Review

Safety Promises of Diterpenes Concerning on Toxicogenetic Effects

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Abstract

It is doubtless that, the safety assessment for any substance is a lengthy process. Otherwise, lab setup and suitable test system relevant towards the human physiology are the two most common burning questions. A number of rodents, microorganisms and phyto-based assay systems are currently used world-wide. The diterpenes on this planet are more than 200 years and the research in this field is also continuous. Unfortunately, there is very poor toxicological information on the toxicogenetic status on them. Diterpenes are considered as cytoprotective agents, this makes rare of their toxicological data. This short-review sketches a safety profile of some diterpenes on the basis of cytogenotoxic behaviors.

Key Words: Diterpenes; Non-Carcinogenic; Non-Mutagenic; Anti-Genotoxic

Introduction

Among the other phytochemicals, in the recent decade, diterpenes procure much attention of the medicinal scientists. Many of them are under clinical trials. They have varieties of biological effects such as antioxidant [1-3], anti-inflammatory [4-6], antimicrobial [7,8], antiviral [9], antiprotozoal [10,11], cytotoxic [12], anticancer [13,14], antigenotoxic and antimutagenic [15-17], chemopreventive [18,19], antinoceptive [20,21], immunostimulatory [22,23], organoprotective (e.g.-neuro-, cardiac-, hepatic-, pulmonary-, etc.), antidiabetic, lipid-lowering, anti allergic, anti platelet, antithrombotic, and antitoxin activities [24,25]. Their activity mainly depends on the concentration and activity sites. At low concentration, they may act as antioxidant, while at cytotoxic at high. Therefore, the diterpenes are more cytotoxic rather than genotoxic and mutagenic in nature [26].

Any disease, more specifically the cancer is a genetic and epigenetic-oriented complicated disease. In this context, we need a multi-edged sword-like therapy. Essential oils (EOs) are a type under this category. However, every treatment has some adverse or side effects on a particular biological system. How safe the diterpenes are? This text offers a safety database profile of some vastly studied diterpenes, emphasized on cytogenotoxic behaviors.

Search Stratagem

A search was made in the Pub Med database (from April 1984 to December 2016) with the keyword “diterpenes” paired with the following terms: ‘antigenotoxic’, ‘non-carcinogenic’, ‘non-mutagenic’ and ‘non-toxic’. A total 398 articles were found, among them 312 were discarded by reading the title, while 26 and 40 by abstract and data duplication, respectively. Final concentration was made on 20 articles, where non-carcinogenic and non-mutagenic, anti-genotoxic, and non-toxic corresponded to 30, 50 and 20% articles, respectively. The general steps of data search, exclusion and inclusion criteria are shown in Figure 1.

Diterpenic Safety Profile

Nowadays, the medicinal plant-derived lead compounds are in the spotlight. It is due to their doubtless popularity from the past and ability to treat various diseases [27]. Plants contain numerous important phytochemicals. EOs are one of them. The EOs are mainly used in pharmaceutical, agronomic, food, sanitary, cosmetic, and perfume industries. Being a family member, diterpenes are also used in the same purposes. However, in the recent decades, a number of diterpenes and their derivatives have been introduced in the therapeutic purposes [24]. For any substance, risk assessment prior to test in a biological system is crucial, which is also called ‘safety assessment’. Although, it is a time consuming matter, but to date a number of methodologies have been developed for rapid checking toxicity or cytogenotoxicity profiles such as Artemia salina, Allium cepa, certain microorganisms such as bacteria (e.g. - Salmonella sp.), fungi (e.g. - Saccharomyces cerevisiae), rodents (e.g. - mice, rats), culture cell lines and so on. The tests performed are generally termed as: toxicity, cytotoxicity/carcinogenicity, genotoxicity and mutagenicity.

Generally, diterpenes are considered as cytoprotective constituents. Most of them are known to have potent antioxidant and antimicrobial activities. For this reason, many of them are used...
as preservatives in foods and drinks. These kinds of substances are better to be used in health promotion [28]. Examples of some diterpenes or their derivatives, with non-cytogenotoxic effects have been introduced as follows:

12-0-tetradecanoyl phorbol-13-acetate (TPA) is evident to exert non-carcinogenic effects on in two liver cell-lines HepG2 and JTC-15 [29]. TPA exerted similar effects in L5178Y-F9 clone [30], OuaR CHO-K1 cell [31], 3PC cell line [32], HL-60 cells [33] and C3H/10T1/2 cultures [34]. The NIH 3T3 cells when treated with 10, 50 and 100 µM of apigenin and 100 ng/ml of TPA demonstrated a significant suppression of TPA-induced C-JUN and C-FOS expressions [35]. TPA also provided anti-tumor-promoting effects of skin application of GTP to SENCAR mice [36].

In a study, the polyphenolic fraction isolated from green tea (GTP) (1-24 mg) in mice exerted an anti-skin tumor-promoting effect [37]. The trans-dehydrocrotonin (t-DCTN) from the bark extract of Croton cajucara in bone marrow cells of Swiss mice produces an insignificant number of micronucleus (MN) and chromosome aberration (CA) [38]. Terpenoids, including two new labdane diterpenes named marrubiacetal A and desertine from dichloromethane and methanol extracts of Marrubium deserti de Noé were found to inhibit β-galactosidase induction caused by the mutagenic agent nitrofurantoin [39]. The pimarane-type diterpene, pimaradienoic acid (PA: 20, 40 and 80 mg/kg) in Chinese hamster lung fibroblasts (V79 cells) and in male Swiss mice induced DNA damage in the hepatocytes at high dose (comet assay). However, no genotoxic effect was observed in the micronucleus test using V79 cells [40]. The casearin X, a clerodane diterpene from Casearia sylvestris in the micronucleus test in mouse bone marrow cells and the comet assay in mouse blood cells protected DNA from damage induced by airborne pollutants from sugar-cane burning [41]. The juice of Vitis coignetiae was found antimutagenic toward dimethylbenzo[a]anthracene (DMBA), aflatoxin B1, and benzo[a]pyrene in the Ames test. Moreover, the caftaric acid, isolated from this plant was anti-mutagenic toward DMBA and prevented TPA-induced inflammation in mice [42].

Chemical structures of some important diterpenes have been shown in Figure 2.

Manool (0.5-8.0 µg/mL) from Salvia officinalis is evident for antigenotoxic (micronucleus test) potential in Chinese hamster lung fibroblasts (V79) and human hepatoma cells (HepG2) [16]. Islam et al has been introduced a number of antigenotoxic, antimutagenic and antitoxin diterpenes by these days [43].

**Few More Lines on Diterpenic Safety Promises**

As anticancer agents, the overall action of diterpenes may not be tolerable to the normal cells. A number of diterpenes and their derivatives, such as andrographolide [44], phytol [45], carnosol, carnosic acid [1], rosmadial, rosmarinic acid [3], jatrophane diterpenes [46] and so on are evident for their antioxidant or cytoprotective capacity. The diterpenes from Crossopetalum gaumeri reduced the cell viability of HeLa (cervix) and Hep-2 (lung carcinoma) human tumor cells rather than normal Vero (African green monkey kidney) cells [47]. Some diterpenes have been proven for anti-inflammatory in a number of biological test systems [48,49], while others can impart beneficial immunological functions [22,23,50,51].

The use of antioxidants with chemotherapeutic agents is limited. It is due to the antioxidants may:

- reduce the efficacy of the chemotherapeutic agent;
- enhance the chance of cancer cell escaping;
- drug resistance and/or stimulation of cancer cell’s repairing systems; or
- chance of pro-oxidative effects on normal cells.

Moreover, the detection of the level of oxidative stress is crucial prior to a particular antioxidant therapy [26]. To be mentioned that, to date, a number of diterpenes such as fruticulin C, 7α-methoxy-19-acetoxy-royleanone, 7α,19-diacetoxy-royleanone, and 7-dehydroxy-conacytone [52], isocoronarin D, methoxycoronarin D, ethoxyxcoronarin D, and benzoyl eugenol [53] have been reported to have chemo preventive capacity in a number of human cells.

Furthermore, excessive angiogenesis or inhibition of angiogenesis...
Figure 2: Structure of some important diterpenes
and proliferation of normal cells is not desired for any anticancer treatment. In a study castor oil palmitate and kahweol palmitate (75 and 100 μM) did not disturb the angiogenesis and proliferation in normal HMVECs [54]. In another study, triptolide-loaded micelles in SKOV3 cells significantly increased in tumorigenicity inhibition via inhibiting proliferation, apoptosis, invasion, and migration in comparison to the control group [55]. Mir et al. also suggested that, androgropholide showed a differential effect on cell cycle phases in LNCaP, C4-2b and PC3 cells, where it did not affect the primary prostate epithelial cells [56].

Conclusion

Diterpenes are lead molecules in the treatment of diseases and health promotion. They are mostly cytoprotective in nature than the mutagenic, genotoxic and carcinogenic, which enriches their safety profile in biological systems. Although, this text introduces a few diterpenes or their safety, dosages/concentrations in some test systems, but the evidences are sufficient to say the overall safety profile of them. Therefore, a comprehensive revision is welcome on this topic ‘Diterpenic safety traits’.

References


