 mM magnesium sulfate, pH 7.7 (Buffer A). This suspension was passed through a French Pressure Cell (American Instrument Company) at 17,000 p.s.i. and then centrifuged at 80,000 × g for 20 min. These resulting supernatant fluids are hereafter referred to as extracts.

One gram of frozen *E. coli* cells was thawed and suspended in 5 or 10 ml of Buffer A. An extract of this cell suspension was prepared as described above.

Protein concentrations were determined by the method of Lowry et al. (16) with human serum albumin as the standard.

**RESULTS**

**Studies with Extracts of *L. casei***

**Levels of Activity**—Table II lists the phosphoribosyltransfer activities toward hypoxanthine, guanine, xanthine, and adenine in extracts of a wild strain and a 6-mercaptopurine-resistant strain of *L. casei* cultured under various conditions. The levels of activity toward hypoxanthine and guanine in the extracts of the resistant strain were appreciably lower than those of the wild strain. This difference between the wild and resistant strains was more pronounced when the cells were cultured in Medium 1, than when cultured in Medium 3 (see Table II for composition of media). Under all conditions of cell culture used, the activity toward guanine in the extracts of the resistant strain was about twice that toward hypoxanthine; whereas these activities were nearly equal in the extracts of the wild strain. The levels of activity toward xanthine and adenine, in contrast to those toward hypoxanthine and guanine, were similar in both wild and resistant strains and did not vary greatly with conditions of cell culture.

The presence of purines in the culture media did not induce higher phosphoribosyltransferase levels. Even with resistant cells cultured in Medium 4, where the primary source of purines was xanthine, the level of activity toward this substrate was similar to that of cells cultured in other media (Table II). On the other hand, the level of activity toward guanine was appreciably lower in cells of the resistant strain which were cultured in the presence of guanine (Medium 1) as compared with those cultured in its absence (Medium 3).

The wild or the resistant strain of *L. casei* could be stored at -21° as a cell suspension for at least several weeks without significant loss in the extractable phosphoribosyltransfer activities toward hypoxanthine, guanine, xanthine, and adenine. Extracts of these cells, however, when stored in this manner, suffered appreciable losses in their activity toward xanthine. Only 2 to 5% of the original activity toward xanthine was detected after 16 days at -21°. The levels of the activity toward hypoxanthine, guanine, and adenine were essentially unchanged after this treatment.

**Heat Inactivation**—When an extract of the wild strain of *L. casei* was incubated at 60° the activities toward hypoxanthine and guanine were most stable and decreased at essentially identical rates (Fig. 1). The decrease in the activity toward adenine was faster. The activity toward xanthine was the most sensitive to this heat treatment.

**Product Characterization**—A pyrimidine phosphoribosyltransferase from bovine erythrocytes has been shown to catalyze phosphoribosyltransfer to nitrogen atom 3 but not nitrogen atom 9 of xanthine (18, 19). Hypoxanthine and guanine were not substrates for this enzyme. It was therefore of interest to determine the position of phosphoribosyltransfer to xanthine catalyzed by the extracts of *L. casei*.

(9-Ribosylxanthine) 5'-phosphate is much more resistant to acid hydrolysis than is (9-ribosylxanthine) 5'-phosphate (19). The product of the reaction catalyzed by the *L. casei* extract was 90% hydrolyzed to xanthine after 2 min at 100° in n HCl. Hydrolysis was essentially complete after 20 min. Under these conditions, the 3-ribosyl derivative is much more stable. The enzymatic product obtained with extracts of *L. casei* therefore appears to be (9 ribosylxanthine) 5'-phosphate.

**Sephadex Column Chromatography**—When a freshly prepared extract of the wild strain of *L. casei* cultured in Medium 1 was chromatographed on Sephadex G-100 the peak of phosphoribosyltransfer activity toward xanthine was eluted first, followed by a peak of activity toward adenine, and then by the overlapping activity peaks toward hypoxanthine and guanine (Fig. 2). A similar sequence of elution was obtained with the 6-mercaptopurine-resistant strain cultured under the same...
Fig. 2. Sephadex G-100 elution profile of the phosphoribosyltransferase activities of an extract of a wild strain of *L. casei* cultured in Medium 1 for 21 hours at 38°C. One milliliter of the extract contained 10.8 mg of protein and was capable of catalyzing phosphoribosyltransfer to xanthine (Xan), adenine (Ade), guanine (Gua), and hypoxanthine (Hyp) at the respective rates of 62, 35, 733, and 691 mpmoles per min. Extract (2 ml) was applied to a column (3 × 37.5 cm) which had been previously equilibrated with Buffer A at 23°C. The flow rate was 63 ml per hour. The void volume of the column was 61 ml. Phosphoribosyltransfer activities recovered were 53% with xanthine, 81% with adenine, 81% with guanine, and 94% with hypoxanthine.

Fig. 3. Sephadex G-100 elution profile of the phosphoribosyltransferase activities of an extract of a 6-mercaptopurine-resistant strain of *L. casei* cultured in Medium 1 for 21 hours at 38°C. One milliliter of the extract contained 21 mg of protein and was capable of catalyzing phosphoribosyltransfer to xanthine (Xan), adenine (Ade), guanine (Gua), and hypoxanthine (Hyp) at the respective rates of 100, 889, 69, and 33 mpmoles per min. Extract (2 ml) was applied to a column (3 × 34 cm) which had been previously equilibrated with Buffer A at 23°C. The flow rate was 43 ml per hour. The void volume of the column was 53 ml. Phosphoribosyltransfer activities recovered were 91% with xanthine, 81% with adenine, 81% with guanine, and 94% with hypoxanthine.

Conditions (Fig. 3), except that two separate peaks of activity toward guanine were discernible. The peak eluted first contained 10% of the total activity toward guanine and was accompanied by the phosphoribosyltransfer activity toward xanthine. The second peak of activity toward guanine was accompanied by the activity toward hypoxanthine.

GMP synthesis catalyzed by material from the activity peak toward xanthine rapidly decreased as the reaction progressed (Fig. 4), although XMP synthesis followed a more usual time course. GMP synthesis catalyzed by the second activity peak was essentially linear until 20% of the substrate had been converted to ribonucleotide. A time course for GMP synthesis similar to that shown in Fig. 4 was observed by Brockman et al. (8) with an extract of a 6-mercaptopurine-resistant strain of *Streptococcus faecalis* which preferentially catalyzed phosphoribosyltransfer to xanthine.

The peak of activity toward hypoxanthine in the chromatogram of the resistant strain (Fig. 3) catalyzed phosphoribosyltransfer to 6-mercaptopurine at one-third the rate of transfer to hypoxanthine, whereas the peak of activity toward xanthine lacked significant activity toward 6-mercaptopurine. The enzymes with activities toward xanthine, adenine, and hypoxanthine-guanine exhibited average particle weights of 95,000, 65,000, and 44,000 (± 10%), respectively. The values for the hypoxanthine-guanine-phosphoribosyltransferases from the wild and resistant strains were not significantly different. These particle weight values were estimated from the elution volumes of the phosphoribosyltransfer activities from Sephadex columns which were calibrated with proteins of known molecular weights (20). It is important to point out that these values are not presented as molecular weight values, but rather as apparent particle weights which might be of some use for future comparisons with values obtained with purified preparations.

**Kinetic Studies—**A comparison of some of the kinetic parameters of the hypoxanthine-guanine phosphoribosyltransferase from the resistant and wild strains of *L. casei* revealed some differences. Fractions (stored for several days at −21°C) from the Sephadex columns in Figs. 2 and 3 were used for these studies.

The *K*ₐ of hypoxanthine for the hypoxanthine-guanine phosphoribosyltransferase from the wild strain was 4 μM, whereas

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*Adenine phosphoribosyltransferase in fractions from the column in Fig. 2 exhibited varying particle weights when chromatographed in the presence of various proteins of known molecular weight.*
that from the resistant strain was 7 \mu M. The \( K_m \) value for guanine for this enzyme from the wild strain was 9 \mu M, and for that from the resistant strain, 8 \mu M.

6-Mercaptopurine exhibited competitive inhibition with \(^{14}C\)-hypoxanthine as the variable substrate. The \( K_i \) values of 6-mercaptopurine obtained from the magnitude of this inhibition were 7 \mu M with the wild strain enzyme, and 12 \mu M with the resistant strain enzyme.

The \( K_m \) value for xanthine for the xanthine phosphoribosyltransferase taken from the Sephadex eluate shown in Fig. 3 was 1 \mu M. Nonradioactive guanine did not effectively inhibit the \(^{14}C\)-XMP synthesis catalyzed by this enzyme. The \( K_i \) value for guanine was in the range of 100 \mu M. Likewise, nonradioactive xanthine did not effectively inhibit the low guanine phosphoribosyltransfer activity of these fractions. At 0.1 mM \(^{14}C\)-guanine, 0.25 mM xanthine was required to obtain 50% inhibition of the \(^{14}C\)-GMP synthesis.

Studies with Extracts of E. coli

Levels of Activity—Extracts of E. coli were capable of catalyzing phosphoribosyltransfer to hypoxanthine, guanine, xanthine, and adenine at 73, 35, 20, and 41 \( \mu \)moles per min per mg of protein, respectively. These activities are in the same range as those observed with extracts of L. casei (Table II).

Heat Inactivation—At 60\degree\ the activities toward guanine and xanthine decreased at the same rate (Fig. 5). The activity toward hypoxanthine decreased at a faster rate than these

![Fig. 5. Rate of heat inactivation of purine phosphoribosyltransfer activities at 60\degree in an extract of E. coli.](image)

![Fig. 6. Sephadex G-100 elution profile of the phosphoribosyltransfer activities of an extract of E. coli B.](image)

![Fig. 7. Ecteola-cellulose elution profile of the hypoxanthine phosphoribosyltransfer activities of an extract of E. coli B.](image)
Table III
Relative stabilities of chromatographically obtained phosphoribosyltransferases of E. coli in storage at –21°

| Source of activity | Time at –21° | Activity with hypoxanthine | Activity with guanine | Ratio of activity with hypoxanthine to activity with guanine |
|--------------------|--------------|-----------------------------|-----------------------|----------------------------------------------------------|
|                    | days         | Before storage | After storage | Before storage | After storage | Before storage | After storage |
| First activity peak | 4            | 35             | 10           | 29            | 29            | 1.2             | 0.29          |
| from Sephadex column (Fig. 6). | | | | | | | |
| Second activity peak | 17           | 79             | 27           | 18            | 14            | 4.4             | 1.0           |
| from Ecteola column (Fig. 7) | | | | | | | |
| Third activity peak | 17           | 9.5            | 4.2          | 30            | 25            | 0.32            | 0.17          |
| from Ecteola column (Fig. 7) | | | | | | | |

activities, while the activity toward adenine was the most unstable.

_Sephadex Column Chromatography_—When an extract of _E. coli_ was chromatographed on Sephadex G-100, the activity toward hypoxanthine was eluted first, closely followed by the overlapping activities toward guanine and xanthine (Fig. 6). The activity toward adenine was eluted last. The apparent particle weights estimated from this chromatogram were 75,000 for the activity toward hypoxanthine, 62,000 for that toward guanine and xanthine, and 28,000 for that toward adenine.

_Ecteola-cellulose Column Chromatography_—When extracts of _E. coli_ were chromatographed on Ecteola-cellulose the phosphoribosyltransferase activities toward guanine and xanthine were resolved into two distinct peaks (Fig. 7). The activity peak eluted first had a 4-fold higher rate of phosphoribosyltransfer to hypoxanthine than to guanine. Conversely, the second peak of activity had a 4-fold higher rate of phosphoribosyltransfer to guanine than to hypoxanthine. Rechromatography of the latter peak on Ecteola-cellulose resulted in a single peak of overlapping activities toward guanine, xanthine, and hypoxanthine at the relative rates of 5, 4, and 1, respectively.

_Stability at –21°_—Fractions from the Sephadex and Ecteola columns (Figs. 6 and 7) containing high activity toward hypoxanthine lost much of this activity after storage at –21°, whereas no or relatively small losses in the activity toward guanine were observed (Table II). Both peaks of activity toward guanine from the Ecteola column (Fig. 7) had similar stabilities.

_Kinetic Studies_—Michaelis constants were determined with fractions (stored for several days at –21°) from both activity peaks from the Ecteola column (Fig. 7). The _K_m values for guanine (1 μM) and for xanthine (50 μM) were the same for both activity peaks. The _K_m value for hypoxanthine determined with the first peak of activity was 4 μM. In xanthine, the _K_m value for hypoxanthine determined with the second activity peak was 80 μM.

**DISCUSSION**

The levels of xanthine phosphoribosyltransfer activity in extracts of the wild and 6-mercaptopurine-resistant strains of _L. casei_ were similar, whereas the levels of activity toward hypoxanthine and guanine in the resistant strain were appreciably lower than those in the wild strain (Table II). The activity toward xanthine also differed from that toward hypoxanthine and guanine in stability to storage at –21° (see "Results") and to heat treatment (Fig. 1). Most striking was the chromatographic separation of the activity toward xanthine from that toward hypoxanthine and guanine (Figs. 2 and 3). These observations show that _L. casei_ has a xanthine phosphoribosyltransferase distinct from its hypoxanthine-guanine phosphoribosyltransferase. In the elution profile of the column in Fig. 3, the xanthine phosphoribosyltransferase was accompanied by some activity toward guanine which exhibited a peculiar time course (Fig. 4). Inhibition of both activities by nonradioactive xanthine or guanine (see "Results") suggested that they are not catalyzed by the same enzyme. However, because of the low levels of activity involved, a final decision must await further purification of these activities.

The level of guanine phosphoribosyltransfer activity extractable from _L. casei_ cultured in different media varied in parallel with the activity toward hypoxanthine (Table II). Further, both activities had similar heat stabilities (Fig. 1) and elution volumes from Sephadex columns (Figs. 2 and 3). These observations indicate that _L. casei_ has a hypoxanthine-guanine phosphoribosyltransferase similar to those studied from other sources (2, 3, 5, 21). This enzyme from the 6-mercaptopurine-resistant strain differed from that of the wild strain in the relative rates of reaction with hypoxanthine and guanine and the affinity for hypoxanthine and 6-mercaptopurine. These differences suggest that a genetic alteration of the hypoxanthine-guanine phosphoribosyltransferase, similar to those described with _S. typhimurium_ (21), has occurred. It is important to note that although the resistant strain enzyme had a somewhat reduced affinity for 6-mercaptopurine, it was still capable of catalyzing the synthesis of the ribonucleotide of this analogue. It seems probable that both the reduced levels of the enzyme activity (Table II) and its modified catalytic properties contributed to the resistance of this organism.

Another way of interpreting the difference between the hypoxanthine-guanine phosphoribosyltransferase activities in the wild and resistant strains of _L. casei_ is to postulate the existence of multiple forms of this enzyme in the wild strain. It is conceivable that the resistant strain possesses only that isoenzymic form which is least efficient toward 6-mercaptopurine. Indeed, the broad peak and varying ratios of the activity toward hypoxanthine and guanine in the resistant strain differed from that of the wild strain in the relative rates of reaction with hypoxanthine and guanine and the affinity for hypoxanthine and 6-mercaptopurine. These differences are consistent with this view. However, attempts to resolve any isoenzymic forms of the hypoxanthine-guanine phosphoribosyltransferase in extracts of the wild strain of _L. casei_ by Sephadex and DEAE-cellulose chromatography have thus far been inconclusive.

The properties and relationships of the phosphoribosyltransfer activities toward hypoxanthine, guanine, and xanthine in _E. coli_ were quite different from those in _L. casei_. At 60°, the activities toward guanine and xanthine in _E. coli_ extracts decreased at the same rate (Fig. 5), while the activity toward hypoxanthine decreased more rapidly. Chromatography on Sephadex G-100 did not resolve the hypoxanthine, guanine, and xanthine phosphoribosyltransfer activities (Fig. 6). However,
on Ecteola-cellulose, these activities were separated into two distinct peaks (Fig. 7). The marked differences between the two activity peaks in their affinities and reaction rates with hypoxanthine indicate that in E. coli two different enzymes or enzyme forms catalyze phosphoribosyltransfer to hypoxanthine, guanine, and xanthine. With one of these, hypoxanthine is the most efficient phosphoribosyl acceptor whereas with the other, guanine is the most efficient acceptor. No distinct xanthine phosphoribosyltransferase was detected in extracts of E. coli.

The difference in the stability of the hypoxanthine and guanine phosphoribosyltransfer activities (Table III) of the first activity peak from the Ecteola column (Fig. 7) suggests that this peak might be composed of more than one enzyme. The similar affinities for guanine and xanthine with both activity peaks further suggest the possibility of partial co-chromatography. Yet another possibility, that these activity peaks are attributable to distinct catalytic forms of the same enzyme, has not been eliminated. Further studies on these enzymatic activities are in progress.

In extracts of both L. casei and E. coli, the activity toward adenine was distinct from the activities toward hypoxanthine, guanine, and xanthine. This was most clearly shown by the chromatographic separations (Figs. 2, 3, and 6) and rates of heat inactivation (Figs. 1 and 5).

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