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Application of sesquiterpene lactone: A new promising way for cancer therapy based on anticancer activity

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ABSTRACT

Cancer is one of the most dangerous diseases that are rapidly increasing globally. After heart disease, it is the second leading cause of death, accounting for seven million deaths each year. Chemotherapy is the use of cytotoxic drugs on cancer cells. But the use of common chemotherapy drugs poses a problem due their high side effects and low efficacy. As a result, efforts are on to find new potent compounds with low side effects. The compounds extracted from plants have been studied in this regard due to their prevalence. Sesquiterpene lactones are a group of natural compounds that were first detected in Asteraceae dark plants. These compounds exercise their effects by reacting with functional groups available on proteins and enzymes, especially the thiol group. Owing to the high side effects as an antitumor synthetic drugs, efforts are being made to find drugs with high efficiency and low side effects. Their high structural ranges have attracted the attention of many researchers as a potential source of new anticancer drugs.

1. Introduction

While many efforts have been made in recent decades to improve cancer treatment, chemotherapeutic agents have been recognized to be highly effective and have successfully reached a clinical stage; cancer is still one of the causes of death in many countries around the world. Therefore, one of the main priorities of many pharmaceutical companies and research organizations is to find new therapies for cancer treatment [1]. A lot of research has been done to find more effective therapeutic compounds with fewer side effects. However, the two major shortfalls with anticancer drugs are multi-resistance and the low efficacy in *in vivo* systems due to low bioavailability [2]. The ultimate goal of chemotherapy treatment is to search for compounds with a selective effect on cancer cells. One of the ways to improve the possibility of solving this problem is to use plants to treat cancer. From a distant past, plants in all cultures have been used as a source of medication due to their health benefits.

Secondary metabolites are not essential for the growth and development of the organism, but they serve as a mechanism for adaptation to the environment [3]. The term *natural product* is synonymous to the term *secondary metabolite*. These compounds have a diverse structure and a molecular weight of less than 3000 Da. The data from Newman et al, [4] review showed that, natural products and/or their novel structures used for the purpose of final drug discovery, is still at large. For instance, in cancer research between 1940 and 2014, of the 175 approved small molecules, 131 (75%) were other than synthetic, with 85 (49%) actually being either natural products or directly derived therefrom.

More than 80,000 species of 250,000 known herbs are used for health and therapeutic purposes, and more than 60% of the commonly used anticancer drugs are made from natural resources. A wide range of biological activities and a wide variety of plant-derived compounds have led to an effective continuation of plant screening to find chemotherapy and chemo-proactive compounds [5]. Sesquiterpene lactones exhibit great structural diversity and a broad range of biological activities and are found mainly in genus from Asteraceae family like *Artemisia, Arnica, Ambrosia, Helenium, Tanacetum,* and *Vernonia* (Fig. 1) [5,6].

2. Sesquiterpene lactones

Asteraceaes are a highly developed group of plants, whose members are rich in bioactive compounds (secondary metabolites), including polyacetylenes, diterpene and sesquiterpene lactones [7]. These compounds include a large group of low molecular weight secondary metabolites [6] that have various biological activities. These compounds are the largest group of natural compounds having more than 5000 different structures, most of which are found in Asteraceaes. These

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Fig. 1. Some plants that contains sesquiterpene lactones. a. Chamazulene (German chamomile). b. Helianthus annuus (common sunflower). c. poppy (Papaveraceae). d. Leucanthemum vulgare (oxeye daisy). e. Artemisia (Mugworts plant). A. Upper left b. Upper right c. Middle d. Lower left e. Lower right.

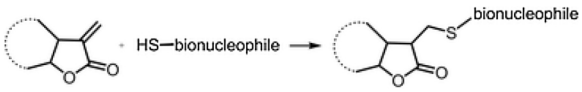

Fig. 2. An overview of Michel's reaction; binding to the thiol groups on the enzymes and proteins that alter the structure and function of the sesquiterpene lactone reaction10.

compounds have been considered owing to their high therapeutic activities [5,8]. They are classified into five groups in terms of structure: 1. Germacranolides, 2. Elemanolides, 3. Eudesmanolides, 4. Guaianolides, and 5. Pseudoguaianolides. The different biological activities of sesquiterpene lactones are related to the difference in the structures of these compounds [9].

Sesquiterpenes are natural terpenoids with a 15-carbon skeleton. This compound can be hydrocarbon or oxygen-based and contain alcohol, ketone, aldehyde, acid, and the lactone group. When the Sesquiterpene skeleton contain a lactone, the compound is called sesquiterpene lactone, and “oid” is added to it as a suffix [5]. Sesquiterpene lactones are one of the super families of sesquiterpene consisting of colorless, crisp, and dry lipophilic compounds made up of three isopropyl units [7,9]. These compounds have low thermal stability and, in most cases, reversed-phase high-*performance* liquid chromatography are used to isolate and analyze these compounds. More attention is paid to them for their biological and pharmacological activities [5].

3. Sesquiterpene lactone nucleus

The biological activity of sesquiterpene lactones depends on three biochemical properties of these compounds: 1. alkylating center reaction, 2. side chain and lipophilicity, and 3. molecular geometry and electronic properties. These activities of sesquiterpene lactones are due to the structure of α-Methylene-γ-lactone [9].

In 1969, Hartwel and Abbott [10] investigated more than 50 types of sesquiterpene lactones and found an indirect relationship between the presence of α-methylene-γ-lactone and the biologic activity of sesquiterpene lactones. Subsequent studies showed that this structure exhibited biological activity in the exo mode and did not have this effect in the endo mode. The α-methylene-γ-lactone section of sesquiterpene lactones is connected to the nucleophilic structures of the target molecules through Michel's reaction, such as the cysteine thiol amino acid group in proteins [9]; they have their effects and change the spatial and chemical structure through alkylating transcription factors and various enzymes. Through Michel's reaction, sesquiterpene lactones cause the enzymes and transcription factors to be alkylated in their thiol groups (Fig. 2). This reaction is the main factor behind the biological effects of the sesquiterpene lactones [7].

On one hand, studies have shown that higher lipophilicity of the side chain of the sesquiterpene lactones leads to a greater ability to enter the cell, resulting in high cytotoxicity, and, on the other hand, an allowed limit is also defined by steric hindrance for this property. This lipophilicity reduces the solubility in water by reducing the bioavailability of these compounds [9]. Many studies have been done to increase bioavailability and solubility. One of these methods is the addition of amino group to the α-methylene-γ-lactone section of the compounds to increase its solubility [11]. Another method for the parthenolide sesquiterpene lactones is the use of nanoparticle derivatives of this compound, which increases their solubility and bioavailability. This method increases the anticancer effects of the derivative compound compared to the parthenolide [12]. Another feature that affects the biological activity of these compounds is structural flexibility, which increases the biological activity of these compounds [9]. Several biological activities, including antimicrobial activity [13], antimigraine[14], digestive and analgesic [14], anticancer, and the enhancement of cardiac muscle functions [15] can be mentioned for these herbal compounds.

Tada et al. [16], described a general technique for synthesizing iminium tetrahydrothiophene encapsulated in dimeric Nuphar alkaloids. Sulfur atom of thiaspirane pharmacophore was electrophilic. This α-thioether reacts with glutathione or thiophenol at ambient temperature to break the C—S bond and resulting in the formation of a disulfide.