

## Controversies surrounding coumarin in cassia: the good, the bad and the not so ugly

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*In the world and Indian market, the cinnamon available is not the true cinnamon (*Cinnamomum verum*), but its avatar, viz. the fake cinnamon (*C. cassia*). The latter contains coumarin, which at high doses, has been found to cause hepatotoxicity, carcinogenesis and liver/lung tumours in rodents. However, such ill effects in humans due to coumarin are rare and only associated with high doses. A toxicological reevaluation of coumarin aimed to derive scientifically founded maximum limits is imperative.*

Cinnamon, from the genus *Cinnamomum* is obtained from the inner bark of several trees and is the second most important spice (next to black pepper) sold in the world markets. Though widely used as a spice, cinnamon has unique medicinal properties due to various components such as cinnamaldehyde, eugenol, cinnamyl acetate and cinnamyl alcohol, in addition to a wide range of other volatile substances including safrole, coumarin and cinnamic acid esters<sup>1</sup>.

The cinnamon commonly sold in Europe is cassia or cassia cinnamon (*Cinnamomum cassia*, syn. *C. aromaticum* or *C. burmannii*) and not the more expensive and rarer true cinnamon (*C. verum* J. S. Presl., syn. *C. zeylanicum*). To quote the Wikipedia entry, Cassia cinnamon's flavour is less delicate than that of true cinnamon; for this reason, the less expensive cassia is sometimes called 'bastard cinnamon' or 'fake cinnamon'. Even in the Indian market what is primarily available in the name of *C. verum* is its alter ego, namely *C. cassia*. In Europe, the United States, and Canada, *C. burmannii* or Indonesian cassia has replaced the more expensive true *C. verum* and more than 90% of the 'cinnamon' imported to the US during the last five years was *C. burmannii*<sup>2</sup>.

Be that as it may, the fear surrounding cassia is not due to its less delicate fragrance or its taste or appearance, but is largely due to the presence of 'coumarin', a compound that has been implicated to cause certain undesirable effects in clinical trials, especially on rodents.

### Coumarin

Coumarins, are a class of compounds that contain a 1,2-benzopyrone skeleton. They are chemical compounds, which occur either free or as glycoside, naturally

in many plants, including vegetables, spices, fruits and medicinal plants<sup>3</sup>. Coumarin (2H-chromen-2-one) (1), the simplest member of this class has been used as a flavouring agent in food, alcoholic beverages and tobacco<sup>4</sup>. It is also widely used in the perfumery, soap and cosmetic industries and as a valuable odour fixative. It also has several other unrelated industrial uses. As an additive in perfumes and fragranced consumer products, concentration of coumarin ranges from <0.5% to 6.4% in fine fragrances to <0.01% in detergents<sup>5</sup>.

Coumarin concentrations in plants range from <1 mg/kg in celery, 7000 mg/kg in cinnamon and up to 87,000 mg/kg in cassia<sup>5</sup>. Coumarin concentrations are much higher in *C. cassia* than in *C. verum*. For example, levels were as low as 190 mg/kg in *C. verum* and between 700 and 12,200 mg/kg in *C. cassia*<sup>6,7</sup>. In one detailed analysis, powdered cassia bark contained 1250–1490 mg/kg of coumarin and its essential oil contained 4370 mg/kg of coumarin. Conversely, *C. verum* bark powder registered 2.4 mg/kg and its essential oil 40 mg/kg of coumarin<sup>8</sup>. However, coumarin levels in *C. cassia* can vary widely even within a single tree for instance between stick, bark and powder<sup>9</sup>. In the sticks, coumarin level<sup>9,10</sup> was found to range between 9,900 and 12,180 mg/kg, whereas the content in ground cinnamon ranged between 1740 and 7670 mg/kg (ref. 9), 2650–7017 mg/kg (ref. 11) and 5–3094 mg/kg (ref. 12). Overall, coumarin levels have been consistently reported to be at least 1500 mg/kg in cassia powder and <1000 mg/kg in cassia sticks<sup>13</sup>. According to the German Federal Institute for Risk Assessment, 1 kg of cassia powder contains approximately 2100–4400 mg of coumarin. This means 1 teaspoon of cassia cinnamon powder will contain 5.8 to 12.1 mg of coumarin. Such

high levels of coumarin in cassia have raised serious safety concerns<sup>2,7,14</sup>.

### The good

The good news about coumarin is that it has been used to treat patients with advanced cancer or to prevent recurrence of serious cancers in a number of controlled clinical trials<sup>15</sup> and published clinical trials of isolated coumarin have rarely cited hepatotoxicity, supporting the concept that most people are not susceptible to these effects, at least at usual doses. Conversely, at low doses (typically 7–10 mg/day), coumarin has been used as a 'venotonic' to promote vein health and small venule blood flow. Additionally, coumarin has been used clinically in the treatment of high-protein lymphedema of various etiologies<sup>16,17</sup>. Several clinical studies of 400 mg/day of coumarin reported success in treating lymphedema following mastectomy or other surgeries<sup>18–20</sup>. In isolation, or in combination with cimetidine, coumarin has undergone clinical trials for the treatment of several types of malignancies in humans, including clinical trials in the US, Europe and Japan as an antineoplastic for the treatment of lung, prostate and kidney<sup>21–24</sup>. As an antineoplastic, daily dose regimens have been as high as 7 g/day.

### The bad

The bad effects of coumarin were evidenced in clinical trials wherein it caused liver tumours in rats and mice and Clara cell toxicity and lung tumours in mice indicating possible carcinogenicity of this compound. Since then, an extensive body of research has focused on understanding the etiology of these tumours. Data from these studies support a conclusion that

coumarin is not DNA-reactive and that the induction of tumours at high doses in rodents is attributed to cytotoxicity and regenerative hyperplasia. While, scientific data on coumarin showed a non-genotoxic carcinogenic effect, it also showed that a subgroup of individuals was sensitive to hepatotoxic effect from coumarin<sup>9</sup>. Evidence of such hepatotoxic effects of this compound in animal models led the US Food and Drug Administration to ban coumarin as a food flavouring agent<sup>25</sup>. Besides, coumarin is often conflated with coumadin (or dicoumarol or Warfarin), which is a blood thinner. However, this fear is unfounded and there is no evidence that suggests anti-coagulant effects from naturally occurring coumarin. Also, the International Agency for Research on Cancer (IARC) has classified coumarin as belonging to group 3 ('not classifiable as to its carcinogenicity in humans') because no epidemiological data relevant to the carcinogenicity of coumarin were available and there was only limited evidence in experimental animals for the carcinogenicity of coumarin.

However, based on the non-observed-adverse-effect level (NOAEL) for hepatotoxicity in animal experiments, the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) established a tolerable daily intake (TDI) of 0.1 mg/kg body weight. Subsequently, in 2006, the German Federal Institute for Risk Assessment (BfR) confirmed this value using human data from coumarin administration as a medicinal drug<sup>26</sup> and set an upper limit of 0.5 mg/kg body weight for coumarin in Germany (i.e. for a 75 kg male adult, the TDI would be 37.5 mg of coumarin; [http://www.bfr.bund.de/cm/349/frequently\\_asked\\_questions\\_about\\_coumarin\\_in\\_cinnamon\\_and\\_other\\_foods.pdf](http://www.bfr.bund.de/cm/349/frequently_asked_questions_about_coumarin_in_cinnamon_and_other_foods.pdf); accessed on 29/01/2014).

The European Parliament and Council also evaluated the maximum coumarin limits and in 2008, the European Regulation (EC) No. 1334/2008 was enacted with the following maximum limits for coumarin: 50 mg/kg in traditional and/or seasonal bakeryware containing a reference to cinnamon in the labelling, 20 mg/kg in breakfast cereals including muesli, 15 mg/kg in fine bakeryware, with the exception of traditional and/or seasonal bakeryware containing a reference to cinnamon in the labelling, and 5 mg/kg in desserts. For foods and beverages in

general, the maximum level was set at 2 mg/kg, with the exception of special caramels and alcoholic beverages for which the maximum level set was 10 mg/kg. Another important regulation was that coumarin should not be added as such to food and beverages and it may only be contributed through the use of natural flavourings provided that the maximum levels in the final product ready for consumption are not exceeded. Nevertheless, the ongoing human exposure to coumarin has resulted in a significant research effort focused on understanding the mechanism of coumarin-induced toxicity/carcinogenicity in rats and mice and its human relevance.

### The not so ugly

Although negative effects of coumarin have been observed on rats and mice in clinical trials, such effects in humans following coumarin exposure are rare, and only associated with high doses, especially oral therapies. Therefore, things are *not so ugly* as far as coumarin is concerned though side effects such as mild dizziness, diarrhea, or (with very high doses) vomiting have been reported following coumarin treatment. The only potentially serious side effect reported is an alteration in liver function. Several authors have reported on the incidence of hepatotoxicity in patients given high-dose (50–7000 mg/day) coumarin therapy. Earlier trials indicated that doses up to 7000 mg/day were well-tolerated, except for nausea and vomiting<sup>26</sup>. Elevated liver function tests due to probable causes other than hepatotoxicity in patients treated with very high doses of coumarin have been reported in several trials. However, their liver function returned to normal without adverse effects following cessation of coumarin therapy<sup>27,28</sup>. Besides, no alteration in hepatic enzymes has been reported for any patients receiving coumarin by dermal application<sup>20</sup>. Similarly, there are no reports of adverse liver effects in humans administered dermal doses of coumarin even at clinical doses for extended periods of time.

In cases where administered oral doses of coumarin for therapeutic purposes have affected the liver in humans, it is apparent that it has consistently taken several weeks or months to induce a change of hepatic enzymes; and there has

been little consistency in the oral dosing regimen that may result in altered hepatic function. Hepatotoxicity in humans exposed to bolus oral doses appears to be an idiosyncratic response that is potentially influenced by multiple outside and inherent factors<sup>29</sup>. Interestingly, normal liver function could be restored by cessation of treatment, although in some cases the liver function returned to normal despite continued coumarin administration. Similar to hepatotoxicity, no carcinogenic responses to coumarin have been reported in humans and though readily absorbed through the skin, no toxicity has been reported following dermal exposure to coumarin even at clinical doses for extended periods of time.

In case of humans, exposure is through the diet and from its use in personal care products. Dietary contributions of coumarin are estimated to be 0.02 mg/kg/day (ref. 5). With coumarin-containing foods only accounting for 5% of total solid foodstuffs, the maximum daily intake for a 60-kg consumer would be 1.2 mg coumarin/day. Also, when used in cosmetic products for its fragrance, the realistic daily exposure would be 2.289 mg/kg/day or 0.04 mg/kg/day for a 60-kg consumer<sup>5</sup>. It is, therefore, presumed that the total daily human coumarin exposure from the diet and cosmetics would be 0.06 mg/kg/day. This exposure level is over 2000 and 3000 times lower, respectively, than those which produce liver tumours in rats<sup>30</sup> and lung tumours in mice<sup>31</sup>.

Besides, it is to be noted that such acute, chronic and carcinogenic effects of coumarin in the rat and mouse are based on long-term studies that have been performed at maximally tolerated doses, with coumarin intakes over 4500 times the estimated human exposure from the diet and cosmetic products. Preliminary results from early studies indicated that coumarin was a toxin, but it has been shown since, that the rat is a poor model to compare with the human for this particular metabolism<sup>32</sup>. Moreover, these studies demonstrate that threshold doses exist for coumarin-induced toxicity and carcinogenicity, below which such effects are not observed.

Besides, studies have shown differences in coumarin metabolism in primates and other animals. The species-specific target organ toxicity is shown to be related to the pharmacokinetics of

coumarin metabolism, with data showing rats to be particularly susceptible to liver effects and mice to be particularly susceptible to lung effects. In contrast to the rodent model, the major metabolic pathway in primates does not result in hepatotoxic metabolites<sup>5,29,33</sup>. Human clinical data indicated that a majority of people were less sensitive to coumarin than the rodent models used to study the toxic effects of this compound. Therefore, coumarin toxicity appears to be species-specific and non-genotoxic and is directly related to specific metabolism/detoxification capabilities following bolus oral exposure<sup>29</sup>. The TDI value in humans can only be reached by simply consuming staple foods containing coumarin or can be exceeded by consuming high doses of cassia in its various forms over a prolonged period of time. It is apparent that under normal circumstances, exposure to coumarin through cassia-containing foods will never reach the levels that can be considered toxic.

There are claims that cinnamon bark or its aqueous extracts have antidiabetic activity and there are also a number of cinnamon-based dietary supplements in the market that promise lowering of glucose and lipid levels in type II *Diabetes mellitus*, a severe chronic disease. However, such claims are circumspect and inconclusive<sup>34,35</sup>. The high coumarin levels in such medications/supplements indicate that the manufacturers use the fake cinnamon (*C. cinnamom*) and not the true cinnamon (*C. verum*). They recommend a daily long-term dose in the gram range although the safety of a dose of this amount has not yet been demonstrated. Also, taking cinnamon powder for lowering blood sugar levels can exceed the tolerable daily intake of 0.1–0.5 mg coumarin per kg body weight established by the AFC and BfR. Therefore, daily intake of ground cassia bark or its aqueous extracts is not advisable because safety assessment of coumarin-containing foods is complicated as a toxicological basis for the maximum limits appears to be missing. Besides, ingesting substantial amounts of coumarin on a daily basis may pose a health risk to individuals who are more sensitive to this compound<sup>36</sup>. Published results suggest that there is still a need for a continued regulation of coumarin in foods. While, it is too early

to malign cassia for all the ill effects of coumarin, it appears that a toxicological re-evaluation of coumarin with the aim to derive scientifically founded maximum limits is imperative.

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