Procyanidins are not bioavailable in rats fed a single meal containing a grapeseed extract or the procyanidin dimer B₃

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Flavanols are the most abundant flavonoids in the human diet where they exist as monomers, oligomers and polymers. In the present study, catechin, the procyanidin dimer B₃ and a grape-seed extract containing catechin, epicatechin and a mixture of procyanidins were fed to rats in a single meal. After the meals, catechin and epicatechin were present in conjugated forms in both plasma and urine. In contrast, no procyanidins or conjugates were detected in the plasma or urine of any rats. Procyanidins were not cleaved into bioavailable monomers and had no significant effects on the plasma levels or urinary excretion of the monomers when supplied together in the grapeseed extract. We conclude that the nutritional effects of dietary procyanidins are unlikely to be due to procyanidins themselves or monomeric metabolites with the intact flavonoid-ring structure, as they do not exist at detectable concentrations in vivo. Future research should focus on other procyanidin metabolites such as phenolic acids and on the effects of the unabsorbed oligomers and polymers on the human gastrointestinal tract.

**Procyanidin: Condensed tannins: Catechin: Epicatechin: Flavanol: Absorption: Metabolism: Rat**

Flavanols are a unique class of flavonoids that are present as monomers, oligomers and polymers in the human diet. Oligomers and polymers are called proanthocyanidins or condensed tannins. They are made up of (epi)catechin or (epi)gallocatechin that are known as procyanidins or pro-delphinidins respectively. Red wine, berries, apples, tea and chocolate are among the richest food sources (Guyot et al. 1998; Hammerstone et al. 1999, 2000; de Pascual-Teresa et al. 2000; Foo et al. 2000). Consumption of flavanol monomers, dimers and trimers was recently estimated to range from 18 to 31 mg/d from an average Spanish diet, with wine and apples as the main sources (Arts et al. 2001). However, the average degree of polymerization of proanthocyanidins commonly varies between four and ten (Santos-Buelga & Scalbert, 2000) and the total flavanol intake should therefore be much greater. The complexity of their chemical structures and the difficulty in their reliable estimation has so far hampered the precise estimation of their intake, which may range from several tens to several hundred mg/d depending on the diet (Santos-Buelga & Scalbert, 2000).

In spite of their abundance in foods, as well as numerous in vitro and in vivo studies demonstrating diverse biological activities (Pingzhang et al. 1994; Liao et al. 1995; Clifford et al. 1996; Hayek et al. 1997; Pumberg et al. 1998; Schramm et al. 1998, 2001; Xu et al. 1998; Koga et al. 1999; Puter et al. 1999; Sato et al. 1999; Yamakoshi et al. 1999, 2001; Damianaki et al. 2000; Keevil et al. 2000; Reiner et al. 2000a, b; Santos-Buelga & Scalbert, 2000), strikingly little is known about the absorption and metabolism of flavanols and more particularly of the proanthocyanidins. The monomers catechin and epicatechin as well as the gallate esters present in green tea are absorbed in both human subjects and animals (Hackett et al. 1983; Lee et al. 1995; Piskula & Terao, 1998; Donovan et al. 1999a, 2002; Koga et al. 1999; Richelle et al. 1999; Baba et al. 2000; Reiner et al. 2000).

Absorption of proanthocyanidins has been reported in several earlier studies. However, doubts remain about these results due to the use of procyanidin extracts that were not well characterized and to analytical methods that were not specific enough. Procyanidins were reported in the urine of rats and mice after consumption of grape-seed extracts, but detection was based on radioactivity levels that may have originated from monomers, other...
components of the extract, or metabolites (Laparra et al. 1977; Harmand & Blanquet, 1978). In contrast, studies in chickens and sheep indicated that polymeric fractions free of monomers were not absorbed (Jimenez-Ramsey et al. 1994; Terrill et al. 1994), but these animal models are not generally indicators of human bioavailability. In cultured human intestinal Caco-2 cells, a well-established model of human intestinal absorption, similar levels of monomers and oligomers were absorbed in comparison with polymers which were not absorbed (Déprez et al. 2001).

In the present study the absorption and metabolism of the monomers catechin and epicatechin were compared with those of the pure procyanidin dimer B₃, and a grape-seed extract containing both monomers and oligomers after a single meal in rats. The primary objective was to determine whether, like the structurally related monomers, procyanidin oligomers are absorbed and present as conjugated metabolites in urine and plasma. An additional objective was to determine whether procyanidin oligomers such as the dimer B₃ could be cleaved into monomers and subsequently absorbed in that form as has been recently suggested (Spencer et al. 2000, 2001). Finally, we sought to determine if procyanidin oligomers, which are generally consumed together with monomers, could alter the absorption or metabolism of monomers.

**Materials and methods**

**Chemicals and reagents**

(+)-Catechin, (-)-epicatechin and (+)-taxifolin were purchased from Extrasynthèse (Genay, France). The 3′- and 4′-O-methylated conjugates of catechin and epicatechin were synthesized using a mixture of 250 mg (+)-catechin or (-)-epicatechin, 500 mg K₂CO₃ and 1 ml methyl iodide in 20 ml acetone which was placed in an ultrasonic bath for 2.5 h. The 3′- and 4′-O-methylated conjugates were purified by semi-preparative HPLC and the positions of the methyl groups were confirmed by one-dimensional-difference nuclear Overhauser effect spectroscopy (Donovan et al. 1999b). Procyanidin B₃ (catechin-(4α → 8)-catechin) was purified from willow-tree catkins and characterized as previously described (Déprez & Scalbert, 1999). Procyanidin B₁ (epicatechin-(4β → 8)-catechin) was synthesized by depolymerization of procyanidins from pine bark in the presence of catechin as previously described (Hemingway & McGraw, 1983). Procyanidin B₂ (epicatechin-(4β → 8)-epicatechin) was obtained from Extrasynthèse. The grape-seed extract used in this study was an ethyl acetate extract of grapeseeds supplied by Indena (Milan, Italy). β-Glucuronidase (G-0876) and arylsulfatase (S-9626) were purchased from Sigma (St Louis, MO, USA).

**Analysis of the grape-seed extract**

Grapeseeds contain monomers as well as procyanidin oligomers and polymers. Ethyl acetate, used to produce the extract used in the present study, is specific for monomers but does not extract large polymers (Waterhouse et al. 2000). Flavanol monomers and dimers were analysed by reversed-phase HPLC. A solution of grapeseed extract (3 mg/ml) was prepared in dimethylsulphoxide and diluted in acetonitrile (200 ml/l) in 30 mM-Na₂HPO₄ buffer at pH 3·0 prior to analysis. Analysis was performed by HPLC using a 150 × 4·6 mm Hypersil BDS C₁₈–5 μm column (Life Sciences International, Cergy, France). Mobile phases consisted of 30 mM-Na₂HPO₄ buffer at pH 3·0 containing acetonitrile (50 ml/l, phase A) and acetonitrile (500 ml/l phase B). The separation was performed at 35°C with a flow rate of 1 ml/min. The gradient went from 0 to 100% B in 70 min and remained at 100% B until 73 min. The phase was then returned to 100% A from 73 to 75 min and remained at 100% A until 95 min. Detection was performed with a multi-electrode CoulArray Model 5600 system (Eurosep, Cergy, France) with potentials set at 25, 100, 150, 300, 350 and 400 mV.

**Animals and diets**

Male Wistar rats weighing approximately 170 g were housed in metabolic cages allowing the collection of 24 h urine samples with a dark period from 08.00–20.00 hours and access to food from 08.00–16.00 hours. The rats were fed a standard semipurified diet containing (g/kg): wheat starch 755, casein 150, mineral mixture 35 (AIN93M; ICN Biochemicals, Orsay, France), vitamin mixture 10 (AIN76; ICN Biochemicals), corn oil 50. The diet was fed for 2 weeks prior to the experiment.

The rats were then randomly divided into five groups of fifteen rats. Each group received a different experimental meal of 20 g each. The control group consumed only the standard semipurified diet. The catechin group consumed a meal consisting of the standard semipurified diet supplemented with 20 mg catechin. The B₃ group consumed a meal consisting of the standard semipurified diet supplemented with 20 mg procyanidin dimer B₃. The two other groups consumed a meal supplemented with 200 (GS1) or 400 (GS2) mg grapeseed extract. These concentrations were chosen in order to provide the same amount of catechin as the catechin group (20 mg, group GS1) or twice that amount (40 mg, group GS2). The GS1 meal also provided 14 mg epicatechin, 11 mg procyanidin B₁, 7 mg procyanidin B₂ and 3 mg procyanidin B₃ and the GS2 meal twice these amounts. All animals were maintained and handled according to the recommendations of the Institutional Ethics Committee, in accordance with the decree no. 87-848.

**Sampling procedure**

Five rats from each group were anaesthetized with sodium pentobarbital (40 mg/kg body weight intraperitoneally) 3 h after providing the meal (absorption in the small intestine), 9 h after providing the meal (to determine if absorption occurred in the large intestine after contact with intestinal microflora) and 24 h after providing the meal (to collect urine samples). For each time point, blood was drawn from the abdominal aorta into heparinized tubes and plasma was immediately acidified by the addition of 10 μl 1 M-acetic acid/ml plasma. This procedure prevents flavanol degradation during storage, but
does not precipitate proteins. The resulting samples were stored at −20°C. The 24 h urine samples were also collected and stored at −20°C until analysis.

Analysis of plasma and urine samples

Plasma samples (175 µl) were acidified to pH 4.9 with 20 µl 0.58 M acetic acid. Urine samples were diluted 100-fold in sodium acetate buffer (0.1 M, pH 4.9). All samples were spiked with taxifolin, the internal standard, and incubated for 15 min at 37°C in the presence of 1200 U β-glucuronidase and 75 U arylsulfatase. The incubation time and conditions for enzymatic hydrolysis of flavanols were optimized in a kinetic study over a 4 h period. No further increase in aglycone formation was observed after 15 min. The samples were then extracted by the addition of 500 µl methanol containing 200 µM HCl and centrifuged for 5 min at 14,000 g. The supernatant fraction was analysed by HPLC as described later. The recovery of flavanols from plasma and urine was determined by adding a mixture of catechin, epicatechin, procyanidin dimer B3 and taxifolin (1 µmol/l each) to control plasma and urine. The plasma samples were frozen at −20°C and then thawed, incubated for 15 min at 37°C with the β-glucuronidase and arylsulfatase and extracted and analysed exactly as described for the samples. The absolute recovery using this procedure was 103.0 (SEM 0.1) %, 94.5 (SEM 0.3) %, 98.9 (SEM 0.1) %, 96.9 (SEM 0.1) % for catechin, epicatechin, 3′-O-methylcatechin, and 3′-O-methylleucatechin respectively, and 70.4 (SEM 0.3) % for procyanidin B3. Plasma and urinary concentrations reported here were corrected for the losses during the extraction procedure using the internal standard, taxifolin.

Analysis was performed by HPLC with multi-electrode coulometric detection. Conditions and mobile phases were as described earlier for the grapeseed extract except that the mobile-phase gradient and electrode potentials were modified for plasma and urine. The gradient went from 0–50 % B in 15 min and remained at 50 % B until 20 min. From 20–25 min the phase was at 100 % B and from 0–50 % B in 15 min and remained at 50 % B until 20 min. The phase was then reconditioned with 100 % A from 20–25 min. From 20–25 min the phase was at 100 % B and from 0–50 % B in 15 min and remained at 50 % B until 20 min. The phase was then reconditioned with 100 % A.

Levels of flavanols in plasma

Plasma levels of catechin, epicatechin and their 3′-O-methylated forms at 3, 9 and 24 h in each of the groups are shown in Fig. 2. Plasma levels in the catechin group and the GS1 group can be directly compared as these meals provided equal amounts of catechin. Total amounts of catechin and 3′-O-methylcatechin in plasma were not significantly different after the catechin and GS1 meals at any of the time points indicating that no other precursor of catechin was present in the GS1 meal.

A difference was observed in the percentage of catechin

Results

Flavanols in the grapeseed extract

A chromatogram of the grapeseed extract used in this study is shown in Fig. 1. Catechin and epicatechin give a similar response pattern over the different electrodes of the electrochemical detector with a maximal intensity at 150 mV. This response pattern is clearly different from that of the dimers B1, B2 and B3 which gave a maximal response at 350 mV. Two other peaks with similar electrochemical behaviour (retention times 14 and 16 min) are unknown peaks probably structurally related to the dimers. The extracted flavonoid contained (g/kg DM): catechin 102, epicatechin 73, procyanidin B1 55, procyanidin B2 37, and procyanidin B3 16.

Nature of flavanols in plasma

HPLC chromatograms of rat plasma after hydrolysis by β-glucuronidase and arylsulfatase from the control, catechin, procyanidin B3, and the GS1 group are shown in Fig. 2. In rats fed the control meal, no peaks that corresponded to catechin, epicatechin, their methylated forms or any of the procyanidins were detected in plasma. In rats fed the catechin meal, catechin and 3′-O-methylcatechin were detected in plasma. 4′-O-methylcatechin was not detected in plasma.

No procyanidin dimer (B1, B2 or B3) could be detected at any time point studied in the plasma of any rats fed procyanidins (dimer B3 and grapeseed meals). Procyanidins were not absorbed into the systemic circulation of rats as no plasma samples contained any procyanidins at concentrations higher than 20 nmol/l, which is the limit of detection of the HPLC method used here.

In rats fed the procyanidin B3 meal, neither catechin nor 3′-O-methylcatechin could be detected in the plasma even when plasma was sampled at 9 and 24 h after contact with intestinal microflora. Thus, procyanidin B3 was not a precursor for catechin in plasma.

The plasma of the rats fed the grapeseed diets (GS1 and GS2) contained catechin, epicatechin and their 3′-O-methylated conjugates. There were no other peaks on any of the chromatograms that had the characteristic behaviour of flavanols indicating that there were no other metabolites in the hydrolysed plasma that conserved the flavonoid-ring structure.

Levels of flavanols in plasma

Plasma levels of catechin, epicatechin and their 3′-O-methylated forms at 3, 9 and 24 h in each of the groups are shown in Fig. 3. All plasma levels are reported after hydrolysis by β-glucuronidase and arylsulfatase. Plasma levels in the catechin group and the GS1 group can be directly compared as these meals provided equal amounts of catechin. Total amounts of catechin and 3′-O-methylcatechin in plasma were not significantly different after the catechin and GS1 meals at any of the time points indicating that no other precursor of catechin was present in the GS1 meal.

A difference was observed in the percentage of catechin
in methylated form after the catechin diet and the diets containing grapeseed extract. Three hours after beginning the catechin meal, 55 (SEM 2) % catechin was methylated whereas only 37 (SEM 3) % and 30 (SEM 1) % catechin was methylated after the GS1 and GS2 meals respectively ($P < 0.05$). No significant differences in methylation were observed 9 h after the meal and approximately 60 % of the metabolites were methylated in all three groups. At 24 h, only methylated forms existed in the plasma from all three groups.

**Excretion of flavanols in urine**

In all groups, 24 h urine hydrolysed by β-glucuronidase and arylsulfatase contained the same metabolites that were detected in plasma. After the catechin meal, catechin and 3'-O-methylcatechin were detected in urine. In rats fed the procyanidin B$_3$ meal, the dimer B$_3$ was not detected in the urine of any rats in this group. In addition, no catechin or 3'-O-methylcatechin could be detected in the same urine. The urine of the rats fed the diets GS1 and GS2 contained catechin, epicatechin and their 3'-O-methylated conjugates, however, none of the procyanidins present in the diet (B$_1$, B$_2$, B$_3$) was detected in the urine samples of any rats in the GS1 and GS2 groups.

Levels of flavanols excreted over the 24 h period expressed as percentage of the catechin and epicatechin intake are shown in Table 1. Over the 24 h period, 37 (SEM 4) % of the catechin dose was excreted in urine after the catechin meal and 43 (SEM 3) % of the catechin
A dose was excreted after the GS1 meal. The proportion of catechin excreted after the catechin and GS1 meals was not significantly different indicating that the grapeseed extract did not contain any other precursor of catechin.

After the GS1 and GS2 meals 43 (SEM 3) % and 32 (SEM 4) % of the catechin dose was excreted in urine respectively. The excretion of epicatechin was similar to catechin with 40 (SEM 3) % and 29 (SEM 4) % of the epicatechin dose excreted in urine after the GS1 and GS2 meals, respectively. The proportion of both the catechin and epicatechin doses excreted in urine over the 24 h period was significantly less after the GS2 meal compared with the GS1 meal ($P < 0.05$) and may reflect a slower elimination of metabolites or a lower absorption after higher doses of administration.

The proportion of metabolites that were excreted in methylated form was slightly (although not significantly) decreased after the GS1 and GS2 meals compared with the catechin meal. After the catechin meal, 69 (SEM 3) % catechin in urine was methylated, whereas only 61 (SEM 3) % and 54 (SEM 2) % catechin was methylated after the GS1 and GS2 diets respectively. Catechin was more extensively methylated than epicatechin. After the GS1 meal, 61 (SEM 3) % catechin was methylated whereas only 47 (SEM 2) % epicatechin was methylated ($P < 0.05$). After the GS2 meal 54 (SEM 2) % catechin was methylated, whereas only 45 (SEM 2) % epicatechin was methylated ($P < 0.05$).

**Discussion**

In the present study the absorption and metabolism of the monomeric flavanols (catechin and epicatechin) were compared with those of flavanol oligomers (procyanidins) after

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**Table 1.** Urinary excretion of flavanols over a 24 h period after a single meal containing catechin, procyanidin B3 or a grapeseed extract*  
(Mean values with their standard errors for five rats per group)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Catechin</th>
<th>3’OMC</th>
<th>Total catechin</th>
<th>Epicatechin</th>
<th>3’OME</th>
<th>Total epicatechin</th>
<th>Procyanidins B1, B2, B3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Catechin§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molar %</td>
<td>11</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Methylation(%)</td>
<td>69a</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molar %</td>
<td>16</td>
<td>4</td>
<td>25</td>
<td>3</td>
<td>20</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Methylation(%)</td>
<td>61ab</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS2**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molar %</td>
<td>15</td>
<td>2</td>
<td>17</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Methylation(%)</td>
<td>54b</td>
<td>2</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

3’OMC, 3’-O-methylcatechin; 3’OME, 3’-O-methylepicatechin; B3, procyanidin B3; ND, not detectable.

a,bMean values within a column with unlike superscript letters were significantly different ($P<0.05$).

* For details of diets and procedures, see p. 300.

† Excretion is expressed as a molar percentage of the dose of catechin and epicatechin administered.

‡ Procyanidins B1, B2 and B3 were not detected in any urine samples.

§ 20 mg catechin.

‖ 20 mg B3.

† GS1, 20 mg catechin + 14 mg epicatechin + 11 mg procyanidin B1 + 7 mg procyanidin B2 + 3 mg B3.

** GS2, 40 mg catechin + 28 mg epicatechin + 22 mg procyanidin B1 + 14 mg procyanidin B2 + 6 mg B3.
a single meal in rats. Flavanol analysis in plasma and urine was performed by HPLC with coulometric detection, which has conclusively shown that oligomeric procyanidins are not present at detectable levels in the plasma or urine of rats. The doses of the different dimers used in this study, 20 mg procyanidin B1, B2, and B3, were as well as 22 mg procyanidin B2, and 14 mg procyanidin B3, in the GS2 diet were quite high and these procyanidins would have been easily detected in plasma if absorbed. Catechin levels in the plasma of rats after a similar dose of catechin have been easily detected in plasma if absorbed. Catechin GS2 diet were quite high and these procyanidins would be attributed to the presence of epicatechin in the extract which, like catechin, is methylated by catechol-O-methyltransferase and could function as a competitive inhibitor.

Procyanidins may have biological effects even though they are not absorbed into the systemic circulation. As reducing agents, they may be active in the gastrointestinal tract and modify the outcome of diseases of the gastrointestinal tract such as colorectal cancer (Hagerman et al. 1999; Scalbert & Williamson, 2000). As chelating agents they may interact with minerals such as Fe(III) and influence their bioavailability (Santos-Buelga & Scalbert, 2000). They may also reduce the levels of Bifidobacterium and Enterobacteriaceae in the colon and limit faecal odour (Yamakoshi et al. 2001). Furthermore, more biological effects of procyanidins in inner tissues could be mediated by some metabolites formed in the colon and then absorbed through the colon barrier. Procyanidin B3 dimer and procyanidin polymers can be degraded by microflora in the large intestine into bioavailable phenolic acids similar to those formed from catechin itself (Scheline, 1970; Groenewoud & Hunding, 1986; Déprez et al. 2000). Studies have identified mono- and dihydroxylated phenylpropionic, phenylactic and hippuric acid as well as various phenylvalerolactones as flavanol metabolites in plasma (Das, 1971; Hackett et al. 1983; Pietta et al. 1998; Li et al. 2000). These metabolites may further increase the antioxidant capacity of plasma or may have activity within the intestine. They may also have other biological activities that deserve further exploration.

Our present results also indicate that procyanidins were not hydrolysed into bioavailable monomers in the rat stomach, small intestine, or large intestine. Recent in vitro experiments suggested that procyanidins from chocolate were hydrolysed into bioavailable flavanol monomers in warm, acidic conditions thought to reflect those in the human stomach (Spencer et al. 2000). Procyanidins B3 and B4 were also reported to be hydrolysed to epicatechin in the isolated rat small intestine (Spencer et al. 2001). The degree of polymerization of proanthocyanidimes has also been reported to decrease in the small intestine (Abia & Fry, 2001). Other authors also suggested that procyanidin dimers might be degraded into catechin monomers by microflora in the colon although they did not report the presence of catechin as an intermediate breakdown product in their in vitro experiments (Groenewoud & Hunding, 1986; Déprez et al. 2000). In the present study, no catechin was detected in the plasma or urine of the rats fed the meal containing 20 mg purified procyanidin dimer B3 indicating that this procyanidin was not cleaved into a bioavailable source of catechin in the stomach or large intestine. In addition, catechin levels were not different after the GS1 and catechin meals which contained the same amounts of catechin. These results show that there were no precursors of catechin provided by the grapeseed extract and that procyanidins were not cleaved into bioavailable monomers at any point during the digestive process in rats.

Procyanidins and monomeric flavanols are generally associated and consumed together in foods (de Pascual-Teresa et al. 2000; Santos-Buelga & Scalbert, 2000). Our results indicate that procyanidins have a very limited effect, if any, on the metabolism of the absorbed monomers. The only significant difference observed in the present study was a reduced amount of methylation at 3 h when catechin was supplied in the grapeseed-extract diets. However, reduced methylation may also be attributed to the presence of epicatechin in the extract which, like catechin, is methylated by catechol-O-methyltransferase and could function as a competitive inhibitor.

In the present study the procyanidin dimers B1, B2, and B3 were not absorbed in rats. They were also not cleaved into bioavailable monomers such as catechin in the stomach or large intestine. We conclude that the nutritional effects of dietary oligomeric flavanols are unlikely to be due to procyanidins themselves or monomeric metabolites with the intact flavonoid-ring structure as they do not exist at appreciable concentrations in vivo. Future research should focus on other metabolites formed in the large intestine, as well as on the effects of the unabsorbed oligomers and polymers on the gastrointestinal tract.

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References


