

## Is there a role for dietary salicylates in health?\*

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Acetylsalicylic acid (aspirin<sup>TM</sup>; 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<sub>2</sub>-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<sup>TM</sup> (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 *et al.* 2001). Such epidemiological observations are now corroborated by results from several double-blind randomised placebo-controlled intervention trials (Baron *et al.* 2003; Benamouzig *et al.* 2003; Sandler *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 *et al.* 1993; Mahmoud *et al.* 1998; Shpitz *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

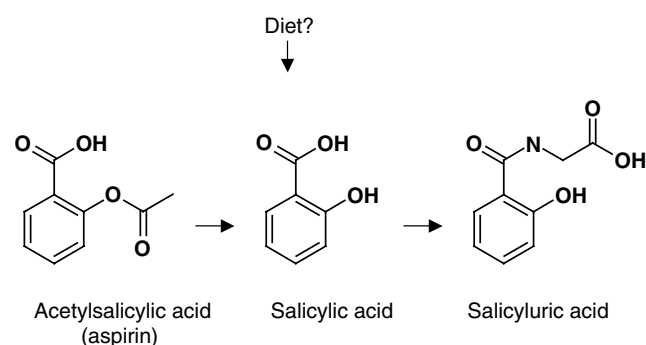
bound to plasma proteins and widely distributed to all tissues in the body (Needs & Brooks, 1985). The serum half-life of aspirin is only 20 min, whereas that of its major de-acetylated metabolite can range from 2 h to 30 h (Davidson, 1971). Consequently, it is more likely that the anti-carcinogenic 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 and whether they are released from the food matrix to allow biological effects. Possible mechanisms by which salicylates may modify the key cellular events associated with the pathogenesis of colon cancer are also discussed.

**Abbreviation:** PGHS-2, prostaglandin H<sub>2</sub>-synthase.

\*This paper is dedicated to the memory of John Paterson.

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

### 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 stimulation of flowering, germination and growth regulation (Pierpoint, 2002). The use of willow (*Salix* spp.) and meadowsweet (*Filipendula ulmaria*) in ancient times to treat a variety of medical conditions through fever reduction and pain relief has been ascribed to their high content of salicylic acid and related compounds (Jeffreys, 2004). However, salicylic acid is also present in plants of dietary relevance, having been detected in many fruits and vegetables (Robertson & Kermode, 1981) since being identified in strawberries at the beginning of the 20th century (Anon, 1903). Despite the ubiquitous presence of salicylic acid in plant-based foods, estimating dietary intakes remains problematical. For example, Swain *et al.* (1985) suggest that a normal diet could provide 10–200 mg natural salicylates/d, in contrast to Radtke *et al.* (1998) and Venema *et al.* (1996) who estimate daily intakes of only 0.1–10 mg and 0–5 mg respectively. The wide range of salicylate values recorded for similar plant-based food items (Table 1) may reflect factors such as varietal differences, shelf-life and growing conditions or even methodology of determination. For example, higher salicylic acid contents of soups made from organically-grown fruit and vegetables compared with corresponding conventionally-reared pesticide-treated products (Baxter *et al.* 2001) may reflect enhanced activation of the systemic acquired resistance response to pathogen insult. There are differences in sensitivities between the various methodologies used for salicylate determination. For example, UV spectrophotometric methods that rely on metal ions binding with phenol and carboxyl groups of salicylic acid (for example, see Nordic Committee on Food Analysis, 1999) could be confounded by reaction with structurally-related compounds, thus leading to overestimation of dietary intakes of salicylic acid (Wood *et al.* 2005). Consequently, values for salicylic acid contents of foods in earlier literature should perhaps be treated with caution. Studies using HPLC with alkaline- or acid-hydrolysis and compound validation by MS are

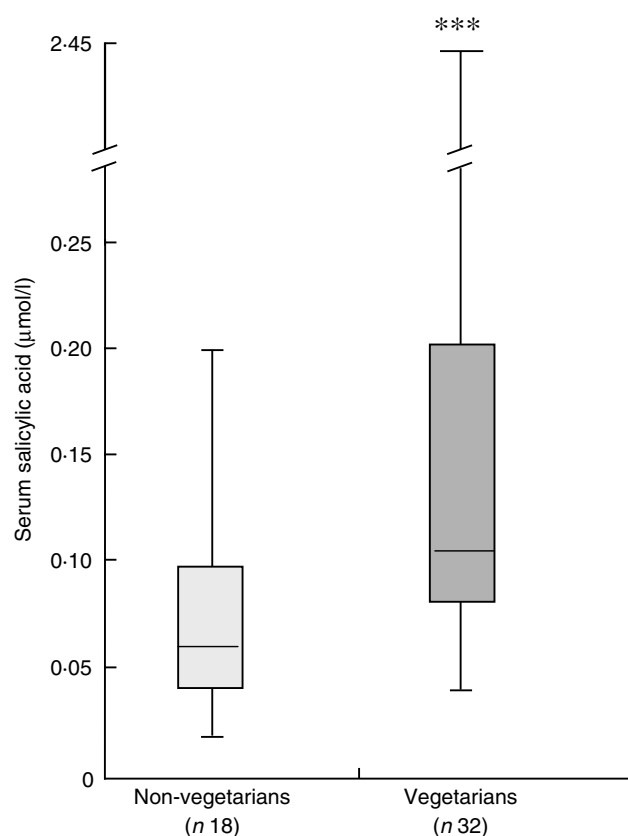
**Table 1.** Reported values for salicylate content of similar food items

Food	Total salicylates (mg/kg) (Swain <i>et al.</i> 1985)	Total salicylates (mg/kg) (Venema <i>et al.</i> 1996)
Apple	5.9	0.02
Canned apricot	14.2	0.1
Orange	23.9	0.02
Strawberry	13.6	0.7
Currants	30.6–50.6	0.4
Raisins	66.2–78.0	1.0
Cucumber	7.8	0.1
Tomato	5.3	0.4
Cinnamon	152	23.8
Curry powder	2180	5.5
Paprika (hot powder)	2030	3.0
Rosemary ( <i>Rosmarinus officinalis</i> ; dried powder)	680	28.4
Thyme ( <i>Thymus vulgaris</i> ; dried leaves)	1830	12.8
Oregano ( <i>Oreganum vulgaris</i> ; dried powder)	660	19.9
Red wine	3.5–9.0	0.3–7.1

preferred for the construction of dietary salicylate databases. Using data from such studies (Swain *et al.* 1985; Venema *et al.* 1996; Baxter *et al.* 2001), together with the application of a semi-quantitative food-frequency questionnaire (Scottish Collaborative Group food-frequency questionnaire version 7.0; Scottish Collaborative Group, 2005) for forty-one individuals (51–71 years), cautiously and provisionally provides estimates for daily intake of 9.9 (range 1–31) mg/d; G McNeill, G Munro and GG Duthie, unpublished results). This value is comparable with intakes of other dietary compounds with phenolic structures such as vitamin E, flavanones and flavonols (Duthie *et al.* 2003). However, salicylate intake is markedly increased by the consumption of foods containing spices (Table 1). For example, substantial amounts of salicylates are found in cumin, paprika and turmeric (16290, 1040 and 3500 mg/kg respectively) and a portion of vindaloo curry (545 g) contains 94 mg salicylate, which is similar to that of a low dose of aspirin (Baxter *et al.* 2005).

### 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 are 0.04–2.47  $\mu\text{mol/l}$  for vegetarians and 0.023–25.40  $\mu\text{mol/l}$  for individuals taking  $\leq 150$  mg aspirin/d; Blacklock *et al.* 2001; Lawrence *et al.*

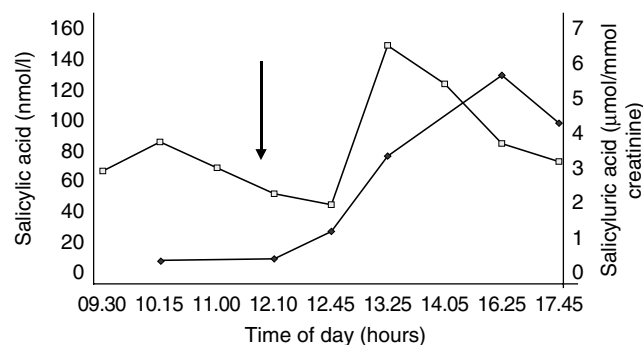


**Fig. 2.** Concentrations of salicylic acid in the serum of non-vegetarians (□) and vegetarians (■) not taking salicylate drugs. Values are medians (—) with ranges represented by vertical bars and 95% CI (□, ■). Median value is significantly greater for vegetarians than that for the non-vegetarians (Mann Whitney U test): \*\*\* $P < 0.001$ . (Adapted from Blacklock *et al.* 2001.)

2003), again suggesting substantial absorption from ingested fruit and vegetables. This finding is supported by the results of a placebo-controlled intervention study (Duthie *et al.* 2005) that show that daily consumption of cranberry juice containing 5 mg natural salicylates is associated with a marked increase in salicylic acid and its major metabolite, salicyluric acid, in urine within 1 week of the intervention. In addition, consumption of a salicylate-rich vindaloo curry clearly results in increases in salicylic acid and salicyluric acid in plasma and urine respectively (Fig. 3).

#### 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,  $\beta$ -catenin. This step in turn may lead to the formation of complexes with transcription factors that activate numerous genes that



**Fig. 3.** Increases in salicylic acid in the serum (□) and salicyluric acid in the urine (◆) of a subject before and after consuming a curry containing 80 mg natural salicylates. ↓, Curry started.

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  $H_2$  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  $\leq 150$  mg aspirin/d (Blacklock *et al.* 2001; Lawrence *et al.* 2003). Serum concentrations of salicylic acid for vegetarians can be  $>2000$  nmol/ml (Paterson & Lawrence, 2001). This finding suggests that potentially-preventative levels could be achieved by eating salicylic acid-rich foods, particularly at concentrations as low as

100 nmol/ml can inhibit the transcription of PHGS-2, an enzyme implicated in colon cancer pathogenesis.

### Acknowledgement

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