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Cuminaldehyde: A Potential Drug Candidate

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Abstract

Cuminaldehyde is one of major constituents identified in the essential oil of a number of commonly used spices such as green cumin (*Cuminum Cyminum L.*) which has been traditionally used for the treatment of dyspepsia, diarrhea, abdominal colic and Jaundice. Cumin essential oil has multiple pharmacological actions including antioxidant, antidiabetic, anti-inflammatory, antibacterial and anticancer effects. Therefore, a great deal of attention has been given to investigate the role of cuminaldehyde in mediating cumin's multiple therapeutic benefits. This short review highlights the most significant recently reported findings which unravel the extent to which cuminaldehyde contributes to the therapeutic effects of its producing herbs. Apart from its non-medical effects as natural bio-fumigant, cuminaldehyde is a promising potential drug candidate against various diseases.

Keywords: Cuminaldehyde; Anticancer; Antidiabetic; Anti-inflammatory; Neuroprotection; Antimicrobial; Fumigant

Introduction

Cuminaldehyde (Figure 1), an oxidized aldehyde monoterpene, is a major essential oil component [1-3] in green cumin seeds (*Cuminum cyminum Linn*, Family *Apiaceae*) which is a widely used spice cultivated natively in Egypt and later spread to various geographical locations mainly Asia, North Africa and Southern Europe, Mexico and Chile with India and Iran as the major producing countries [4-6]. Cuminaldehyde has also been determined in high amount in other commonly used spices such as true Cinnamon tree [7] and Black zira [8]. Cuminum cyminum is traditionally used to ease abdominal colic [9], treat dyspepsia [10,11], diarrhoea and jaundice [12]. It also has antioxidant [6,13] antibacterial [2] and antifungal effects [14]. Anticonvulsant activity of cumin oil was also reported [15]. In this review, recent findings suggesting different promising medical effects of cuminaldehyde will be discussed in the light of established therapeutic effects reported for the whole *Cuminum cyminum* essential oil.

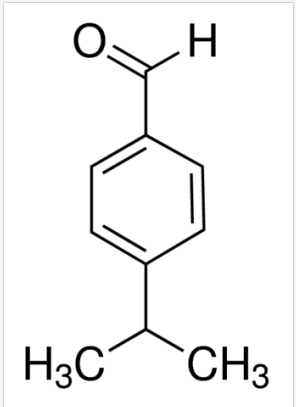

Figure 1: Chemical structure of cuminaldehyde (*4-Isopropylbenzaldehyde*).

Medical Effects (Figure 2)

Antidiabetic effects of cuminaldehyde

It has been reported that cuminum cyminum has antidiabetic effects [16] as it was effective in reducing elevated blood glucose levels, enhancing insulin secretion and exerting antioxidant protective effects on insulin secreting β cells in diabetic rats compared to clinically used oral hypoglycaemic agent glibenclamide [12,17]. Likewise, patients diagnosed with type II diabetes exhibited improved control over hyperglycaemia and enhanced insulin sensitivity after 8 week treatment with 50 or 100 mg / kg / day green cumin [18]. Indeed, cuminaldehyde has been found to contribute to the antidiabetic effects of cumin. Earlier, cuminaldehyde demonstrated significant but relatively lower inhibitory effects on *aldose reductase* and *alpha glucosidase* than an orally approved antidiabetic drug acarbose [19]. Later, Patil et al. [20] 2013 showed that cuminaldehyde had glucose dependent insulinotropic effects in diabetic rats, an effect which was found to be mediated through blocking ATP sensitive potassium channels and increasing intracellular calcium concentration in cultured rat pancreatic cells. Moreover, cuminaldehyde protected pancreatic β cells against cytotoxicity induced by streptozotocin [20].

Anticancer effects of cuminaldehyde

Over the past decade, a growing body of evidence has shed lights on the antineoplastic activity of Cuminaldehyde. Nitoda et al. [21] demonstrated inhibitory effects of cuminaldehyde at low concentrations on melanin synthesis by mouse melanoma cell line but not by human melanoma cells, although cuminaldehyde became rather cytotoxic at higher concentrations for both cancer cell lines. Recent studies have provided insight into the mechanisms of cuminaldehyde cytotoxicity. First, cuminaldehyde was found to trigger pro-apoptotic proteins such as caspase 3 and 9, alter the integrity of mitochondria and inhibit the malignancy-increased activity of DNA integrity-conserving enzymes including *topoisomerase* I and II, thereby enhancing apoptosis and growth inhibition of human colorectal adenocarcinoma cells [7]. Such anticancer effects of cuminaldehyde were validated in a mouse model of colorectal cancer, demonstrating reduced tumour size elicited by cuminaldehyde-enhanced apoptosis [7]. Another study using NCI-H520 Cells featuring human lung squamous cell carcinoma exhibited similar results with broad stimulatory effects on the apoptosis pathway manifested with increased expression of pro-apoptic bax and bac and decreased expression of bcl-XL and bcl-2, apoptosis suppressing factors [22]. In the previous study, cuminaldehyde induced apoptosis was also evidenced by the increased release of mitochondrial cytochrome c as well as elevated activity of lactate *dehydrogenase* in the culture medium [22]. Also, cuminaldehyde increased lysosomal vacuolation and acidic compartment volume [7,22]. Despite its promising antitumor effects, cuminaldehyde is considered a safe drug candidate as it showed no cytotoxicity on PC12 cells using MTT cytotoxicity assay [23].

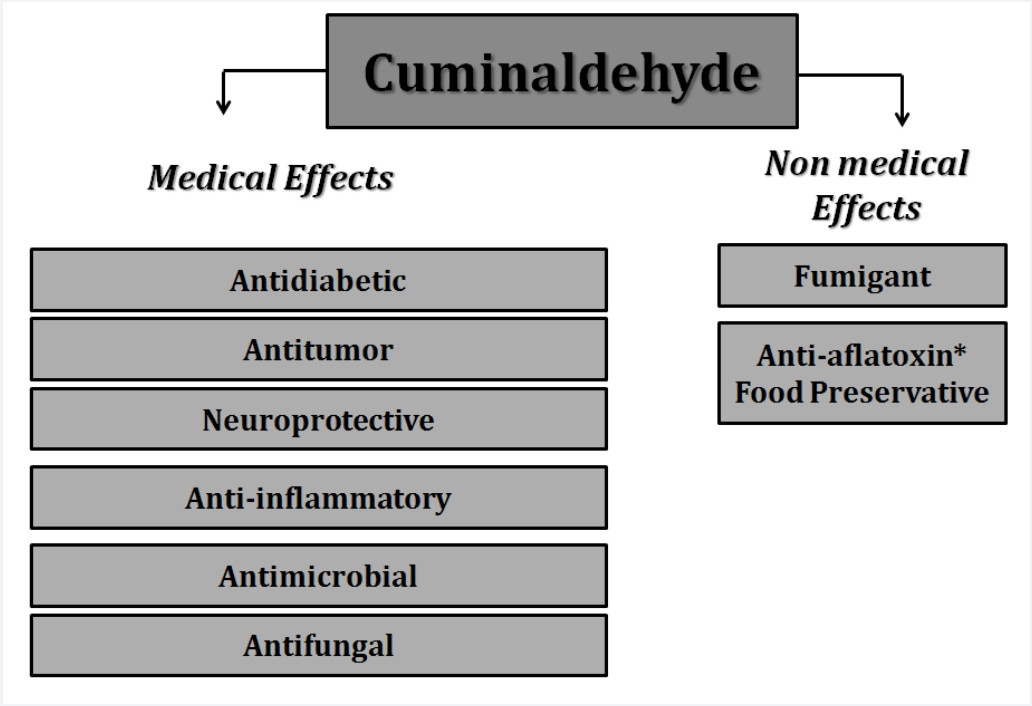

Figure 2: Medical and non-medical effects of cuminaldehyde.

*Effects have been determined for *Cuminum cyminum* essential oil which contained cuminaldehyde as a major constituent.

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Cuminaldehyde possesses neuroprotective effects

Cuminum cyminum has been shown to act centrally. For example, cumin extract was found to have nootropic effects and to attenuate scopolamine-induced amnesia in rats [24]. Cumin essential oil attenuated morphine-induced conditioned place preference [25] and this effect was suggested to involve inhibition of the central nitric oxide synthesis [26]. On the other hand, cuminaldehyde has been recently found to exert protective effects against neurodegenerative diseases in particular Parkinson's disease. This was evidenced by its long lasting suppressing effects on the fibrillation of alpha synuclein, the pathogenesis hallmark of Parkinson's disease, compared to baicalein, a standard alpha synuclein fibrillation suppressor [23]. Additional investigation suggested that cuminaldehyde impaired β-structural assembly of alpha synuclein fibrils, thereby inhibiting its fibrillation [23]. On the contrary, inhibitory effects of cuminaldehyde on alpha synuclein fibrillation was weakened by essential oil of Myrtus communis [27], indicating that essential oils from natural sources are not always beneficial.

Potential anti-inflammatory effects of cuminaldehyde

With regard to supressing inflammatory process, cumin essential oil was found to be effective in reducing different features of lipopolysaccharide induced inflammation in cultured macrophage cells including decreased mRNA expression of pro-inflammatory cytokines such as interleukin 1 and 6, inducible *nitric oxide synthase* and *cyclooxygenase type* II [3]. Cumin oil also reduced protein levels of nuclear factor-kappa B, phosphorylated extracellular signal regulated *kinase* and *phosphorylated c-Jun N-terminal Kinase* [3]. In this study by Wei et al. [3], it should be pointed out that cuminaldehyde accounted for 48.77 % of the whole content of cumin essential oil, suggesting potential anti-inflammatory effects of cuminaldehyde. Cuminaldehyde itself competitively inhibited the activity of *15-lipoxygenase*, an enzyme involved in the production of inflammatory mediators such as leukotrienes, using *lipoxygenase* inhibition assay [28].

Antimicrobial and antifungal activity

As stated earlier, cumin essential oil was reported to have antibacterial and antifungal effects [2], antimalarial [13], and it inhibited the growth of aflatoxin-producing fungi such as *Aspergillus flavus* [14], proposing that cuminaldehyde could partially mediate such effects as it constituted a considerable portion of the whole cumin essential oil. An Iranian clinical study on female patients suffering from recurrent *vulvovaginal candidiasis*, cumin oil demonstrated marked antifungal activity against *candida albicans* strains identified in vaginal samples isolated from infected women using the broth microdilution method [29]. Cuminaldehyde was one major component of cumin essential oil (18.8%) used in the former study, indicating that it could contribute to the reported fungicidal effects of cumin essential oil.

Non-medical effects: Fumigant applications (Figure 2)

Apart from its promising medical effects, cuminaldehyde showed profound antifungal activity against a soil-borne *Fusarium oxysporum* [8], supporting its powerful fumigant use against phytopathogenic fungi. Cuminaldehyde was also found to selectively inhibit the *acetylcholinesterase* in insects and pests feeding on and damaging plants and therefore it could be safely used as an excellent natural bio-fumigant [30-32].

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