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Review paper

A review on genotoxic and mutagenic effects of monoterpenes

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Abstract

This review sketches genotoxic and mutagenic potentials of monoterpenes, which find outs some important genotoxic, mutagenic as well as non-genotoxic and non-mutagenic monoterpenes. Monoterpenes are the important natural products.

Keywords: *Essential Oils; Terpenes; Toxicity; Safety.*

1. Introduction

Nowadays, natural products gain much attention in the prevention and treatment of various diseases. Terpenes and terpenoids are the natural products, members of the essential oils (EOs) having important biological activities (Islam and Ali 2016). EOs are considered as efficient and safe alternatives to preserve food, cosmetic and pharmaceutical products (Hernandes et al. 2017). However, some terpenic EOs are known for their insecticidal and mutagenic effects (Hooper et al. 1979).

Safety is a major concern of any product prior to install into a biological system. On the other hand, compounds having multi-dimensional-like actions are the good swords for the treatment of diseases (Islam 2016).

Substances having toxic effects may impart genotoxic and/or mutagenic effects in the cells. Although these kinds of effects may be beneficial and/or harmful, but always harmful to the normal cells. This review aims to sketch safety potentials of monoterpenes. Therefore, a search was made in the PubMed, Science Direct, Scopus, Medline, Elsevier and Springer databases for the published articles as a source of evidence.

2. Findings

In the above-mentioned databases, 68 of published articles were found in the topic genotoxic and mutagenic activities of monoterpenes, which covers 48.15 and 51.85%, respectively. After reading the abstracts and contents, 27 articles have been selected for this revision.

2.1. Monoterpenic genotoxic/non-genotoxic effects

Thymol significantly increased DNA damage in human lymphocytes at higher concentrations (20, 50, 100, 150, and 200 µg/mL), probably through induction of reactive oxygen species (Radaković et al. 2015). On the other hand, citronella, a mono terpenoid found in the essential oil extracted from Cymbopogon plants showed an antifungal effect, probably *via* alteration of membrane homeostasis by increasing the hypersensitivity of the fungi to membrane-perturbing agents, reducing ergosterol levels, and diminishing glucose-induced H^+ extrusion as well as inducing oxidative and genotoxic stresses in *Candida albicans* (Singh et al. 2016).

In a study, alpha-terpinene in Wistar rats (0.5, 0.75 and 1.0 mL/kg, p.o. for 10 days) exhibited cytotoxic and genotoxic effects to the brain cells by inducing loss of cell viability and DNA damage, as well as causing alterations in Na^+/K^+-ATPase and NTPDase activity, what may contribute to the memory deficit of treated animals (Baldissera et al. 2016).

Beta-Myrcene (7-methyl-3-methylene-1,6 octadiene) obtained from *Cymbopogon citratus* Stapf. oil in male and female Wistar rats at 0.1, 0.5 and 1.0 g/kg, p.o. did not produce mutagenic or genotoxic effects (Zamith et al. 1993). On the other hand, perillyl alcohol, a dietary monoterpene (naturally-occurring occurring monocyclic terpenes) in MCF-7 cells reduced CYP1B1 mRNA abundance induced by dimethylbenz[a]anthracene (DMBA). Thus inhibit and down-regulate CYP1B1, which could protect against polycyclic aromatic hydrocarbon (PAH)-induced carcinogenesis (Chan et al. 2006).

Carvacrol (monoterpenoid phenol) and thymol in HepG2 and Caco-2 cells significantly protect the cells toward DNA strand breaks induced by a potent oxidant hydrogen peroxide (Slamenová et al. 2007). Similar effect was also observed by Horváthová et al (2006). Thymol in human leukemic K562 cells exerted a DNA-protective effect, probably *via* reducing oxidative stress (Horvathova et al. 2007).

The principal bioactive phenols in olive-leaf extracts (OLEs, rich in oleuropein and luteolin) in SMART test showed anti-genotoxic and non-significant mutagenic effects (Anter et al. 2011) while schizonepetin, a naturally-occurring monoterpene at 0, 60, 120, and 240 mg/kg bw/day in mice and rats for 35 days after oral administration (p.o.) did not show genotoxic effects (Liu et al. 2012).

In a study, a series of secondary amines combining monoterpenoid and amino adamantane moieties have been synthesized and tested for cytotoxic effects against human cancer cells CEM-13, MT-4, and U-937, which revealed significant cytotoxic rather than a genotoxic effect on cells (Suslov et al. 2015). In normal human skin explants obtained from young healthy women (n = 7) *Thymus vulgaris* leaf extract and thymol were found to prevent UV-induced skin damage. It may be due to inhibition of proliferation, cytotoxicity, and genotoxicity in skin cells (Cornaghi et al. 2016). The same effect by these compounds was also previously reported by Calò et al (2015).

2.2. Monoterpenic mutagenic/non-mutagenic effects

Valepotriates are epoxide-bearing triesters of the monoterpene alcohol 4,7-dimethylcyclopenta-(c)-pyrane were found to mutagenic for TA100, WP2 and WP2 uvrA- at concentrations up to about 1.0 muM/plate when S9-mix was added to the test system, which was inversely related to the protein content of the S9-mix used (von der Hude et al. 1985). In another study, the valepotriates valtrate/isovaltrate and dihydrovaltrate in *Salmonella*/microsome test and the SOS-chromotest developed mutagenic activity in these test systems only in the presence of S9 mix, whereas both baldrinals showed mutagenic effects in both tests with and without metabolic activation (von der Hude et al. 1986).

Citral (mixture of terpenoids) in male or female F344/N rats exposed to 1,000, 2,000, or 4,000 ppm did not exert the carcinogenic effect in male B6C3F1 mice exposed to 500, 1,000, or 2,000 ppm. However, equivocal evidence of carcinogenic activity in female B6C3F1 mice was based on increased incidences of malignant lymphoma (National Toxicology Program 2003). On the other hand, linalyl acetate but not other EOs of lavender oil showed mutagenic effects in peripheral human lymphocytes, which can be related to the aneugenic activity (Di Sotto et al. 2011).

Ethanol extracts of roots of *Galianthe thalictroides* K. Schum. (Rubiaceae) And the indole monoterpene alkaloids 1 obtained from this plant were tested for genotoxic effects through *Drosophila melanogaster* wing Somatic Mutation and Recombination Test – SMART. Although, the ethanol extracts did not show genotoxic effect, but alkaloid 1 showed significant mutational events with SMART (Fernandes et al. 2013).

In an *in vitro* test, myrcene (up to 1,000 µg/mL) did not exert mutagenic effects in the test systems (human lymphoma) (Kauderer et al. 1991). Thymol (a natural monoterpene phenol derivative of cymene) and borneol (belongs to the family of bicyclic monoterpenes), were screened for mutagenic activity using *Salmonella typhimurium* strains TA97, TA98 and TA100, with and without S9 metabolic activation, and 20 min standard preincubation time, indicating non-mutagenic effects of them (Azizan et al. 1995).

Citral is a major component of *Cymbopogon citratus* (lemongrass oil) at 60 mg/kg (p.o.) treated for one week showed an anti-clastogenic effect in mice (Rabbani et al. 2006). On the other hand, the monoterpene indole alkaloid brachycerine from Psychotria brachyceras in *Saccharomyces cerevisiae* N123 strain in the presence and absence of H_2O_2 showed antioxidant and antimutagenic effects probably *via* scavenging of OH radicals (do Nascimento et al. 2007). Moreover, EOs from seven *Lamiaceae* species did not exert mutagenic effects in two *Salmonella typhimurium* strains (De Martino et al. 2009).

In a study, the safety of the *Leucosidea sericea* extracts and iridoid (a type of monoterpenoids in the general form of cyclopentanopyran) content of *L. sericea* stems and leaves tested through Ames test did not exert mutagenic effects (Aremu et al. 2011). On the other hand, thymol did not show any mutagenic effect at any concentration assayed (0-250 µM) in Ames *Salmonella* test (LLana-Ruiz-Cabello et al. 2014).

3. Conclusion

Monoterpenes have both genotoxic and mutagenic effects in biological test systems. However, many of them have been found non-genotoxic and non-mutagenic in a number of biological test systems. Their activity may depend on the test concentrations/doses in the test systems. Adequate laboratory screenings concerning on toxicological assessment of monoterpenes are necessary.

4. Conflict of interest

None declared.

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