FIG EXTRACT

SYNONYMS

Fig fruit
Ficus carica

CHEMICAL STRUCTURE

Ill defined (complex mixture)

CHEMICAL FORMULA

A review of the literature by De Vincenzi *et al* (1989) produced one reference with quantitative levels of volatile components of fig. The major volatiles present in fresh fig are ethanol [144 mg/kg], acetaldehyde [7-40 mg/kg], ethyl acetate [9mg/kg] and methanol [5 mg/kg]. Forty six other volatiles are listed, occurring at levels ranging from 0.01 – 1.8 mg/kg. These include 8 alcohol's, 17 carbonyls/aldehydes, 7 carbonyls/ketones, 1 hydrocarbon, 5 acids, 3 esters, 1 furan (0.05 mg/kg), 1 base and 2 epoxides. [De Vincenzi *et al*., 1989]

IDENTIFIER DETAILS

CAS Number	:	90028-74-3 (68916-52-9)
CoE Number	:	198
FEMA	:	-
EINECS Number	:	289-868-1
E Number	:	-

SPECIFICATIONS

Melting Point: Ill defined (complex mixture)
Boiling point: Ill defined (complex mixture)

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
-	-	-	-

FDA Status:

Section Number	Comments
-	-

HUMAN EXPOSURE

Natural Occurrence: Immense genus of tropical trees and shru bs distinguished by their peculiar fruit [*syconium*] consisting of a pear shaped or globose receptacle enclosing numerous diclinous flowers. Fairly large trees having numerous branches, large leaves, and edible fruits [Fenaroli, 1995]. Naturally occurring fruit [Opdyke., 1979]. It is the edible part of the fig tree [*Ficus carica*] [Dechamp *et al*., 1995].

Reported Uses: The dried pulp reduced to powder may be used as a carrier for powder flavours. The tincture and extract may be used for liquors, pastes, and sometimes tobacco flavouring [Fenaroli, 1995].

TOXICITY DATA

Carmines (2002), Rustemeier *et al* ., (2002), Roemer *et al* ., (2002) and Vanscheeuwijck *et al.,* (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen (Ames assay) a mammalian cell cytotoxicity assay (neutral red uptake), determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including fig juice concentrate at levels up to 796 ppm, "did not increase the overall toxicity of cigarette smoke " [Carmines *et al* ., 2002].

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of f lavourings and casings, were added in different combinations to reference cigarettes. The addition of fig extract at 11,700 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in v itro* micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

Renne *et* al., (2006) evaluated the effects of tobacco flavouring and casing ingredients on both mutagenicity, and a number of physiological parameters in Sprague-Dawley (SD) rats. Test cigarettes containing a mixture of either 165 low-uses or eight high-use flavouring ingredients which included fig at 2000 ppm, were compared to a typical commercial tobacco blend without flavouring ingredients. The Ames assay (TA 98, 100,102, 1535 and 1537 ±S9) did not show any increase in Mutagenicity from "low" or "high" cigarette smoke condensate compared to the control. SD rats were exposed by nose-only inhalation for 1h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13wk of exposure or following 13 wk of reco very from smoke exposure. Biological endpoints assessed included; clinical appearance, body weight, organ weights, and lesions (both gross and microscopic). The results of these studies did not indicate any consistent

differences in toxicological effect s between smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes [Renne *et al.,* 2006].

In Vivo Toxicity Status

Dermal toxicity

A skin prick test on 3 patients suffering from facial exanthema and edema [patient 1] or orolaryngeal itch and edema [patients 2 & 3] following ingestion of figs revealed that patients 2 & 3 were sensitive to fresh Figs and to *Ficus benjamina* leaves [Hemmer *et al*., 1999].

A mouse skin painting study by Gaworski *et al.* , (1999) investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including fig juice concentrate at 5 ppm. The authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate". It should be noted that the cigarettes contained a typical American blend humectant and sugar component [*i.e.* glycerine 20,000 ppm, propylene glycol at 24,000 ppm, and brown invert sugar at 24,000 ppm] [Gaworski *et al*., 1999].

Inhalation toxicity

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90 day nose-only smoke inhalation study in rats [Vanscheeuwijck *et al.* , 2002]. These ingredien ts included fig juice concentrate at 796 ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study along with that from a number of other biological and chemical studies indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck *et al*., 2002].

When tested at 5 ppm in cigarettes, in a 13-week inhalation study, the presence of fig juice concentrate "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats. "[Gaworski *et al.* , 1998]. However, it should be noted that the cigarettes had been spiked with a number of flavour ingredients in combination prior to smoking, and they contained a typical American blend humectant and sugar component (*i.e.* glycerine 20,000 ppm, propylene glycol at 24,000 ppm, and brown invert sugar at 24,000 ppm) [Gaworski *et al*., 1998].

The addition of fig extract at 11,700 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of fig extract to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004]

Other relevant studies

Epidemiological studies have suggested that intake of fresh fruits reduces cancer risk, particularly for lung, stomach and pancreas. It has been suggested that this anticarcinogenic effect may be related to the capacity for fruits to induce phase enzyme s. In a simple screening study using a cultured normal hepatocyte cell line [RL34, which is sensitive to phase inducers], a number of common fruits, including fig, were investigated to determine their glutathione-S-transferase [GST] induction potencies . Fig samples were extracted using ethyl acetate and the extract was then dissolved in dimethylsulfoxide to give a final concentration of 25 g/ml in the assay. GST activity was measured using 1-chloro-, 2 4-dinitrobenzene as a substrate for conjugation a nd the protein level measured by western blotting. The fig extract was found to slightly induce GST activity [1.37-fold increase]. The authors point out however that phase enzymes can also inactivate cytoplastic and other cancer controlling drugs [Nakamura *et al*., 2000].

Several studies, including the study by Deneo-Pellegrini *et al.,* (1996) have demonstrated a reduced risk of colorectal cancer, dependent upon total consumption of vegetables and fruit. In this instance, a case-control study was carried out in Uruguay. Dietary patterns of individuals prior to diagnosis or symptoms of cancer were assessed in detail through the use of a food frequency questionnaire. A reduction in risk for total vegetable intake and total fruit intake were noted [Deno-Pellegrini *et al*., 1996].

A similar study for laryngeal cancer in Uruguay also demonstrated a reduction in risk associated with an increase in fruit and vegetable consumption [De Stefani *et al*., 2000].

Behavioural data

The mentholic extract of Ficus platyphylla stem bark was studied on locomotor activity, pentobarbital sleep time, exploratory behaviour, amphetamine-induced hyperactivity, apomorphine-induced stereotypy, active avoidance and performance on treadmills (rota-rod) in mice and rats. Results revealed reduced locomotor and exploratory activities in mice, prolonged pentobarbital sleep time in rats, attenuated amphetamine-induced hyperactivity and apomorphine-induced stereotypy in mice, in a dose-dependant manner. This extract was also shown to significantly reduce the active avoidance response in rats, with no significant effect being recorded on motor coordination as determined by the performance on rota-rod. The researcher reported that the extract ‘may possess sedative principles with potenti al neuroleptic properties’, [Chindo *et al*., 2003].

In Vitro Toxicity Status

Carcinogenicity and mutagenicity

Additional information concerning the in vitro mutagenicity of this material may be found in "An Interim report on data originating from Imperia l Tobacco Limited's Genotoxicity testing programme September 2003 " or "An updated report on data originating from Imperial Tobacco Limited 's external Genotoxicity testing Programme – Round 2, August 2007".

Roemer *et al.,* (2002) reported on a study in whic h cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different *in vitro* assays. The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neu tral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included fig juice concentrate at levels up to 796 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al*., 2002].

A number of foods have long been associated with the modulation of certain physiological functions including the immune, nervous and endocrine systems. In an experiment m easuring nitrite formation as an indicator of nitric oxide production [the authors suggest that this would infer macrophage activation], a water extract of the fig fruit did not effect nitrite formation of a macrophage cell line [RAW 264.7] [Miwa *et al*., 1990].

A study in which the antioxidant properties of aromatic herbs, olives and fresh fruit was assessed (using an enzymatic sensor) revealed a sample of homogenised fig to have a relative antioxidant capacity of 0.23 (0.03). The highest antioxidant capacity reported in this study was that obtained for medlar and apricot giving values of 0.66 and 0.55 respectively, [Campanelle *et al* ., 2003].

Other relevant studies

A single report in 1995 details the "first report of anaphylactic reaction caused by fig ingestion". A 77-year-old woman already suffering from a latex allergy suffered an anaphylactic reaction following fig ingestion. The authors make claim that the reaction is mediated by an IgE dependant mechanism and suggest a possible cross-reactivity b etween fig and *F.benjamina*. In a brief statement the authors also state that phototoxic reactions have previously been observed after contact with the fig itself [Dechamp *et al* ., 1995]. As already stated cases of food allergy to fig are usually related to a cross-sensitisation to weeping fig (*Ficus benjamina*) or 'latex fruit syndrome '. However, two cases of oral allergy syndrome to figs has been reported in patients whose main allergic manifestations were related to grass or birch pollen sensitisation. In this study both fig skin and pulp were examined for the presence of potential allergens by IgE immunoblotting. The researches in this study concluded that oral allergy syndrome to fig which is accompanied by respiratory symptoms, can be present in individu als not previously sensitised

to weeping fig or having any signs of 'latex-fruit syndrome'. Different parts of the fig were noted to have different allergenicities with the most important allergens being associated to proteins in the skin of the fruit, [An tico *et al*., 2003].

Other reports in literature reiterate that allergy to the fig fruit is a rare occurrence, and that it occurs as a result of previous inhalation of proteins from *Ficus benjamina* [latex]. Gandolfo *et al*., (2001) go on to describe an isolated case in 1997 where a woman suffered anaphylaxis following ingestion of dried fig. The woman had previously been sensitised to *Ficus benjamina* that belongs to the same family as the common fig [*Ficus carica*] [Díez-Gómez *et al*., 1998; Hemmer *et al*., 1999; Gandolfo *et al*., 2001; Hemmer *et al*., 2001].

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