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Review

Terpenoids as anti-colon cancer agents – A comprehensive review on its mechanistic perspectives

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ABSTRACT

Multistep model of colon carcinogenesis has provided the framework to advance our understanding of the molecular basis of colon cancer. This multistage process of carcinogenesis takes a long period to transform from a normal epithelial cell to invasive carcinoma. Thus, it provides enough time to intervene the process of carcinogenesis especially through dietary modification. In spite of the in-depth understanding of the colon cancer etiology and pathophysiology and its association with diet, colon cancer remains a major cause of cancer mortality worldwide. Phytochemicals and their derivatives are gaining attention in cancer prevention and treatment strategies because of cancer chemotherapy associated adverse effects. Being the largest group of phytochemicals traditionally used for medicinal purpose in India and China, terpenoids are recently being explored as anticancer agents. Anticancer properties of terpenoids are associated with various mechanisms like counteraction of oxidative stress, potentiating endogenous antioxidants, improving detoxification potential, disrupting cell survival pathways and inducing apoptosis. This review gives a comprehensive idea of naturally occurring terpenoids as useful agents for the prevention of colon cancer with reference to their classes, sources and molecular targets. Based on the explored molecular targets further research in colon cancer chemoprevention is warranted.

1. Introduction

Worldwide, colon cancer has become a major public health issue with 1.2 million new cases and more than 600,000 deaths per year (Jemal et al., 2011). Colon cancer which was once considered as a disease of the western countries has now become prevalent in Asian countries like India, China, Japan, Singapore and South Korea (Sudarshan et al., 2013). Colon cancer begins with a generalized disorder of cell replication with a shift of the replicative zone to the upper parts of the crypts (Tanaka, 2009). The reigning dogma in colorectal carcinogenesis since the late 1980s has been the multistep model created by Fearon and Vogelstein. This model postulated that CRC was caused by the accumulation of mutations that drive tumor initiation and then progression (Fearon and Vogelstein, 1990). Inactivation of the *APC* gene initiates the CRC. Harboring *APC* mutated cell transforms the normal crypt to aberrant crypts which can be visualized as aberrant crypt foci (ACF) that eventually results in the genesis of small polyps. Additional mutations in *K-ras* or *BRAF,* transforming growth factor beta (TGF-β) pathway, the p53 pathway and other pathways transform small polyps to large polyps that lead to cancer progression (Rajagopalan et al., 2003). This progression from adenoma to invasive carcinoma probably takes 10–40 years (Ilyas et al., 1999) and provides a great opportunity for colon cancer prevention if diagnosed early. Cancer chemoprevention is an effective strategy for preventing or delaying the process of carcinogenesis by chronic administration of natural, synthetic or biologic chemical agent (Steward and Brown, 2013). Understanding the complexity of carcinogenesis and the adverse effects associated with chemotherapy strengthens the belief that “Prevention is better than cure”. Natural products are of particular interest as chemopreventive agents due to their low toxicity profiles and potential effectiveness. Researchers and clinicians also focused on searching natural products with multi-targeted potentials for effective chemoprevention (Greenlee, 2012). Terpenes are the dietary agents that showed immense potential in cancer prevention in the last decade but still need an elaborative preclinical and translational research.

‘Terpenes’ - the major constituents of plant resin and essential oils are a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$. ‘Terpenoids’ are the hydrocarbons and their oxygenated, hydrogenated and dehydrogenated derivatives of plant origin of the general formula $(C_5H_8)_n$ where ‘n’ refers to the number of isoprene units. Terpenoids are classified as mono, di, oligo, and polyterpenes.

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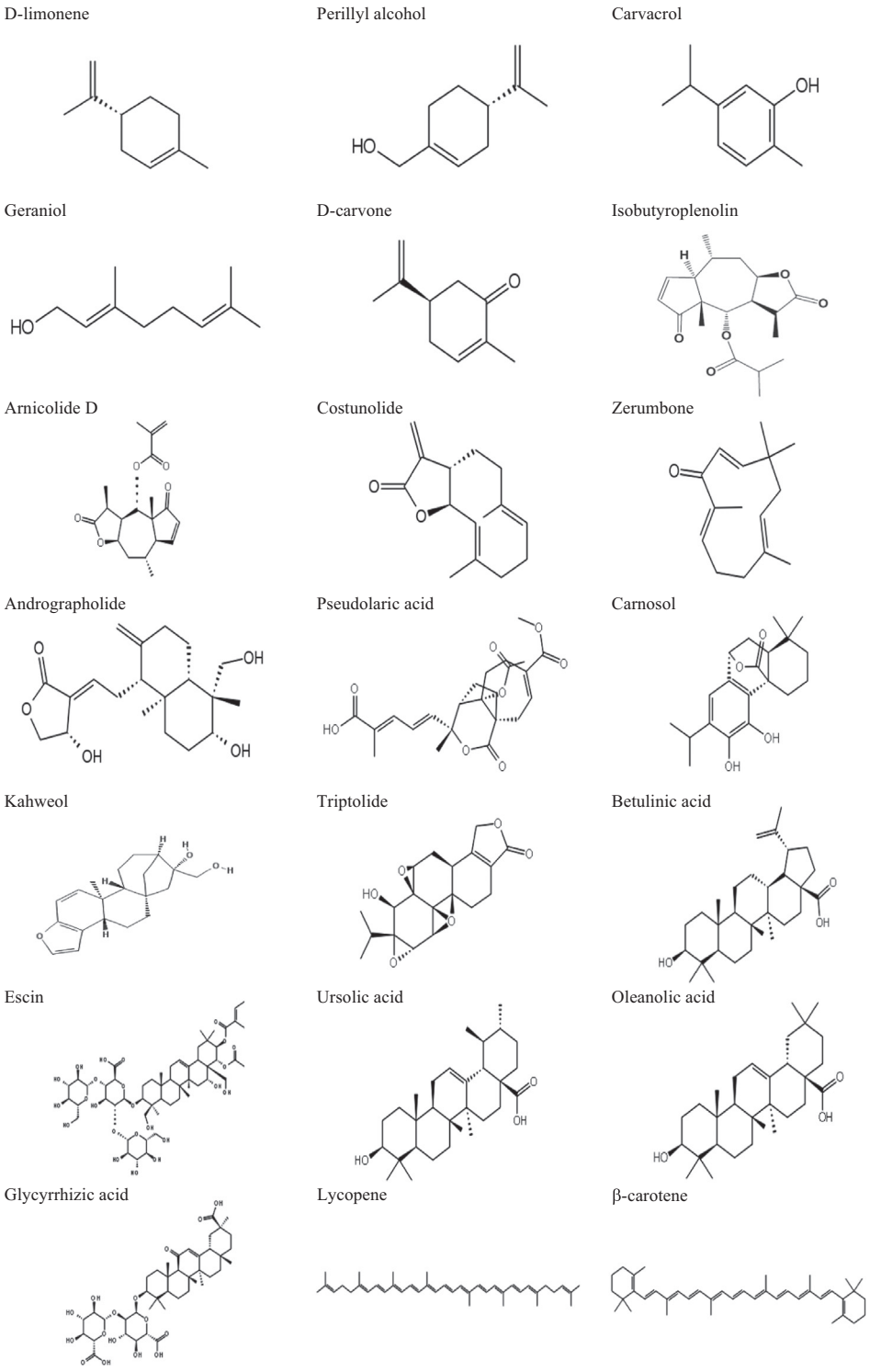

Fig. 1. Chemical structure of terpenoids.

Terpenoids consist of approximately 25,000 chemical structures with potential practical applications in the fragrance and flavor industries, as well as in the pharmaceutical and chemical industries (Caputi and Aprea, 2011). *In vitro*, *in vivo* and human epidemiological trials suggest the antiproliferative role of terpenoids against various kinds of cancers (Huang et al., 2012). This review aims to summarize the implications of various terpenoids (Fig. 1) in chemoprevention of colon cancer and provide data for future translational anti-cancer research in the context of dietary intervention of colon carcinogenesis.

2. Monoterpenes

Monoterpenes are naturally occurring hydrocarbons composed of the condensation of two isoprenes and is a component of fragrance oils extracted from leaves. As a naturally occurring monocyclic monoterpene of citrus oils, *d*-limonene is shown to exert chemopreventive or chemotherapeutic efficacy against various types of cancer (Sun, 2007) including colon cancer (Table 1). *d*-limonene's anti- colon cancer effect was attributed via apoptosis induction and modulation of polyamine