Acetylsalicylic acid (aspirin™; 2-acetoxybenzoic acid) has been used for >100 years for pain relief and to treat inflammatory conditions and fevers. More recently, regular intake has been associated with decreased incidence of certain cancers, particularly colon cancer. After absorption aspirin is very rapidly hydrolysed to salicylic acid (2-hydroxybenzoic acid). The anti-cancer effects of aspirin may be a result of salicylic acid reducing the transcription of prostaglandin H\textsubscript{2}-synthase and thereby the synthesis of pro-inflammatory and potentially-neoplastic prostaglandins. Salicylic acid is widely present in plants and functions as a hormonal mediator of the systemic acquired resistance response to pathogen attack and environmental stress. Thus, it is present in a large range of fruit, vegetables, herbs and spices of dietary relevance. Consequently, the recognised effect of consuming fruit and vegetables on lowering risk of colon cancer may be partly attributable to salicylates in plant-based foods. The present review discusses which types of fruit and vegetables are the richest source of salicylates and whether they are sufficiently released from the food matrix to modify the key cellular events associated with the pathogenesis of colon cancer.

Salicylic acid: Aspirin: Fruit and vegetables: Colon cancer

For >100 years aspirin™ (acetylsalicylic acid; Fig. 1) has been used to provide pain relief and to treat inflammatory conditions and fevers (Jeffreys, 2004). More recently, regular intake of aspirin has also been associated with a decreased incidence of some cancers, particularly colon cancer (Bosetti \textit{et al}. 2001). Such epidemiological observations are now corroborated by results from several double-blind randomised placebo-controlled intervention trials (Baron \textit{et al}. 2003; Benamouzig \textit{et al}. 2003; Sandler \textit{et al}. 2003) that indicate that daily consumption of a 75–80 mg aspirin tablet can lead to a 40–50% decrease in the risk of developing colon cancer (as indicated by a reduction in colo-rectal adenomas). This apparent efficacy of aspirin is also supported by an ability to inhibit the development of aberrant crypt foci in the colon of animals and man (Craven & DeRubertis, 1992; Reddy \textit{et al}. 1993; Mahmoud \textit{et al}. 1998; Shpitz \textit{et al}. 1998, 2003); i.e. early dysplastic pathological lesions that may predict the risk of fulminant colon cancer (Fenoglio-Preiser & Noffsinger, 1999). Aspirin is a prodrug, in that after absorption from the stomach and small intestine it is very rapidly hydrolysed to salicylic acid (2-hydroxybenzoic acid; Fig. 1) by carboxylases in the liver and blood, where it is tightly bound to plasma proteins and widely distributed to all tissues in the body (Needs & Brooks, 1985). The serum half-life of aspirin is only 20 min, whereas that of its major de-acetylated metabolite can range from 2 h to 30 h (Davidson, 1971). Consequently, it is more likely that the anti-carcinogenic effects of aspirin can be ascribed to salicylic acid than to the parent molecule.

Considerable epidemiological evidence suggests that regular consumption of fruit and vegetables decreases the risk of developing several cancers, including colon cancer (Riboli & Norat, 2003). As plants contain natural salicylates they are likely to be present in a wide range of fruit, vegetables, herbs and spices of dietary relevance. Thus, it has been suggested that the recognised effects of consuming fruit and vegetables on lowering risk of colon cancer may be partly attributable to salicylates in plant-based foods (Paterson & Lawrence, 2001). Accordingly, the present brief review considers whether dietary salicylates have a role in health by assessing which types of fruit and vegetables are the richest sources of salicylates and whether they are sufficiently released from the food matrix to modify the key cellular events associated with the pathogenesis of colon cancer.
Salicylates in foods and dietary intakes

Salicylic acid is a plant secondary metabolite largely generated by the phenylpropanoid pathway from trans-cinnamic acid and benzoic acid. It is central to the plant’s systemic acquired resistance system, acting as a signalling molecule for the synthesis of specific proteins that increase resistance to pathogen attack. Other possible roles include the formation of specific proteins that increase cinnamic acid and benzoic acid. It is central to the plant’s transduction pathways from the major urinary metabolite, salicyluric acid.

Fig. 1. Structures of acetylsalicylic acid (aspirin), salicylic acid and the major urinary metabolite, salicyluric acid.

### Evidence for dietary uptake of salicylic acid

Although there is some uncertainty concerning the quantitative estimation of the salicylate content of plant-based foods, evidence for dietary as opposed to pharmaceutical sources is suggested by the detection of salicylic acid and associated metabolites in plasma and urine of individuals not taking aspirin or related preparations (Paterson et al. 1998; Blacklock et al. 2001; Baxter et al. 2002). Moreover, serum (Fig. 2) and urinary concentrations of salicylates for vegetarians are significantly greater ($P<0.001$) than those for omnivores and overlap with those for individuals taking low-dose aspirin (serum salicylic acid concentrations of 0·04–2·47 μmol/l for vegetarians and 0·023–2·540 μmol/l for individuals taking ≤150 mg aspirin/d; Blacklock et al. 2001; Lawrence et al.

### Table 1. Reported values for salicylate content of similar food items

<table>
<thead>
<tr>
<th>Food</th>
<th>Total salicylates (mg/kg) (Swain et al. 1985)</th>
<th>Total salicylates (mg/kg) (Venema et al. 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>5·9</td>
<td>0·02</td>
</tr>
<tr>
<td>Canned apricot</td>
<td>14·1</td>
<td>0·1</td>
</tr>
<tr>
<td>Orange</td>
<td>23·9</td>
<td>0·02</td>
</tr>
<tr>
<td>Strawberry</td>
<td>13·6</td>
<td>0·7</td>
</tr>
<tr>
<td>Currants</td>
<td>30·6–50·6</td>
<td>0·4</td>
</tr>
<tr>
<td>Raisins</td>
<td>66·2–78·0</td>
<td>1·0</td>
</tr>
<tr>
<td>Cucumber</td>
<td>7·8</td>
<td>0·1</td>
</tr>
<tr>
<td>Tomato</td>
<td>5·3</td>
<td>0·4</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>152</td>
<td>23·8</td>
</tr>
<tr>
<td>Curry powder</td>
<td>2180</td>
<td>5·5</td>
</tr>
<tr>
<td>Paprika (hot powder)</td>
<td>2030</td>
<td>3·0</td>
</tr>
<tr>
<td>Rosemary (Rosmarinus officinalis; dried powder)</td>
<td>680</td>
<td>28·4</td>
</tr>
<tr>
<td>Thyme (Thymus vulgaris; dried leaves)</td>
<td>1830</td>
<td>12·8</td>
</tr>
<tr>
<td>Oregano (Oreganum vulgare; dried powder)</td>
<td>660</td>
<td>19·9</td>
</tr>
<tr>
<td>Red wine</td>
<td>3·5–9·0</td>
<td>0·3–7·1</td>
</tr>
</tbody>
</table>
A role for dietary salicylates in the prevention of colon cancer?

A general characteristic of the early stages of cancer development is a disregard by the cell of signals to stop proliferating and differentiating, and the autonomous generation of signals that promote growth. In the case of colon cancer this transition appears to arise from a stepwise accumulation of genetic changes initiated by mutations in the adenomatous polyposis coli tumour suppressor gene that normally blocks the signalling molecule, b-catenin. This step in turn may lead to the formation of complexes with transcription factors that activate numerous genes that stimulate cell proliferation or inhibit apoptosis (Hawk et al. 2004). How dietary salicylic acid may interfere with this process to reduce the risk of developing colon cancer is unclear. One possibility relates to the ability of aspirin to inhibit prostaglandin H2 synthase (PGHS-2) and thus prevent the conversion of arachidonic acid to potentially-tumour-promoting cyclic prostanoids. Unlike its acetylated form, which at pharmacological concentrations may reversibly bind to the active site of PGHS-2 hindering access to arachidonic acid, salicylic acid has little direct effect on the activity of the enzyme (Hare et al. 2003). However, at concentrations observed in the serum of vegetarians (Fig. 2) salicylic acid appears to inhibit PGHS-2 gene transcription, thus inhibiting PGHS-2 mRNA synthesis and promoter activity (Xu et al. 1999; Wu, 2000). It is, therefore, feasible that sufficient salicylates could be obtained from regular consumption of plant-based diets to decrease disease risk by PGHS-2 inhibition, although effects through PGHS-2-independent mechanisms also need to be considered.

Conclusions

Salicylic acid has anti-inflammatory and anti-neoplastic properties, is found in a wide range of fruit, vegetables, herbs and spices, and is absorbed from the food matrix into the circulation of human subjects. It has previously been unclear whether there is sufficient salicylate in foods to contribute to the recognised beneficial effects of a plant-based diet. Janssen et al. (1996) have concluded that the amounts of bio-available salicylates in a ‘normal’ diet are too low to affect disease risk. There is certainly great variability in the reported salicylate contents of foods, which may reflect varietal, environmental and analytical differences between studies. However, serum and urinary concentrations of salicylic and salicyluric acids respectively are greater in vegetarians than in non-vegetarians, and overlap with those for individuals consuming ≤150 mg aspirin/d (Blacklock et al. 2001; Lawrence et al. 2003). Serum concentrations of salicylic acid for vegetarians can be >2000 μmol/ml (Paterson & Lawrence, 2001). This finding suggests that potentially-preventative levels could be achieved by eating salicylic acid-rich foods, particularly as concentrations as low as

Fig. 2. Concentrations of salicylic acid in the serum of non-vegetarians (□) and vegetarians (□) not taking salicylate drugs. Values are medians (—) with ranges represented by vertical bars and 95% CI (■). Median value is significantly greater for vegetarians than that for the non-vegetarians (Mann Whitney U test): ***P<0.001. (Adapted from Blacklock et al. 2001.)
100 nmol/ml can inhibit the transcription of PHGS-2, an enzyme implicated in colon cancer pathogenesis.

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References


