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LITERATURE AND SCIENTIFICALLY CARVONE IS AN ANTICANCER AGENT

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Abstract

This study reviews the anticancer potential of the terpenoid Carvone (CAV). For this, a databasic search has been done in the PUBMED and SCIENCE DIRECT till May 2018. Findings suggest that CAV exerted anticancer activity by cytotoxic, tumor suppression and immunological effects, antiproliferative and inhibition of cancer cell migration, and chemopreventive mechanisms. More researches are necessary for the determination of exact molecular mechanisms of CAV's anticancer effects. Together with the previous scientific reports on its biological effects, this review claims that CAV may be one of the important chemotherapeutic agents.

Keywords: *Carvone, cancer therapy, toxicity*

Introduction

Carvone (CAV), a terpenoids most abundant in the essential oils of Carum carvi (caraway), Mentha spicata (spearmint), and dill (Simonsen, 1953). CAV is commonly used in the food and flavor industry (De Carvalho et al., 2006). R-(−)-carvone is used as an air freshener and is used in aromatherapy and as an alternative medicine, while S-(+)-carvone is evident for its anti-obesity activity (Alsanea and Liu, 2017).

CAV has various important biological effects, including antioxidant (Costa et al., 2012), antiinflammatory (Marques et al., 2014), antimicrobial (Morcia et al., 2012; Mun et al., 2014; Peixoto et al., 2015; Chan et al., 2016; Porfírio et al., 2017), antiallergic (Karlberg et al., 2001; Nilsson et al., 2004), neuropharmacological (de Sousa et al., 2007; Sánchez-Borzone et al., 2014; Jusoh et al., 2018), immunomodulatory (Lasarte-Cia et al., 2018), anti-hyperglycemic (Muruganathan and Srinivasan, 2016), antimanic (Nogoceke et al., 2016), spasmolytic (Souza et al., 2013; de Sousa et al., 2015), bronchodilatory (Kundu et al., 2016), anticonvulsant (de Almeida et al., 2008; Costa et al. 2012; Marques et al., 2014), anxiolytic (Hatano et al., 2012), cardiovascular effect (Kundu et al., 2014), and antinociceptive (Gonçalves et al., 2008) activity. Some research evidence suggesting that CAV has anticancer effects. Therefore, this review aims at sketching the anticancer property of this terpenoid.

Methods

A search was done in the *PUBMED* and *SCIENCE DIRECT* databases till May 2018 with the keyword 'Carvone' or 'Carvone derivatives' by compiling with 'Cancer'. No language restrictions were imposed. Only ten scientific reports were seen the above-mentioned databases, those are discussed below.

Findings with Discussion

Cytotoxic effect

Cytotoxicity test is one of the popular studies to check the anticancer effect of a cancer chemotherapeutic agent (Florento et al., 2012). Necrosis due to loss of membrane integrity and die rapidly, apoptosis *via* various molecular mechanisms, as well as toxicogenetics pathways are involved in cell death (Riss et al., 2004). In a study, (S)-(+)-CAV (1->100 µM) was found to exhibit strong to moderate cytotoxic effects (LC_{50}: 1-26.8 µM) against KB3, NCI 60, RPMI-8226 leukemia cell, and HOP-92 non-small cell lung cancer cell lines (Bateman et al., 2009). CAV is also evident to exert cytotoxic effect in HeLa and non-tumoral Vero cell lines (Mesa-Arango et al., 2009). CAV isolated from *Mentha spicata* var. *crispa* at 10 - 400 mg/L significantly reduced cell viability rates of cultured primary rat neuron and N2a neuroblastoma (NB) cells (Aydın et al., 2015).

Tumor suppression and immunomodulatory effects

A tumor suppressor genes (or antioncogenes), genes that protect cells tom be cancerous. Mutation of these genes causes a loss or reduction of their function, lead to progress of cancer. Therefore, upregulation of the tumor suppressor genes is one of the modalities of cancer therapy. In a study, D-CAV (0.2 mM) was found to reduce tumor and pulmonary adenoma formation in N-nitrosodiethylamine (NDEA)-induced carcinogenesis in female A/J mice (Wattenberg et al., 1989).

Immunetherapy in cancer is vastly studied, and it can be used as a combination therapy to to improve tumor microenvironment and thereby improve the treatment effect (Mooradian and Sullivan, 2017). CAV (100 µM/Kg body wt/dose) in Balb/c mice showed an immunemodulatory effect of increasing total antibody production, antibody producing cells in the spleen, bone marrow cellularity and alpha-esterase positive cells significantly compared to the normal animals (Raphael and Kuttan, 2003).

Antiproliferative/anti-migration effect

Among the diverse anticancer mechanisms inhibition of cancer cell proliferation and cell migration are another two mechanisms of a chemotherapeutic agent (Zhang and Wang, 2015). Chen et al. (2006) suggested that L-CAV in human prostate cancer LNCaP cells exerted an antiproliferative effect, possibly *via* extracelular receptor kinase (ERK) activation and $p^{21(waf1)}$ induction. L-CAV (0.01 - 20 mM) is also found to inhibit cell proliferation and migration, possibly by augmenting reactive oxygen species (ROS) and glutathione levels along with an increased levels of p53, Bad; cleaved caspase 3, and cleaved PARP explained p53 and caspase-mediated apoptotic cell

death in human breast cancer (MCF 7 and MDA MB 231) and normal (MCF 10A) cell lines (Patel and Thakkar, 2014).

Chemopreventive effect

Chemotherapy-induced secondary cancer is well-known. In a successful chemotherapy, complete die of cancer cells without disturbing the normal cells' biochemical activities is a prime concern (Chikara et al., 2018). An earlier study reported that CAV isolated from *Anethum graveolens* L. and *Carum carvi* L. in mouse target tissues was evident to show a significant chemopreventive effect (Zheng et al., 1992). Moreover, in a recent study, it has been demonstrated that D-CAV (10 and 20 mg/kg, p.o., for 16 weeks) in rats significantly reduced the incidence of polyps/ aberrant crypt foci (ACF) and ACF multiplicity in 1,2-dimethylhydrazine (DMH)-exposed rats (Vinothkumar et al., 2013). Furthermore, nanoemulsion formulations of the CAV Schiff base were found to show an increased anticancer effect in human colon cancer cells. This study also demonstrates an increased absorption rate of the nanoformulation of CAV in albino rats (Mashooq et al., 2015). Anticancer effects of CAV is shown in Table 1.

CAV's toxicity

Although, CAV is evident to cause Allergic contact cheilitis (Corazza et al., 2002), dermatitis (Quertermous and Fowler, 2010), and uticaria (Hansson et al., 2011) in experimental animals, but in a 2-year gavage study d-CAV (375 or 750 mg/kg, 5 days per week for 2 years, p.o.) did not produce carcinogenicity activity in male or female B6C3F1 mice (National Toxicology Program, 1990).

Together all, this review suggests that CAV has anticancer activity in a number of test systems. Cytotoxic, tumor suppression, immunomodulatory, antiproliferative and inhibition of cancer cell migration, and chemopreventive effects have been observed in literature. Toxicological reports suggest that allergic reactions such as cheilitis, dermatitis and uticaria have been seen in CAV-administered animals. However, no carcinogenic effect has been seen in experimental animals. CAV may be one of the important anticancer terpenoids member of essential oils.

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Conflict of interest

None declared.

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Table 1. Anticancer effects of carvone in various test systems

Carvone	Dose/conc. (route of administration)/test system	Findings	References
D-carvone	0.2 mM to N-nitrosodiethylamine (NDEA)-induced carcinogenesis in female A/J mice (n = 15/16)	Reduced forestomach tumor and pulmonary adenoma formation.	Wattenberg et al., 1989
Carvone isolated from *Anethum graveolens* L. and *Carum carvi* L.	Mouse target tissues	Significant enzyme-inducing effect, possible consideration for chemopreventive agent.	Zheng et al., 1992
Carvone	100 µM/Kg body wt/dose/ Balb/c mice	Increased total antibody production, antibody producing cells in spleen, bone marrow cellularity and alpha-esterase positive cells significantly compared to the normal animals.	Raphael and Kuttan, 2003
L-carvone	Human prostate cancer LNCaP cells	Significant increased the antiproliferative effect, possibly *via* extracelular receptor kinase (ERK) activation and $p^{21(waf1)}$ induction.	Chen et al., 2006
(S)-(+)-carvone	1->100 µM against KB3, NCI 60, RPMI-8226 leukemia cell, and HOP-92 non-small cell lung cancer cell lines	Strong to moderate cytotoxic effects (LC_{50}: 1-26.8 µM).	Bateman et al., 2009
Carvone	HeLa and non-tumoural Vero cell lines	Cytotoxic effect.	Mesa-Arango et al., 2009
d-carvone	10 and 20 mg/kg (p.o.) in rats (n = 6) for 16 weeks	Significant reduction of the incidence of polyps/ aberrant crypt foci (ACF) and ACF multiplicity in 1,2-dimethylhydrazine (DMH)-exposed rats, suggesting an effective chemopreventive agent.	Vinothkumar et al., 2013
L-carvone	0.01 - 20 mM against human breast cancer (MCF 7 and MDA MB 231) and normal (MCF 10A) cell lines	Inhibited cell proliferation and migration possibly by augmenting ROS and glutathione levels. Also increased the levels of p53, Bad; cleaved caspase 3, and cleaved PARP explained p53 and caspase-mediated apoptosis.	Patel and Thakkar, 2014
Carvon isolated from *Mentha spicata* var. *crispa*	10 - 400 mg/L against cultured primary rat neuron and N2a neuroblastoma (NB) cells	Significant reduction of cell viability rates.	Aydın et al., 2015
Nanoemulsion formulations of carvone Schiff base	Human colon cancer cells	Anticancer effect. In Albino rats it showed rapid absorption.	Mashooq et al., 2015