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Review Article

Genotoxic and mutagenic effects of triterpenes: A mini-review

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Abstract

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

Keywords: *Natural Products; Safety Potentials; Triterpenes.*

1. Introduction

Recently, natural products have gained attention to the medicinal scientists due to their applicability and variety of activities. Terpenes and terpenoids are the natural products, members of the essential oils having important biological activities (Islam and Ali 2016).

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. Both acute and chronic these kinds of effects are harmful to the normal cells. This review aims to sketch safety potentials of triterpenes. Therefore, a search was made in the *PubMed*, *Science Direct*, *Scopus*, *Medline*, *Elsevier* and *Springer* databases for the published articles as a source of evidences.

2. Findings

In the above-mentioned databases, 34 of published articles were found on the topic genotoxic and mutagenic activities of triterpenes, which covers 47.22 and 52.78%, respectively. After reading the abstracts and contents, 15 articles have been selected for this revision.

2.1. Triterpenic genotoxic/non-genotoxic effects

Ginsenoside Rh (2) triterpene, a panaxadiol saponin, possesses various antitumour properties. In the oral administration of Rh (2) (5, 10 and 20 mg/kg b.w) did not show genotoxic effect in mice (Wang et al. 2006). Different triterpenes, known as galphimines, have been identified from the active extract of *Galphimia glauca* Cav (Malpighiaceae). Galphimine-B (G-B) possesses anxiolytic activity and is able to selectively inhibit discharges of dopaminergic neurons in the ventral tegmental area in rats. However, the extracts (250, 100 and 50 µg/mL) did not show genotoxic effect in the test system (Aguilar-Santamaría et al. 2007). *Panax ginseng* extract (20 mg/kg b.w.) standardized with ginsenoside Rg3 (ginsenoside Rg3 content was 3.6% w/w, i.e., 36 µg/mg *P. ginseng* extract) and garlic against EDTA-induced significantly improved all the tested parameters of biochemical, genotoxic, and histological changes in rats (n = 5) (Khalil et al. 2008).

Azadirachtin (Aza) 0.00005%, 0.00010%, 0.00015%, and 0.00020% (w/v) Aza-containing *Azadirachta indica* A. Juss extract decreased cytotoxic and genotoxic effects in *Allium cepa* and *Eucrosia bicolor* (Kwankua et al. 2010). Moreover, azadirachtin A (AzaA) is not genotoxic in human lymphocytes and Chinese Hamster ovary (CHO) cells. Moreover, AZA proved to interfere with cell cycle progression as shown by modulation of frequencies of first (M1) and second division (M2) metaphases detected by 5-Bromo-2'-deoxyuridine labeling. The authors suggested that, AZA can act either through a stabilizing activity of microtubules or by inhibition of Aurora A, since both mechanisms are able to generate genetically unstable polyploid cells with multipolar spindles and multinucleated interphases (Mosesso et al. 2012).

Furthermore, aaxifragifolin B and cyclamin triterpene saponins isolated from *Cyclamen libanoticum* Hildebr and *Cyclamen persicum* Mill were tested for their cytotoxicity against SK-BR-3, HT-29, HepG2/3A, NCI-H1299, BXPC-3, 22RV1, and normal DMEM cell lines using WST-1 assay. They showed strong cytotoxic activities against the tested cancer cell lines and the saxifragifolin B was suggested as a potential cytotoxic drug with a preventive effect against possible exposures to genotoxic agents (El Hosry et al. 2014). The ethanolic extract of *Euphorbia hyssopifolia* L. (0.01, 0.1 and 1.0 mg/mL) was carried out in HepG2 cells (alkaline comet assay and cytokinesis-block micronucleus assay - CBMN) suggest that the concentrations above 0.01 mg/mL are genotoxic (Araújo Sde et al. 2015).

2.2. Triterpenic mutagenic/non-mutagenic effects

Cucumarioside in mouse bone marrow micronucleus assay did not show mutagenic effect (Polikarpova et al. 1990). On the other hand, the triterpene glycoside, 3-O-[beta-D-glucopyranosyl-(1''-6')-2'-acetamido-2'-deoxy-beta-D-gluco pyranosyl]olean-12-en-28-oic acid, and new sulfated triterpene, echinocystic acid-3-O-sodium sulfate, isolated from the stem bark of *Tetrapleura tetraptera* were not mutagenic either with or without metabolic activation (Ngassapa et al. 1993). Triterpenes from *Glycyrrhiza glabra*

L. extract were also evident to exert an antimutagenic activity against ribose-lysine (Zani et al. 1993).

In a study, alpha-aescin and phenbendasole made by "Polfa" (Poland) along with phenbendasole produced by "Hoechst" (Germany) did not show carcinogenic effect in *Salmonella*/microsome test (Przybojewska et al. 1994). However, azadirachtin, a promising biopesticide recently introduced into the United States, indicates that this natural product has genotoxic and carcinogenic effects (Rosenkranz and Klopman 1995).

Diosgenone is a major component of the hexane extract from the plant *Solanum nudum* (Solanaceae) was found to show antimalarial activity against the FCB-2 strain of *Plasmodium falciparum* but did not show mutagenic effects in the Ames test with the TA-97a, TA-98, TA-100 and TA-102 strains of *Salmonella typhimurium* (Pabón et al. 2003). The major constituent of *Carmona retusa* (Vahl.) Masam. leaves is an intractable mixture of triterpenes, namely alpha-amyrin (43.7%), beta-amyrin (24.9%), and baurenol (31.4%). At a dosage of 100 mg/kg mouse, the triterpene mixture showed antimicrobial, analgesic and anti-inflammatory activities rather than mutagenic activity (Villaseñor et al. 2004). Triterpene betulinic acid {3b-3-hydroxy-lup-20(29)-en-28-oic} i(1.64, 3.28, and 6.57 mM) solated from the roots of *Scoparia dulcis* (Scrophulariaceae) showed an animutagenic effect in the wings of Drosophila melanogaster (de Freitas et al. 2015).

3. Conclusions

Triterpenes 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 triterpenes are necessary.

4. Conflict of interest

None declared.

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