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Topical Application of *Melaleuca Alternifolia* for Skin Cancer and Other Conditions

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Abstract

Natural plant products consist of varieties of phyto compounds having therapeutic potential to eliminate various lethal conditions. According to the recent statistics, cases for skin cancer are increasing at an alarming rate. Conventional therapeutics for treating cancer has not been completely successful and may result in multi drug resistant cancer. It also has been found to be associated with various toxic side effects and so, lack patient compliance. Therefore, there has been a need to find alternative therapeutic options with lesser side effects, to cure this deadly disease. People have been screening various plant based products with a possibility that, a thorough research on the natural plant products might lead to discovery of new chemical entities as anti-cancerous agents. In the last few decades, essential oil (EOs) have got attention and been under the development for their use in cancer therapy. One of such plant, Tea tree (*Melaleuca alternifolia*), which is an endemic Australian native, has been studied by various scientists for its anticancer potential. This review highlights few of these studies and various other uses of Tea tree oil including its major constituents etc.

Keywords: Essential oil; Anti-cancer agent; Skin cancer; Tea Tree Oil

Introduction

Cancer is a group of many diseases in combination and is having a huge impact on the people across the world. According to the 2016 statistics 1,685,210 people were diagnosed with cancer this year, out of which 595,690 died [1]. The frequency of the cancers diagnosed in year 2016 were in the following sequence (decreasing order) lung cancer, breast cancer, prostate cancer, melanoma or skin cancer, Non-Hodgkin's lymphoma and leukemia [2]. Skin cancer is an abnormal growth on the outer layer of the skin or in the basal cells. A very common risk factor causing skin cancer is Ultraviolet light exposure [3]. Other causes include some medications like chemotherapy and exposure to the ionizing radiations (X-ray).

Skin cancer is mainly divided into the three categories, the basal-cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma Skin cancer treatment [4]. Basal-cell skin cancer (BCC) usually grows slowly and appears as painless raised areas which usually is shiny in appearance and have blood vessels running over it. It could affect the surrounding tissue but is most unlikely to spread all over the body and result in death [5]. On the other hand, squamous-cell skin cancer is a hard lump with a scaly top and most likely to spread to distant area Dunphy [6] and Cakir et al. [5]. Melanomas are the most destructive form of skin cancer with the possible signs including a mole of changed shape, size and color. It has an asymmetrical shape and could bleed or itchy NCI [4]. Some of the cancer including the malignant melanoma and mesothelioma represent cancers that have poor prognosis and respond ineffectively to chemotherapy [7].

Treatment of skin cancer includes topical applications, chemotherapy, radiotherapy and many more. Topical chemotherapy represents a non-invasive and convenient strategy to treat tumors. Current treatment administrations against skin carcinomas e.g. 5-Fluoruracil and Imiquimod, exhibit limited success as tumor recurrence along with the problem of local and systemic noxiousness [8] and thus, there is a need to explore the other potential anticancer agent's sources to find new chemical entities. One of such plant which has been explored is Tea tree, from which Tea tree oil (TTO) has been extracted [9].

Tea Tree Oil and its Constituents

Tea tree oil (TTO) is derived from the leaves and terminal branches of an endemic Australian native *Melaleucaalternifolia* (Maiden and Betche, Cheel, Myrtaceae), which was initially explored by the aboriginal tribal population on the north coast of New South Wales, after knowing its immense germicidal properties [10]. The Melaleuca *alternifolia* plant has a height of 6 m with narrow and alternate leaf placement along with the flowers scattered in interrupted spike.

Table 1: List of the phytoconstituents present in TTO.

S. No.	Main constituents of TTO	% of Existence	Chemical formula and Molecular Weight(MW)
1	Terpinen-4-ol	30-48	$C_{10}H_{18}O$, MW=154
2	γ-terpinene	20.1	$C_{10}H_{16}$, MW=136
3	α-terpinene	5-13	$C_{10}H_{16}$, MW=136
4	1,8-cineole	3.7-15	$C_{10}H_{18}O$, MW=160
5	Terpinolene	1.5-5	$C_{10}H_{16}$, MW=136
6	p-cymene	0.5-8	$C_{10}H_{14}$, MW=134
7	α-terpineol	1.5-8	$C_{10}H_{18}O$,MW=160
8	α-pinene	1-6	$C_{10}H_{16}$, MW=136.23
9	Limonene	0.5-1.5	$C_{10}H_{16}$, MW=136.24
10	Aromadendrene	1.1-3	$C_{15}H_{24}$, MW=204.35
11	δ-cadinene	0.8-3	$C_{15}H_{24}$, MW=204
12	Ledene	0.6-3	$C_{15}H_{24}$, MW=204
13	Sabinene	0.3-3.5	C_{10}H16, MW=136.23
14	Globlol	0.2-1	$C_{15}H2_{60}$, MW=222.37
15	Viridiflorol	0.1-1	$C_{15}H_{26}O$, MW=222.37

TTO: Tea Tree Oil; MW: Molecular Weight; %: Percentage

It largely consists of more than 100 components which are mainly cyclic monoterpenes with equal combination of oxygenated and hydrocarbon forms. The significant ones are: terpinen-4-ol, γ-terpinene, α-terpinene and 1,8-cineole [11]. Terpinen-4-ol, is present in ample amount and considered as the probable mediator of the *in vitro* and *in vivo* therapeutic adequacy [12]. The natural components in the tea tree oil may vary considerably with the climate, population used, and the duration of distillation and the age of the leaves used. The yearly production of TTO is estimated around 400 tonnes year in Australia and is exported throughout the world. It has also been reported to be highly prone for oxidation and degradation in their biological properties hence leading to certain allergic reactions. The major constituents along with its formula and molecular weight are listed below in Table 1.

Pharmacological Activities

Tea Tee oil possess various benefits including antimicrobial activity Carson (2006), antifungal activity Hammer (2003), antiviral activity [13] and anti-inflammatory activity Hart (2000). It is considered as a universal remedy for acne, eczema, burns and various other skin infections. Other indications mentioned are cold, vaginal infections and sore throat. γ-Terpinene of tea tree oil has also been accounted to exhibits antioxidant, anti-microbial and anti-inflammatory properties [14]. Study reveals the application of γ-Terpinene as an anti-inflammatory in the treatment of inflamed gingival tissues [15].

Skin infections and Acne

Tea tree oil is useful to fight dermal infections. Its key component, Terpinen-4-ol possesses antimicrobial activity and thus destroys bacteria that cause acne. It penetrates through the skin and unblocks the sebaceous glands [16]. Activity of the oil against drug resistant bacteria such as Staphylococcus aureus has also been reported and it makes it an important antimicrobial agent for skin infections [17].

Oral Application

Tea tree oil is found to be very effective against oral candidiasis in cancer patients. Study reveals yeasts isolated from the mouths of cancer patients were susceptible to tree tea oil [18]. The anti-inflammatory properties of TTO can be oppressed in the topical use of gel containing TTO to swollen gingival tissues. Remarkably, TTO might be an advantageous non-lethal adjunct to chemotherapeutic periodontal healing [19].

Hair and Scalp

Tea tree oil is an alternative to insecticide such as permethrin. It has shown effective results in eliminating *Pediculosis capitis* [20]. As tea tree oil has antifungal activity against *Pityosporum* ovule. The problem of dandruff can be addressed by tea tree oil with no side effects [21].

Vaginal Infections

Tea tree oil possesses germicidal activity against vaginal pathogens including *Candida albicans* and *Trichomonas vaginalis*. Further no irritation, burning or other side effects are reported [22].

Anticancer Activities

Anti-cancerous activity is one of the total listed activities for TTO, and it has been recognized via performing the various toxic effect experiments on cultured cells. Firstly, its toxicity was tested on a panel of human cell lines including cervical cancer (HeLa), acute lymphoblastic leukemia (MOLT-4), fibroblast, epithelial cells, erythromyeloblastoid leukemia (K562) and B cell

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isolated from the bone marrow of a patient suffering from acute myeloid leukemia (CTVR-1). All these experiments reported the IC50 value ranging from20 to 2700 µg/mL which indicates the potential of TTO as an anti-cancer agent [13,23,24].

It has been proved in an investigation that 1, 8-cineole can induce apoptosis in two human leukemia cells lines Moteki (2002). Moreover, it has also been positively reported that Terpinen-4-ol is responsible for the *in vitro* cell cycle arrest, apoptosis, necrosis and hindrance in cell proliferation which in turn inhibits the melanoma cell growth at dosages that are not noxious to normal fibroblast cells. Both the oil from *M. alternifolia* and its terpene components have been demonstrated to repress the *in vitro* and *in vivo* development of melanoma cells and tumors. In another study, TTO and terpinen-4-ol treated Human Adriamycin resistant melanoma cells underwent caspase dependent apoptosis i.e. the plasma membrane interaction by lipid reorganization [25]. Interestingly, both TTO and terpinen-4-ol were operative against the resistant cell line, signifying them as the effective agents to treat MDR (multidrug resistant) tumors because neither are the substrates for Pglycoprotein.

Another research also suggested that the terpinen-4-ol could induce caspase-dependent apoptosis of the melanoma cells (M14WT) and the impact was more obvious in resistant variant cell population [26]. Two recent studies explored the effectiveness of topical TTO on destructive, subcutaneous, chemo-resistant tumors in entirely immune-competent mice [25]; Ireland et.al. 2012]. TTO induces *in vivo* tumor growth inhibition in the mouse model of murine subcutaneous malignant mesothelioma (AE17) and melanoma (B16) tumor cell lines. It has been reported due to the slight difference in IC_{50} because of the different cell types. Differential dose-response was shown between the tumor and non-tumor fibroblast cells proposing that TTO might evoke its effect by repressing fast dividing cells more promptly than the slower developing non-cancerous cells [25].

To support the finding that primary necrosis occurs after TTO treatment, it has been revealed in transmission electron microscopy examination of AE17 (mice tumor sections) cells. The intercellular spaces have been increased and there is accumulation of cell debris too, along with that cellular organization also alters resulting in nuclear shrinkage, condensation of chromatin, mitochondria swelling, cristae and membrane loss and the alteration of endoplasmic reticulum, and less defined cellular membranes [25].

In another study researchers examined the conceivable mechanism of action underlying anticancer activity of TTO. They inferred that topical utilization of 10% TTO/DMSO appeared to stimulate an immune response (i.e. neutrophils, dendritic, and T cells) and anti-tumor efficacy is facilitated by a direct effect on subcutaneous AE17tumor cells *in vivo* Ireland et al. (2012). After noticing the link between the multidrug resistance phenotype and membrane lipid composition, authors proposed that the greater sensitivity of drug-resistant cells to the TTO treatment could be attributed to the plasma membrane different lipid composition Lavie et al. [27] and Santini et al. [28]. Thus, it was suggested that, the TTO demonstrates cytotoxicity because of the interaction between the oil lipophilic components and phospholipid bilayer of cell membranes with subsequent modification in cell development and activity.

The capacity of TTO and its major component, terpinen-4-ol, has been also stated to meddle with the relocation and invasion processes of drug-sensitive and drug-resistant melanoma cells [29]. The studies showed that when 10% TTO was administered in cancer patients once every day for 4 successive days, it induced a noteworthy, however momentary degeneration of established subcutaneous AE17 tumors and furthermore, slowed down the growth of B16-F10 tumors. Whereas, when we use the mix of the five major TTO components (terpinen-4-ol, -terpinene, -terpinene, 1,8-cineole, and -cymene) at proportionate measurement to those found in 10% TTO, comparative effects on tumor growth were obtained but not, when utilizing the single component. Also, to induce the antitumor effect it is obligatory to use DMSO as a penetration enhancer, at concentrations without any toxic impact [25].

TTO has been shown to be safe for normal cells and it had been supported by the various experiments. Tumor cells are highly sensitive to the TTO thus, the "normal" epithelial and fibroblast cells, as topical agents [30], did not report any toxic effects at concentrations that were seemed to influence melanoma cell survival [24]. Normal cells including the fibroblasts and skeletal muscle fibers adjacent to damaged tumor cells and lymphocytes within tumor sections posses' high tolerance to the topical treatment [31]. Furthermore, it has been stated that the effect of TTO on tumor cells is facilitated by its induction of the rearrangement of the plasma membrane lipids.

Side Effects

It has been assumed that TTO can be used internally and externally to impart the therapeutic property but due to certain limitation which include the allergic reaction, inflammation, redness and rashes which might occur due to the presence of one of the major component of TTO i.e. 1-8 cineole [32]. Oxidation and degradation of the TTO components have been blamed for such side effects, and thus we need to develop a delivery vehicle or mode for such drugs or essential oil is a necessity so as to prevent vitalization, oxidation and degradation of the components and also to have improved bioavailability and increase the retention time on the skin and improve the therapeutic index [33].

Future Perspective

Formulation of Tea tree oil which induces tumor regression is well tolerated and is responsible for inhibiting growth needed to be worked upon [34]. Therefore, formulations of TTO must be developed in such a way that it can be regulated over a more extended time frame with a specific goal to permit more prolonged tumor growth inhibition as well as tumor regression. The *in vivo*

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mechanism of action should be thoroughly investigated, explicitly looking at the possible direct and indirect effects of *Melaleuca Alternifolia*. Additionally, as mentioned above that if TTO is taken in combination with other phytocompounds, it shows synergistic effect and remains more effective for curing cancer [35]. Alternately, a preparation having known amount of each component can be used in a standardized manner to initiate a complete and perpetual tumor growth regression would be consummate.

Discussion

Limitations of the chemotherapeutic agents in the treatment of cancer might be overcome by the various active components present in the tea tree oil, which at the same time also interferes with the multiple signaling pathways. It can also be suggested that they would assist in the development of multi drug resistance. Furthermore, from the information reviewed in this paper, the use of tea tree oil in cancer treatment is really promising, the facts obtained from *in vitro* and *in vivo* preclinical models have, beside obvious strengths, several restrictions and cannot be completely appropriate to humans.

Conclusion

Medicinal plants have always been an important source and played vital role in discovering new therapeutics for human diseases. Therefore, TTO source can act as a good candidate for the development of novel anticancer agents. Based on the literature search, leaves of Melaleuca *Alternifolia* had agreeable occurrences of clinical proof for supporting their anticancer impacts. Therefore, in this manner, it seems that it can be used as an integral therapeutic along with current chemotherapy drugs against different types of tumor. More illustrative *in vivo* studies should be performed to establish the molecular mechanism responsible for anticancer effect of its phytocompounds followed by developing a suitable formulation for evaluation for clinical trials.

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