JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

J. Agric. Food Chem. **2006,** *54,* 2891–2896

Salicylic Acid Content of Spices and Its Implications

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This work was done to determine the salicylate content of a variety of commonly used spices and to assess whether this potential dietary source of salicylate was bioavailable. Spices, Indian cooked dishes, and blood and urine samples taken after ingestion of a test meal were investigated for their salicylate content using high-performance liquid chromatography with electrochemical detection. The serum salicylic acid concentrations in samples from villagers in southern India were also measured and have been compared with typical European values. Salicylic acid was determined in all spices (up to 1.5 wt %) and cooked dishes. The salicylate content of blood and urine was shown to increase following consumption of the meal, indicating that this dietary source of salicylic acid was bioavailable. Salicylic acid levels in the serum from rural Indians were significantly (median almost 3-fold) higher than values previously measured in Western vegetarians. Chemoprotective aspirin is rapidly hydrolyzed to salicylic acid, and this phytochemical may contribute to the low cancer incidence in rural India.

KEYWORDS: Salicylic acid; spices; salicylates; chemoprotection; colorectal cancer

INTRODUCTION

Many investigations of the relationships among health, disease, and dietary factors have indicated that diets containing a substantial proportion of foodstuffs derived from plants may provide protection against a variety of cancers (*1*). Eastwood (*2*) speculated that secondary metabolites of plants, such as alkaloids and phenolic substances, may contribute to this benefit. Aspirin is used widely to treat cardiovascular disease, and it is manufactured, sold, and taken on a massive scale for the analgesic, antipyretic, and anti-inflammatory actions that its consumption produces (*3*). After ingestion, aspirin undergoes extremely rapid hydrolysis ($t_{1/2}$ = 20 min) to generate salicylic acid ($t_{1/2}$ = 2−4 h), and it is this phenolic acid that brings about its persistent anti-inflammatory effect (*4*). People who had taken aspirin regularly over long periods and who, therefore, have been exposed chronically to the effects of salicylic acid experienced a greatly reduced risk of developing atherosclerosis and colorectal and other soft tissue cancers (*5*−*7*). Moreover, several randomized controlled trials (*8*−*10*) have now shown that regular intake of low-dose aspirin decreases the risk of recurrent colonic adenoma formation in predisposed patients.

Salicylic acid and two of its hydroxylated metabolites were found in the serum of people who had not taken salicylate drugs (*11*). Salicylic acid and, in much higher concentration, its metabolite, salicyluric acid, were also present in the urine of these people, and it was suggested that these compounds are of dietary origin (*12*). Significantly higher concentrations of salicylic acid were found in the serum of vegetarians who had not taken salicylate drugs than in the serum of the people with an unrestricted diet, and the range of concentrations observed in the serum of vegetarians overlapped with that of patients receiving 75 mg of aspirin (acetylsalicylic acid) daily. In addition, larger amounts of salicyluric acid were excreted in the urine of vegetarians than in that of nonvegetarians (*13*). Although the amount of salicylic acid in foodstuffs is controversial (*14*−*17*; see also the Discussion), these findings strongly suggest that foodstuffs derived from plants are major dietary sources of this phenolic acid.

Colorectal cancer is a leading cause of death due to cancer in Western populations (*18*). However, the incidence of this form of cancer is very low in India, particularly in rural parts of the country (*19*, *20*). The population of rural India, with an incidence of colorectal cancer which is one of the lowest in the world (*21*), has a diet that could be extremely rich in salicylic acid. It contains substantial amounts of fruits, vegetables, and cereals flavored with large quantities of herbs and spices. Swain et al. (*14*) have reported that certain herbs and spices are rich in salicylic acid and other salicylates. Most of the foodstuffs consumed in rural India are, moreover, likely to have been prepared from plants that were reared without protection from pesticides, herbicides, and fungicides. Because salicylic acid is a defense hormone of plants, the concentration of which is increased when plants become stressed or infected (*22*−*24*), the plants from which this population's foodstuffs were prepared may have higher contents of salicylic acid than those cultivated

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10.1021/jf058158w CCC: $33.50
Published on Web 03/21/2006

in the West. This proposition is supported by the observation that soups prepared from vegetables that had been grown "organically" had significantly higher contents of salicylic acid than soups prepared from conventially grown ingredients (*25*).

A substantial intake of salicylic acid by rural Indians might account for their very low incidence of colorectal cancer. To examine this hypothesis we set out to (a) establish whether salicylic acid was present in a variety of spices that are used frequently and in considerable amounts in Indian cookery, (b) determine the content of salicylates in these materials, (c) determine the content of salicylates in three prepared Indian cooked dishes, (d) investigate, in a pilot study, whether the salicylates present in the cooked food became bioavailable to man and were absorbed, and (e) determine the concentrations of salicylic acid present in the serum of native Indians who live in a rural area near Chennai (Madras).

MATERIALS AND METHODS

Spice samples were purchased from a retailer of foodstuffs supplying the Indian/Pakistani community in Glasgow or imported directly from Dehli, donated by Dr. R. Srivastava. Samples of a few spices were also purchased from a "health food" retailer in Glasgow. Cooked vegetable dishes that had been prepared according to typical Indian recipes were purchased from a local restaurant. Additional ethical approval was obtained to examine samples of blood that had been obtained from 21 native Indians who had not taken salicylate drugs (10 males, 11 females; median age = 32 years). These volunteers live in a rural area near Chennai and have a diet of locally grown vegetables, grains, and pulses flavored with spices and herbs; they were originally recruited for another study in India (*26*) as representative of that community for health, lifestyle, and nutritional status.

Determination of Salicylic Acid. The content of salicylic acid in spices, cooked vegetable dishes, and serum was determined by using the method of Paterson et al. (*11*). The concentrations of the phenolic acid and salicyluric acid in urine were determined according to the method of Baxter et al. (*12*). For the determination of "free" salicylic acid the following process of extraction was employed. Finely powdered spices (50 mg) and portions of urine (0.5 mL) and serum (0.5 mL) were acidified with 1 mol/L HCl so that they contained finally a concentration of 0.1 mol/L. The acidified mixtures were extracted immediately with two 2 mL volumes of ethyl acetate.

Salicylates in plants are present in three principal forms, the "free" phenolic acid and its carboxylic esters and phenolic glycosides (*22*). For the determination of "total" salicylates in food and spices, the salicylic acid extracted from the materials after their treatment with alkali was determined. Powdered spices (50 mg) were suspended in 2 mL of 2.5 mol/L NaOH. To 1 g of homogenized cooked food was added 2 mL of 2.5 mol/L NaOH. After 24 h at room temperature, 1 mL of 5.3 mol/L HCl was added to the alkaline mixtures so that they contained finally a concentration of HCl of 0.1 mol/L. The acidified mixtures then were extracted with two 3 mL portions of ethyl acetate.

Confirmation of the Identity of Salicylic Acid. After treatment of powdered cumin, paprika, and turmeric (50 mg) with alkali (2 mL of 2.5 mol/L NaOH), acidification of the mixtures, and extraction with ethyl acetate, the acidic and neutral hydrophobic substances removed were separated by HPLC, as described by Paterson et al. (*11*), but with the detector switched off. The compound eluted at the retention time of salicylic acid was removed from the eluates, treated with a solution of acetyl chloride in methanol to achieve methylation, and examined by using gas chromatography−mass spectrometry (GC-MS) (*27*).

Assessment of Bioavailability. Blood and urine samples were obtained from a human volunteer (Caucasian male, aged 46 years) who had not taken salicylate drugs and who had fasted for 10 h. The volunteer then consumed 545.3 g of a cooked vegetable dish that the aliquot assay showed to contain 94.03 mg of total salicylates. At intervals of 1 h, blood was removed, and the urine he excreted was collected at ∼2 hourly intervals over the next 6.5 h. The concentrations of salicylic acid in the blood and of salicylic acid and salicyluric acid in the urine were determined as described above.

Table 1. GC-MS of Salicylic Acid Treated with Acetyl Chloride in Methanol and a Compound Extracted from Cumin, Paprika, and Turmeric Isolated by HPLC and Treated with Acetyl Chloride in Methanol

		principal ions in spectrum	
compound	t_R (min)	mass[a]	relative abundance
salicylic acid	7.35	65	39
		92	82
		120	100
		152*	36
substance extracted from cumin	7.45	65	36
		92	82
		120	100
		152*	37
substance extracted from paprika	7.48	65	36
		92	82
		120	100
		152*	35
substance extracted from turmeric	7.45	65	38
		92	81
		120	100
		152*	36

[a] Asterisks indicate the molecular ion. The molecular mass of methyl salicylate is 152.1.

RESULTS

Our methods for the electrochemical (oxidative) determination of salicylic acid in urine (*12*) and in food, spices, and blood (*11*) rely upon separating by HPLC (with programs of stepwise elution) the hydrophobic substances that were extracted into ethyl acetate from strongly acidic aqueous phases. The substance extracted from cumin, paprika, and turmeric that was eluted at the retention time of salicylic acid was removed from the eluates, treated with an esterifying reagent, and examined by using GC-MS. The derivative formed had a gas chromatographic retention time and a mass spectrum identical to those of the methyl ester of salicylic acid (**Table 1**).

The contents of total salicylates and salicylic acid in the spices examined are shown in **Table 2**. For comparison, the contents of these substances reported by previous authors are also included. Our results are distinctly different from most of those reported in the past, and they show very clearly that the typical diet of a rural Indian potentially contains a very large amount of salicylates which could be converted into salicylic acid in vivo. Red chilli powder, paprika, and turmeric contained total salicylates in excess of 0.1% (by weight), and cumin, an ingredient used in very large amounts in Indian cookery, had a content of >1.5% (by weight), most of which was the phenolic acid itself. In addition, the contents of salicylic acid in several batches of cumin, also obtained from the retailer supplying the Glasgow Asian community, were estimated by using a much less sensitive and less specific colorimetric procedure following thin-layer chromatography (TLC) separation. The substances extracted into ethyl acetate from TLC-separated suspensions of cumin (100 mg) in 1 mol/L HCl were redissolved in 1 mL of 1% $NaHCO_3$, and portions of these solutions were treated with a reagent containing Fe(III) in dilute HCl. The absorbance of the colored solutions produced was measured at 527 nm [λ_{max} of the Fe(III)/salicylic acid complex]. These contents ranged from 1084 to 1521 mg of salicylic acid/100 g of cumin.

The contents of total salicylates in three conventionally prepared vegetable dishes were determined. One dish (500 g of food) that was prepared according to a Madras style contained 20.3 mg; another (549 g of food), cooked according to a spicier

Table 2. Content of Total Salicylates (TS) and Salicylic Acid (SA) in Various Spices (Milligrams per 100 g)

	source 1[a]		source 2[b]		reported previously[c]	reported previously[d]		reported previously[e]	reported previously[f]
spice	TS	SA	TS	SA	TS	TS	SA	TS	TS
asafoetida	3.8	0.5							
cardamom (black)	27.0	<0.1							
cardamom (green)	13.2	<0.1							
chilli powder (red)	146.6	3.0							
cinnamon	64.2	4.7	12.0	2.9	15.20	1.0		12.20	2.4
cloves	2.5	0.4			5.74	2.0		trace	
coriander	2.7	0.8			0.20	0.1	trace		
cumin	1629.4	1474.7	980.0	744.9	45.00				
fennel	2.0	<0.1			0.80			0.048	
fenugreek	0.1	<0.1			12.20			0.298	
garlic	5.6	<0.1			0.10			0.305	
ginger	3.5	0.1			4.50				
mustard	26.2	5.2			26.00	0.4	0.2		trace
paprika	104.3	3.0	104.7	10.8	203.00	0.7			0.3
pepper seeds (black)	9.0	7.3			6.20	0.3			0.3
tamarind	9.6	1.1							
turmeric	350.5	23.3	288.9	15.3	76.40	1.7			

[a] Source 1, retailer supplying the Indian/Pakistani community in Glasgow; asafoetida, fennel, and tamarind were imported from India. [b] Source 2, health food shop. [c] Swain et al. (*14*). [d] Herrmann (*33*). [e] Variyar and Bandyopadhyay (*16*). [f] Venema et al. (*15*).

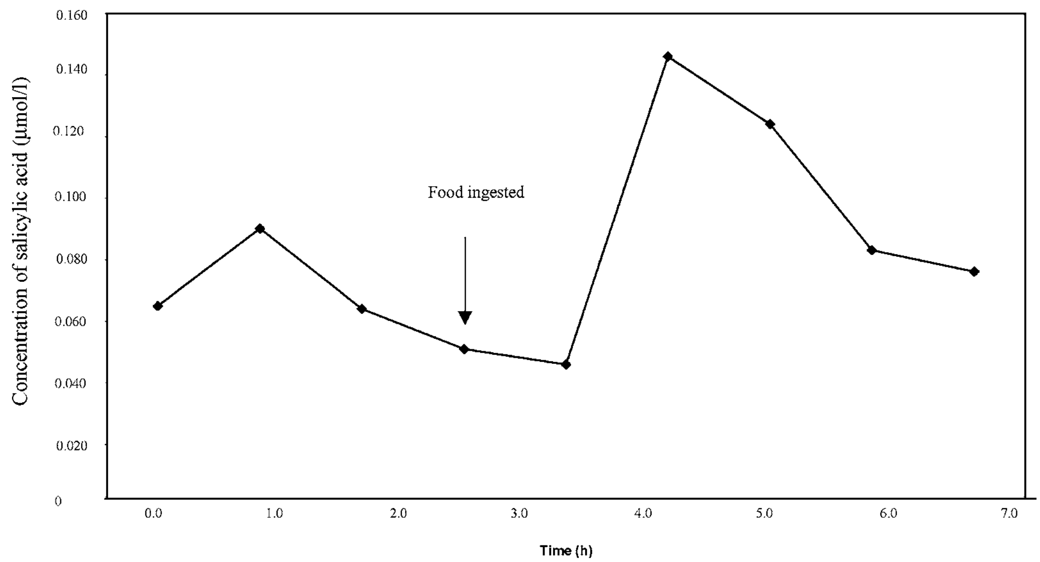

Figure 1. Concentration of salicylic acid in the serum of a volunteer before and after consumption of food rich in salicylates.

Vindaloo recipe, contained 85.9 mg. To determine if the salicylates in this type of cooked food were bioavailable, a volunteer consumed 545.3 g of vegetable Vindaloo in a meal that contained 94.03 mg of total salicylates. Within 1 h of consuming the food, the concentration of salicylic acid in the volunteer's serum increased rapidly and reached a maximum value after ∼1.5 h (**Figure 1**). During the following 1.5 h the concentration of salicylic acid in the serum declined steeply and returned to the range of concentrations encountered prior to dietary exposure to the salicylates ∼5 h after consumption of the food (**Figure 1**). Within 1.5 h of consumption of the food, when the concentration of salicylic acid in serum was near its maximum, salicyluric acid, derived from the salicylates in the food, began to appear in the urine (**Figure 2**). During the following 4 h the amount of the conjugated metabolite excreted increased steadily, and the rate of its excretion had not returned to the value observed prior to consumption of the food even after 6.5 h. Salicylic acid derived from the food ingested appeared in the urine when the rate of excretion of salicyluric acid was at its highest, and it was elevated above the rate of excretion prior to exposure even after 6.5 h. From the cumulative amounts of salicylic and salicyluric acids excreted that were in excess of those predicted from the rates of excretion prior to the test meal, it was calculated that at least 3% of the salicylates in the food had become bioavailable and been absorbed.

The concentrations of salicylic acid found in the serum of individual native rural Indians were not distributed normally; the median values and the ranges found are displayed in **Table 3**. Included, for comparison, are the median concentrations and ranges of the phenolic acid present in the serum of a group of vegetarians of predominantly European descent living in Dumfries and Galloway and a group of nonvegetarians from Dumfries we reported earlier (*28*). The median concentration in the serum of the Indians was significantly higher (∼2.5−3.5-fold higher) than those found in the sera of the other groups ($p < 0.001$ against the vegetarians and $p < 0.001$ against the nonvegetarians; Mann−Whitney *U* tests).

DISCUSSION

In recent years claims have been made for many components of plant cells as being primarily responsible for the health-giving properties of a diet rich in plant foods. The evidence presented

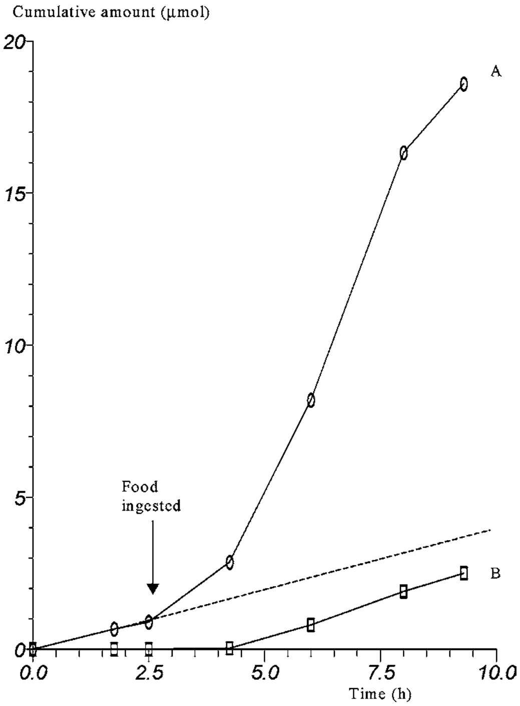

Figure 2. Amount of salicylic and salicyluric acids excreted in the urine of a volunteer before and after consumption of food rich in salicylates.

Table 3. Concentration of Salicylic Acid in the Serum of Various Groups of People[a]

group	no. in group	concn of SA (µmol/L) median	concn of SA (µmol/L) range
South Indians[b]	21	0.263	0.05–0.64
vegetarians[c]	37	0.110	0.04–2.47
nonvegetarians[d]	39	0.070	0.02–0.20
aspirin takers[e] (75 mg/day)	14	10.030	0.23–25.40

[a] The values observed for comparison vegetarians, nonvegetarians, and the people receiving aspirin were determined by Blacklock et al. (*28*). Concentration in the serum of vegetarians was significantly higher than that in serum of nonvegetarians ($p < 0.0001$). [b] Native rural Indians, non-aspirin takers, traditional Indian diet (10 males, 11 females, median age = 32 years). [c] Buddist monks in retreat at Samye Ling Monastry, Eskdalemuir, southwestern Scotland, non-aspirin takers, strict vegetarian diet (24 males, 13 females, median age = 41.7 years). [d] General population of southwestern Scotland, non-aspirin takers, unrestricted diet (21 males, 18 females, median age = 40.5 years). [e] Patients, taking aspirin, drawn from General Practitioner's lists in southwestern Scotland, unrestricted diet (7 males, 7 females, median age = 58.9 years).

in this paper does, taken together with the published efficacy and accepted lability (*29*) of its acetyl ester, aspirin, lay the foundation for salicylic acid as an important phytochemical. We suggest it may well contribute to the low incidence of colon cancer in subjects with a predominantly vegetarian diet flavored with regularly used spices.

Our results confirm the presence of, and enhance prior estimates of, salicylic acid content in a variety of frequently, often copiously, used spices. Sampled cooked dishes were shown to contain pharmacological amounts of salicylic acid, a proportion of which was bioavailable as shown by the significant rise in serum concentration (peak concentration more than double baseline) and the increased cumulative urinary metabolite excretion (∼20-fold increase) in the hours after a test meal.

Most suggestive, in relation to results of prospective intervention studies using low-dose aspirin (*5*−*7*), is the significantly higher median serum salicylic acid concentration in the small group of rural Indians compared with published results in subjects *not* taking aspirin. The median level determined was more than double that observed in a Western vegetarian population whose results, we have previously shown (*28*), overlapped significantly with those from patients on low-dose aspirin.

The major strength of the work presented here is the robustness of the extraction processes and assays (*11*, *12*, *25*) used to measure salicylic acid and its metabolites. One potential weakness is that only three cooked meals were analyzed and that salicylic acid levels after only one test meal are shown. However, published results show salicylic acid absorption from other food sources with known salicylic acid content (*30*, *31*), albeit with the anticipated low bioavailability from a mixed diet (*31*).

Our results on the salicylic acid content of spices are comparable, where comparison is possible, with those of Swain et al. (*14*) save in the cases of cumin and turmeric. Different species of the plants might help to explain the very high content of salicylic acid in our cumin and turmeric, but the enhanced recovery of total salicylate from the spice by our methodology is the likely major reason for the discrepancy in the case of turmeric. The acknowledged (*14*) possible imperfect separation in Swain's chromatography system should, in theory, have enhanced their estimate for cumin given the use of a relatively nonspecific UV detector. Although it might appear to be unlikely that the difference in estimates for cumin could arise from extraction (as 80% efficiency was reported for added salicylic acid in both methods), Swain used 50 g of material and 200 mL of diethyl ether for the extraction step. Therefore, the >30-fold amount of material versus organic solvent may well be a factor in explaining the different estimates. The entirely different separation/detection system also reported here—using TLC and colorimetric detection—gave a salicylic acid content result for cumin in agreement with our more sensitive and specific assay, which was itself corroborated by the GC-MS data. Another factor that may contribute to the difference between Swain's and our own estimate for cumin is the likelihood of interbatch variability in the salicylic acid content of the spice.

Whereas our results for spices are, cumin apart, compatible with those reported by Swain (*14*), they are, where comparison is possible, considerably higher than reported by other workers (*15*−*17*) who used fluorescence detection after HPLC based on the method of Venema (*15*). That method should, from published details, achieve reasonably satisfactory chromatographic separation of salicylic acid, but we suspect the isocratic elution used led to potential coelution of compounds that interfered by quenching to decrease the intensity of fluorescence emission with the sensitivity of the fluoresence detector used. It is revealing that Janssen's (*31*) estimate of dietary salicylate intake from salicyluric acid excretion was compatible only with Swain's (*14*) data on food content. Although Janssen emphasizes, in discussion, the low overall bioavailability set against the total estimated salicylate content of diet, that finding is not unexpected from whole food with the salicylic acid contained in complex matrices. There is, it is well recognized (*29*), great variability in the extent to which aspirin is absorbed: the bioavailability of salicylic acid from food sources is likely to be much more variable still.

We have established that salicylic acid is present in spices and in a cooked meal prepared using a mixture of the same and that this salicylic acid is absorbed, but the question arises whether the extent of its bioavailability is sufficent to provide a chemoprotective effect against colorectal cancer. Giovannucci

(*32*) concluded low-dose (81 mg/day) aspirin taken over one or two decades was sufficient, and chronic exposure to aspirin 75 mg per day [containing 56 mg of salicylic acid at ~60% bioavailability (*29*)] has been shown to provide protection against colorectal cancer. More recently, reported prospective intervention studies using aspirin (*8*−*10*) at 81−325 mg/day showed efficacy in the prevention of colonic adenoma recurrence. The threshold dose for efficacy is not yet known, but in vitro very low concentrations of salicylic acid suppressed Cox 2 transcription (*4*) and there was a distinct overlap in serum salicylic acid levels from patients on 75 mg of aspirin/day and vegetarians (*28*). Approximately a fourth of the vegetarians in that study had serum salicylic acid concentrations above the lowest level observed in the aspirin-taking patients. In keeping with the saturable conjugation of salicylic acid, there were comparable urine levels of that compound in aspirin takers and vegetarians (*13*). The absence of a dose−response correlation in one prospective study using aspirin (*8*) led to the suggestion that a low threshold dose may be required for chemoprotection. It is not inconceivable, moreover, that luminal concentrations of salicylic acid pertaining during food digestion/absorption will be relevant to the chemoprotective action of salicylic acid in colon cancer.

It is, we think, increasingly unlikely that salicylic acid levels are simply a marker for plant food intake. Two major pieces of work are required to further advance our hypothesis that salicylic acid is the link between aspirin, diet, and the prevention of colorectal cancer (*34*). The efficacy of feeding salicylic acid to animals at risk of colon cancer and related pathology needs to be established; preliminary results of this approach are encouraging. Finally, it is necessary to show that in individuals salicylic acid exposure predetermines their future risk of colon cancer.

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Received for review October 11, 2005. Accepted January 24, 2006.

JF058158W