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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).

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### 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.

## References


[1] Anter J, Fernández-Bedmar Z, Villatoro-Pulido M, Demyda-Peyras S, Moreno-Millán M, Alonso-Moraga A, Muñoz-Serrano A, Luque de Castro MD. 2011. A pilot study on the DNA-protective, cytotoxic, and apoptosis-inducing properties of olive-leaf extracts. *Mutat. Res.* 723(2):165-170. doi: 10.1016/j.mrgentox.2011.05.005. https://doi.org/10.1016/j.mrgentox.2011.05.005.

[2] Aremu AO, Amoo SO, Ndhlala AR, Finnie JF, Van Staden J. 2011. Antioxidant activity, acetylcholinesterase inhibition, iridoid content and mutagenic evaluation of *Leucosidea sericea*. *Food Chem. Toxicol*. 49(5):1122-1128. https://doi.org/10.1016/j.fct.2011.02.003.

[3] Azizan A, Blevins RD. 1995. Mutagenicity and antimutagenicity testing of six chemicals associated with the pungent properties of specific spices as revealed by the Ames *Salmonella*/microsomal assay. *Arch. Environ. Contam. Toxicol*. 28(2):248-258. https://doi.org/10.1007/BF00217624.

[4] Baldissera MD, Souza CF, Grando TH, Sagrillo MR, De Brum GF, Nascimento K, Peres DS, Maciel MF, Silveira SO, Da Luz SC, Doleski PH, Leal DB, da Silva AS, Monteiro SG. 2016. Memory deficit, toxic effects and activity of Na (+), K(+)-ATPase and NTPDase in brain of Wistar rats submitted to orally treatment with alpha-terpinene. *Environ. Toxicol. Pharmacol*. 46:1-8. https://doi.org/10.1016/j.etap.2016.06.024.

[5] Calò R, Visone CM, Marabini L. 2015. Thymol and *Thymus vulgaris* L. activity against UVA- and UVB-induced damage in NCTC 2544 cell line. *Mutat. Res. Genet. Toxicol. Environ. Mutagen*. 791:30-37. https://doi.org/10.1016/j.mrgentox.2015.07.009.

[6] Chan NL, Wang H, Wang Y, Leung HY, Leung LK. 2006. Polycyclic aromatic hydrocarbon-induced CYP1B1 activity is suppressed by perillyl alcohol in MCF-7 cells. *Toxicol. Appl. Pharmacol*. 213(2):98-104. https://doi.org/10.1016/j.taap.2005.10.002.

[7] Cornaghi L, Arnaboldi F, Calò R, Landoni F, Baruffaldi Preis WF, Marabini L, Donetti E. 2016. Effects of UV Rays and Thymol/*Thymus vulgaris* L. Extract in an *ex vivo* Human Skin Model: Morphological and Genotoxicological Assessment. *Cells Tissues Organs*. 201(3):180-192. https://doi.org/10.1159/000444361.

[8] De Martino L, De Feo V, Nazzaro F. 2009. Chemical composition and *in vitro* antimicrobial and mutagenic activities of seven *Lamiaceae* essential oils. *Molecules*. 14(10):4213-4230. https://doi.org/10.3390/molecules14104213.

[9] Di Sotto A, Mazzanti G, Carbone F, Hrelia P, Maffei F. 2011. Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes *in vitro*. *Environ. Mol. Mutagen*. 52(1):69-71. https://doi.org/10.1002/em.20587.

[10] Do Nascimento NC, Fragoso V, Moura DJ, e Silva AC, Fett-Neto AG, Saffi J. 2007. Antioxidant and antimutagenic effects of the crude foliar extract and the alkaloid brachycerine of *Psychotria brachyceras*. *Environ. Mol. Mutagen*. 48(9):728-734. https://doi.org/10.1002/em.20349.

[11] Fernandes LM, Garcez WS, Mantovani MS, Figueiredo PO, Fernandes CA, Garcez FR, Guterres ZR. 2013. Assessment of the *in vitro* and *in vivo* genotoxicity of extracts and indole monoterpene alkaloid from the roots of *Galianthe thalictroides* (Rubiaceae). *Food Chem. Toxicol*. 59:405-411. https://doi.org/10.1016/j.fct.2013.05.052.

[12] Hernandes C, Pina ES, Taleb-Contini SH, Bertoni BW, Cestari IM, Espanha LG, Varanda EA, Camilo KF, Martinez EZ, França SC, Pereira AM. 2017. *Lippia origanoides* essential oil: an efficient and safe alternative to preserve food, cosmetic and pharmaceutical products. *J. Appl. Microbiol*. 122(4):900-910. https://doi.org/10.1111/jam.13398.

[13] Hooper NK, Ames BN, Saleh MA, Casida JE. 1979. Toxaphene, a complex mixture of polychloroterpenes and a major insecticide, is mutagenic. *Science*. 205(4406):591-593. https://doi.org/10.1126/science.377495.

[14] Horváthová E, Sramková M, Lábaj J, Slamenová D. 2006. Study of cytotoxic, genotoxic and DNA-protective effects of selected plant essential oils on human cells cultured *in vitro*. *Neuro. Endocrinol. Lett.* 27(2):44-47.

[15] Horvathova E, Turcaniova V, Slamenova D. 2007. Comparative study of DNA-damaging and DNA-protective effects of selected components of essential plant oils in human leukemic cells K562. *Neoplasma*. 54(6):478-483.

[16] Islam MT. 2016. Safety promises of diterpenes concerning on toxicogenetic effects. *BAOJ Chem.* 2(2):1-5.

[17] Islam MT, Ali ES. 2016. Therapeutic interventions of diterpenes: Molecular mechanisms and promises. *World J. Pharm. Pharmaceut. Sci.* 5(10):70-97. Doi: 10.20959/wjpps201610-7804.

[18] Kauderer B, Zamith H, Paumgartten FJ, Speit G. 1991. Evaluation of the mutagenicity of beta-myrcene in mammalian cells *in vitro*. *Environ. Mol. Mutagen*. 18(1):28-34. https://doi.org/10.1002/em.2850180106.

[19] Liu D, Geng T, Zhang L, Yao W, Ding A, Shan M. 2012. Acute and subacute toxicity and genotoxicity of schizonepetin, a naturally occurring monoterpene with antiviral activity. *Food Chem. Toxicol*. 50(7):2256-2262. https://doi.org/10.1016/j.fct.2012.03.002.

[20] LLana-Ruiz-Cabello M, Maisanaba S, Puerto M, Prieto AI, Pichardo S, Jos Á, Cameán AM. 2014. Evaluation of the mutagenicity and genotoxic potential of carvacrol and thymol using the Ames *Salmonella* test and alkaline, Endo III- and FPG-modified comet assays with the human cell line Caco-2. *Food Chem. Toxicol*. 72:122-128. https://doi.org/10.1016/j.fct.2014.07.013.

[21] National Toxicology Program. 2003. NTP toxicology and carcinogenesiss studies of citral (microencapsulated) (CAS No. 5392-40-5) in F344/N rats and B6C3F1 mice (feed studies). *Natl. Toxicol. Program Tech. Rep. Ser*. 505:1-268.

[22] Rabbani SI, Devi K, Khanam S, Zahra N. Citral, a component of lemongrass oil inhibits the clastogenic effect of nickel chloride in mouse micronucleus test system. *Pak. J. Pharm. Sci*. 19(2):108-113.

[23] Radaković M, Djelić N, Stevanović J, Soković M, Radović D, Van Griensven LJ, Stanimirović Z. 2015. Evaluation of the Antigenotoxic Effects of the Royal Sun Mushroom, *Agaricus brasiliensis* (Higher Basidiomycetes) in Human Lymphocytes Treated with Thymol in the Comet Assay. *Int. J. Med. Mushrooms*. 17(4):321-30. https://doi.org/10.1615/IntJMedMushrooms.v17.i4.10.

[24] Singh S, Fatima Z, Hameed S. 2016. Citronellal-induced disruption of membrane homeostasis in *Candida albicans* and attenuation of its virulence attributes. *Rev. Soc. Bras. Med. Trop*. 49(4):465-472. https://doi.org/10.1590/0037-8682-0190-2016.

[25] Slamenová D, Horváthová E, Sramková M, Marsálková L. 2007. DNA-protective effects of two components of essential plant oils carvacrol and thymol on mammalian cells cultured *in vitro*. *Neoplasma*. 54(2):108-112.

[26] Suslov EV, Ponomarev KY, Rogachev AD, Pokrovsky MA, Pokrovsky AG, Pykhtina MB, Beklemishev AB, Korchagina DV, Volcho KP, Salakhutdinov NF. 2015. Compounds Combining Aminoadamantane and Monoterpene Moieties: Cytotoxicity and Mutagenic Effects. *Med. Chem*. 11(7):629-635. https://doi.org/10.2174/1573406411666150518110053.

[27] von der Hude W, Scheutwinkel-Reich M, Braun R, Dittmar W. 1985. *In vitro* mutagenicity of valepotriates. *Arch. Toxicol*. 56(4):267-271. https://doi.org/10.1007/BF00295166.

[28] Von der Hude W, Scheutwinkel-Reich M, Braun R. 1986. Bacterial mutagenicity of the tranquilizing constituents of *Valerianaceae* roots. *Mutat. Res*. 169(1-2):23-27. https://doi.org/10.1016/0165-1218(86)90013-3.

[29] Zamith HP, Vidal MN, Speit G, Paumgartten FJ. 1993. Absence of genotoxic activity of beta-myrcene in the *in vivo* cytogenetic bone marrow assay. *Braz. J. Med. Biol. Res*. 26(1):93-98.