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α-Terpineol, a natural monoterpene: A review of its biological properties

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Abstract: Terpineols are monocyclic monoterpene tertiary alcohols which are naturally present in plant species. There are five common isomers of terpineols, alpha-, beta-, gamma-, delta- and terpinen-4-ol, of which α-terpineol and its isomer terpinen-4-ol are the most common terpineols found in nature. α-Terpineol plays an important role in the industrial field. It has a pleasant odor similar to lilacs and it is a common ingredient in perfumes, cosmetics, and aromatic scents.

In addition, α-terpineol attracts a great interest as it has a wide range of biological applications as an antioxidant, anticancer, anticonvulsant, antiulcer, antihypertensive, anti-nociceptive compound. It is also used to enhance skin penetration, and also has insecticidal properties. This study reviews the relevance of α-terpineol based on scientific findings on Google Scholar, Pubmed, Web of Science, Scopus and Chemical Abstracts.

Collectively, the use of α-terpineol in medicine and in the pharmaceutical industry plays an important role in therapeutic applications. This review will, therefore, support future research in the utilization of α-terpineol.

Keywords: *p*-menth-1-en-8-ol; monoterpene utilization; monoterpenoid alcohol; monocyclic monoterpenoids; terpenic alcohols.

1 Introduction

Terpineols are naturally occurring unsaturated monocyclic mono-terpenoid alcohols and can be found in flowers such as narcissus and freesia, in herbs, such as marjoram, oregano, rosemary and in lemon peel oil. Reports on the level of terpenoids in oils occasionally vary considerably and one wonders how much this is due to the variation in the plants and to the variations in the isolation process as terpineols could also be an artifact [1,2]. In addition, terpineols are interesting because of their wide range of biological properties [3].

There are five common isomers of terpineols; alpha- (α-T), beta- (β-T), gamma- (γ-T), delta- (δ-T) and terpinen-4-ol (T-4-ol) (Figure 1).

α- and β-Terpineol occur in optically active forms and as a racemate. Both α-T and T-4-ol are the most important commercial products and they occur in a large number of essential oils. On the other hand, β-, γ- and δ- terpineols do not occur very often in nature [1]. Terpineols, especially the most commonly used compounds as α-T and T-4-on, exert a wide range of different biological actions on humans, animals, and also plants. They are not only popular fragrance ingredients used in perfumes, cosmetics, and household cleaning products, but also used to flavor foods and beverages. They also possess various important biological and medicinal properties [1-3].

α-T, a volatile monoterpenoid alcohol, is the major component of essential oils of several species of aromatic plants such as *Origanium vulgare* L. and *Ocimum canum* Sims which are widely used for medicinal purposes. α-T can also be isolated from a variety of sources such as

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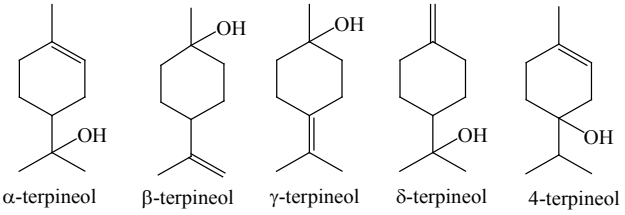

Figure 1: Terpineol isomers.

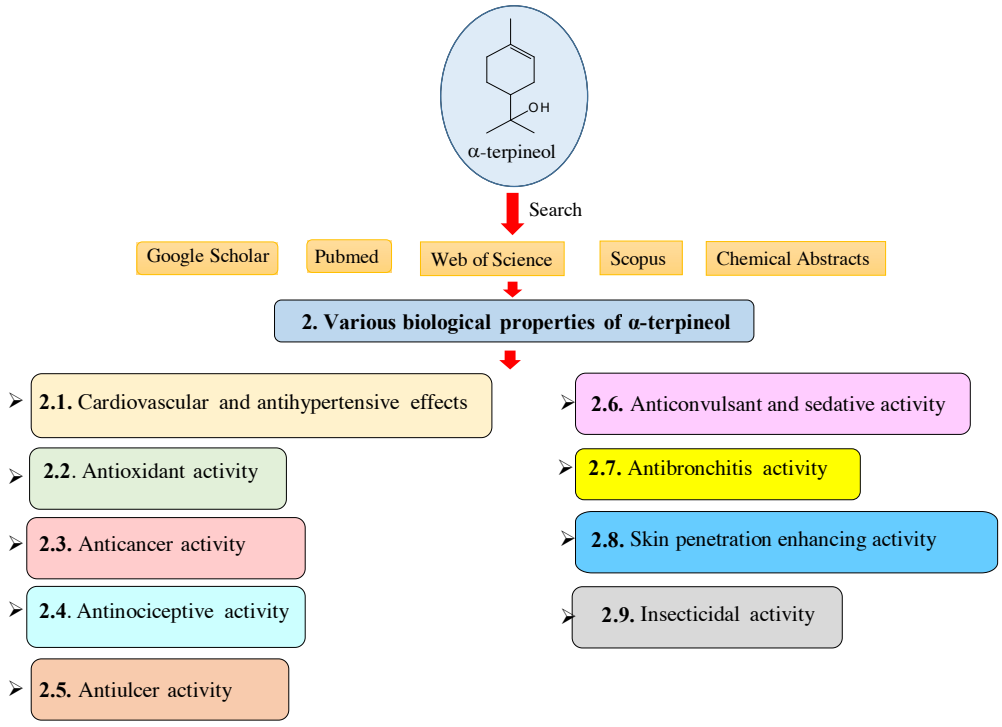

Figure 2: Schematic representation of review section 2.

cajeput oil, pine oil and petitgrain oil [1]. It is a colorless, crystalline solid, smelling of lilac, and is an optically active monoterpenoid that occurs naturally in the (+)-, (-)- and (±) forms. The presence of natural racemic mixtures of α-T was discovered in geranium oils and in Morio-Muscat-wine aroma. α-T enantiomers which are found in the Myrtaceae family, in citrus and lavender oil, were separated by means of a two-columned coupled system and a mixture of two chiral phases, respectively [1,3]. Because of its pleasant odor similar to lilac, α-T is widely used in the manufacturing of cosmetics, soaps, perfumes, antiseptic agents and is considered one of the most frequently used fragrance compounds. Its acetate and other simple esters of α-T are also used in perfumes and aromatic scents. Therefore, the most important reaction for the fragrance industry is its esterification particularly the acetylation of terpinyl acetate [1,4]. In addition, α-T possesses a wide range of biological applications as it exhibits an antihypertensive and antiproliferative effect on human erythroleukemic cells [5,6], as well as anti-inflammatory properties [7], as it was found to be a potent inhibitor of superoxide production [8]. And many studies have reported that α-T has an obvious anticancer effect [9].

This review explores some of the important α-T biological activities from specific papers (Figure 2). We accessed electronic sources from various scientific databases such as Google Scholar, Pubmed, Web of Science, Scopus and Chemical Abstracts and interpreted existing literature on these activities.

2 Biological properties of α-terpineol

2.1 Cardiovascular and antihypertensive effects

Systemic arterial hypertension and cardiovascular diseases increase the risk of mortality and morbidity worldwide [10,11]. Arterial hypertension is considered to be the major risk factor for both heart attack and stroke [12]. Because "*It has been shown that blood pressure levels are strongly and directly related to the relative risks of stroke and heart disease. Endothelial dysfunction in hypertension triggers an imbalance between the production and release of these factors, increasing the generation of reactive oxygen species and diminishing (nitric oxide) NO synthesis and bioavailability. L-arginine is the precursor of NO synthesis by NO synthase (NOS), an enzyme that exists in three isoforms: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS)*" [5]. Furthermore, inhibition of NOS activity and then NO biosynthesis by means of

L-arginine analogs administration such as *L*-nitro arginine methyl ester (L-NAME) leads to hypertension [13,14]. Accordingly, many reports were designed to investigate the cardiovascular and antihypertensive effects of α-T in rats with hypertension induced by L-NAME [5,15]. The NOS inhibitor L-NAME has been used extensively as a mean of inducing hypertension in animal models [5].

Sabino et al. examined the effect of α-T on hemodynamic parameters which was evaluated by the treatment of non-anesthetized rats once a day with different doses of α-T (25, 50 or 100 mg/kg/day) for one week. The results indicated that the induction of a marked hypotensive effect in rats occurred by oral administration of α-T. Hypotension may be exerted due to a decrease in peripheral vascular resistance. The beneficial effects of α-T on isolated mesenteric from L-NAME–induced hypertensive rats were demonstrated, and as a result, α-T in a concentration-dependent manner, relaxed the endothelium-intact mesenteric rings pre-contracted with phenylephrine and depolarization with KCl. Furthermore, α-T-induced relaxation was not considerably reduced by the mechanical removal of the endothelium in phenylephrine pre-contracted mesenteric rings. According to these results, it was proposed that the vasorelaxant activity of α-T is endothelium-dependent and that α-T blocks Ca^{+2} entry through voltage-dependent Ca^{+2} channels, which is involved in the mechanism by which relaxation can be produced. Further results indicated that α-T was able to inhibit contractions induced by the cumulative addition of phenylephrine without endothelium preparations suggesting that α-T could exert its activity on vascular smooth muscle contractile machinery [5].

Several mechanisms for an endothelium-independent vasodilation are in its relaxant activities of vascular smooth muscles. Among these mechanisms are (a) inhibition of agonist-mediated release of Ca^{+2} from intracellular stores, (b) blockage of extracellular Ca^{+2} influx by transmembrane Ca^{+2} channels, (c) inhibition of the contractile apparatus and (d) opening of K^{+} channels. The influx of extracellular Ca^{+2} occurs by means of two kinds of transmembrane Ca^{+2} channels: receptor-operated Ca^{+2} channels (ROCC) and voltage-operated Ca^{+2} channels (VOCC) [16]. α-T attenuated significantly the concentration induced by $CaCl_2$ which indicates that α-T can inhibit vasoconstriction induced by extracellular Ca^{+2} influx through VOCC [5]. It is also known that the $Ca_{v1.2}$ (voltage-gated calcium channel α_1 subunit), which is considered as a Ca_vL (L-type calcium channel) subtype present in various smooth muscle cells (VSMCs), is the main voltage-operated calcium channel found in VSMCs. The $Ca_{v1.2}$ is a subtype of the L-type calcium channel, which is found in different cell types such as myocytes, smooth muscle myocytes and they are responsible for the excitation-contraction coupling, hormone release, and regulation of transcription as well as synaptic integration [17]. In summary, the reduction of calcium influx occurring through the voltage-sensitive Ca_vL channels may result in a decrease in vascular resistance which is attributed to α-T leading to hypotension induction. [5].

In conclusion, α-T-induced hypertension and vasorelaxation are mainly mediated by releasing NO and activating the NO-cGMP (cyclic guanosine 3', 5'-monophosphate) pathway. In addition, oral administration of α-T was able to reduce mean arterial pressure, and in mesenteric artery rings it induced a vascular endothelium-independent vasodilatation, showing alternations in biochemical parameters which indicate an antioxidant effect as well. These data indicate that the ability of α-T to decrease the arterial pressure is mainly depending on restoring the enzymatic antioxidants in L-NAME-induced hypertensive rats and reducing the vascular resistance [5,15].

2.2 Antioxidant activity

"Antioxidants, such as vitamins, enzymes or Fe^{+2}, etc. are able to neutralize free radicals. They exert a health-enhancing effect on the human organism because they protect cells from oxidative damage" [18]. Oxidative stress has an important influence on the development and progression of many diseases, such as cardiovascular diseases, inflammation, neurodegenerative diseases and aging processes. In addition, oxidative stress is mainly characterized by the presence of high bioavailability of reactive oxygen species (ROS) [19]. α-T shows an antioxidant activity, as it was previously mentioned that it is able to suppress the superoxide production by agonist-stimulated monocytes but not neutrophils [8]. *"The antioxidant action of α-T reflects its capacity to act as a preservative in food, cosmetics, and pharmaceutical products, preventing oxidative degeneration of their components"* [20].

Arterial hypertension can be developed from oxidative stress and is believed to result from systemic damage in different target tissues by oxygen free radicals. Non-enzymatic antioxidants (e.g. reduced glutathione) and antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) are the factors which are used to help the performance of intracellular defense against active oxygen species [21]. Reduction of catalase and glutathione peroxidase in L-NAME-treated rats were observed when compared with L-NAME control groups. Based on these data, α-T proved to possess a potent

antioxidant activity against free radicals causing injury [5].

α-T exerts an anti-proliferative effect, therefore, it can be used in the prevention or even treatment of cancer. The anti-proliferative capacity of α-T can be measured using two methods: 2,2-Diphenyl-1-picrylhydrazyl (DPPH), which is a simple and accurate indirect method determining scavenging potential of free radical, and Oxygen Radical Absorbance Capacity (ORAC). This is used as a direct method to determine the ability of lipophilic and hydrophilic substances, via hydrogen atoms transfer, to resist the oxidation reactions with peroxyl radicals. Results revealed that α-T showed very low antioxidant activity in DPPH assays, but it could be compared to commercial antioxidants in the ORAC assay. It was shown that α-T demonstrated a potential antioxidant capacity against peroxyl radicals. Moreover, α-T also exerted cytostatic activities which were found to be very effective against six human cancer cell lines, such as prostate, breast, lung, leukemia and ovarian, especially against breast adenocarcinoma (MCF-7) and chronic myeloid leukemia (K-562). In a range of 181-588 μM the impressive results also revealed that α-T with an antioxidant potential similar to BHA (butylated hydroxyanisole), which is considered to have a potential protective activity in foodstuffs, acts as a natural preservative [20]. Thus, α-T attracts the interest for further research that can culminate in its use as a functional additive, as well as in its role in cancer-prevention *in vivo*. Hereafter, *in vivo* assays must be performed to confirm the antioxidant potential of α-T.

2.3 Anticancer activity

"Cancer is characterized by uncontrolled growth of cells disregarding the normal limits, by invasion and, in the worst case, by metastasis, the expansion of the disease to another non-nearby organ by lymph or blood" [13]. α-T is a bioactive component of *Salvia libanotica* essential oil extract and has shown antitumor activity [9]. *S. libanotica* (Lamiaceae) is a species endemic to the Eastern Mediterranean which induces cell cycle arrest and apoptosis in human colorectal cancer cells, depending on the synergistic action of its three bioactive components: α-T, camphor and linalyl acetate, via caspase activation, mitochondrial damage (cytochrome C release), and PARP cleavage [22].

The link between the development of cancers and chronic inflammation is found to be related to the activation of the transcription factor NF-κB. Since several types of human tumors express mainly NF-κB, blocking this factor was proposed to increase its sensitivity to the action of anti-tumor agents or stopping the proliferation caused by tumor cells [23]. Hassan et al. proved that α-T acts as a potential anticancer agent by suppressing NF-κB signaling. The cytotoxicity of α-T towards 14 different human tumor cell lines representing different hematological and non-hematological malignancies was evaluated *in vitro* where α-T exerted a considerable cytotoxic effect on the cell line of the small cell lung carcinoma, representing a tumor-specific activity. Interestingly, the effective cytotoxic activity of α-T shows a promising effect for treatment of patients with drug-resistant tumors due to the limited effects of resistance represented by α-T [9]. The risk of toxicity against normal lymphocytes is reduced due to tumor selectivity of α-T, helping as an important feature in many of the cytotoxic drugs which are clinically used [24]. *"Treatment with α-T induces cell cycle arrest and apoptosis in the cell line tested in a dose- and time-dependent manner. The results suggest that cell cycle phase arrest by α-T may depend on drug concentration at the shorter exposure time. This finding is consistent with α-T which showed that it is active in including cell cycle changes if combined with linalyl acetate rather than if used alone in colorectal tumor cells"* [9].

Hassan et al. also demonstrated that the inhibition of the NF-κB translocation and activity in tumor cells was exerted by the anticancer activity of α-T in a dose-dependent manner, as indicated by means of the two NF-κB assays. Moreover, the response of NF-κB expression to α-T treatment and other related genes as IL-1R1, IL-1β, ITK, AKT1S1, EGFR, IFNG, BAG1, and TNIK was indicated via microassay analysis showing significant down-regulation. Furthermore, the probable influence of α-T on kinases was examined by using the cell-free assay representing a modest inhibitory effect on AKT, JNK1, JNK2 and IKK beta kinases. The supposed correlation of α-T with AKT kinase and NF-κB inhibitors is attributed to this moderate inhibition of AKT and IKK beta kinases. In addition, the release of cytochrome C due to the disruption of the mitochondrial membrane potential cannot be ignored as an extra cytotoxic mechanism for α-T which helps in the induction of apoptosis in colon cancer cell lines, when linalyl acetate and camphor are combined with α-T [9,22]. On the other hand, the antifungal activity exerted by α-T is also represented by the uncommon structure of mitochondria of the fungi and its cell membrane disruption [25].

Based on the results of many experiments, α-T appears to inhibit the growth and induces cell death in tumor cells by a mechanism that involves inhibition of NF-κB activity and translocation in a dose-dependent manner by means of two NF-κB assays, and is also able to downregulate

many NF-κB related genes expressions such as IL-1β and IL1R1. [9]. It was also indicated that linalyl acetate and α-T exhibit synergistic anti-proliferative effects. The potential combination of treatment showed significant suppression of a basal and tumor necrosis factor (TNF)-α-induced NF-κB activation using DNA binding assays. Moreover, IκB-α degradation and inhibition of p65 nuclear translocation are found to be in correspondence with this suppression. As a result, it is shown that the anticancer activity of α-T is partly mediated by the suppression of NF-κB activation, suggesting its use in a combination with linalyl acetate with chemotherapeutic agents to induce apoptosis [26].

2.4 Anti-nociceptive activity

"Another important activity which is correlated to α-T is the anti-nociceptive activity. A nociceptor is a sensory receptor that responds to potentially damaging stimuli by sending nerve signals to the spinal cord and brain. The anti-nociceptive effect is a reduction in pain sensitivity made within neurons when endorphins or a similar opium-containing substance combines with a receptor" [18]. One of the most important symptoms of an inflammatory disease is a pain. Sanitation of primary afferent nociceptors can result in allodynia and/or hyperalgesia, known as hypernociception in animal models [27]. The main function of pain is to avoid the damage of tissue stimuli via activating the spinal reflex withdrawal mechanisms. Thus, it helps in protecting the tissues of the organism from damaging. In acute pain conditions, pain exists for a while even after healing the injury. Alternatively, chronic pain conditions can be explained by the presence of typical inflammation and neuropathy [28]. Moreover, available anti-nociceptive drugs show low efficacy to relieve painful conditions in patients and possess numerous side effects [29]. Therefore, natural products showing fewer side effects, exert promising therapeutic activities in developing new drugs which can manage certain chronic pain conditions [30].

Golshani et al. reported that the essential oil of *Dracocephalum Kotschyi Boiss* (Lamiaceae), containing α-T as an active component, possesses anti-nociceptive properties [31]. Therefore, many experiments based on these results took place to investigate the anti-nociceptive effect of α-T. The results of another study revealed that α-T possesses both peripheral and central analgesic properties. α-T produced significant ($p<0.01$ or $p<0.001$) analgesic effects by reduction at the early and late phases of paw licking and reduced the acetic acid-induced writhing reflex in mice. Those effects are probably in relation to the inhibition in the peritoneal fluid levels of PGE_2 and $PGF_{2\alpha}$ with the release inhibition of substance P and other inflammatory molecules, such as serotonin, histamine, bradykinin, and prostaglandins [32].

It has been investigated that glutamate plays an important role in transmitting the nociceptive signals from the peripheral nervous system to the spinal cord, mainly the dorsal horn. Moreover, glutamate injections provoked nociceptive responses, which are mediated by neuropeptides (Substance P) released from C fibers, due to the activation of glutamate receptors [i.e., *N*-methyl-D-aspartate acid (NMDA)] that can stimulate the production of a variety of intracellular second messengers. These are NO, then pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and IL-1β, which act synergistically in the excitation of the neurons [33]. Trink et al. indicated that the intravaginal treatment with α-T, one of the main components of *Artemisia princeps* Pamp (Asteraceae) essential oil (APEO), significantly decreased viable *Gardnerella vaginalis* and *Candida albicans* germs in the vaginal cavity by inhibition of the expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), COX-2, iNOS. Based on these results, α-T most potently inhibited the expression of pro-inflammatory cytokines and NF-κB activation [34]. Additionally, it was found that spinal, supraspinal, and peripheral sites of action are involved in the induced nociceptive response by glutamate which is mainly mediated by both non-NMDA and NMDA receptors [35]. Thus α-T produces an inhibition of the nociception induced by glutamate [32]. The anti-inflammatory activity of α-T was assessed in another study, where α-T showed inhibition of bovine cyclooxygenase-1 and 2 (COX-1 and COX-2). α-T exerted selective COX-2 inhibition, where its IC_{50} values against COX-1 and COX-2 were 5.14 mM and 0.69 mM, respectively. This indicated that α-T showed higher COX-2 activity inhibition than Aspirin®, which is the most popular NSAID [36].

Sakurada et al. suggested that the capsaicin-induced pain model examines substances which act on pain of neurogenic origin. Furthermore, capsaicin can be defined as an extracted neurotoxic substance from red pepper, resulting in the irritation of the skin when applied or injected into animals causing a painful sensation and subsequent desensitization to chemically induced pain. Many reports have revealed that capsaicin provokes the release of neuropeptides, nitric oxide (NO), excitatory amino acids (glutamate and aspartate), and pro-inflammatory mediators and also helps in the transmission of nociceptive information to the spinal cord [37]. The analgesic action of α-T was presented by Le Bars et al. involving the supraspinal as well as the spinal

components by the utilization of the hot plate test [38]. The results suggested that α-T (only at a higher dose) has a central analgesic effect, due to the occurrence of time response delay during a hot plate test, when mice were exposed to a nociceptive stimulus [32].

According to Poole et al. releasing primary hypernociceptive mediators are believed to be stimulated by a cascade of cytokines and not directly by means of inflammatory stimuli [39]. Mechanical hypernociception is induced by carrageenan (CG) using this cascade of cytokines. TNF-α is the first cytokine to be set free and subsequently triggers the release of other cytokines such as IL-1β [40]. This can lead to a neurogenic inflammation which contributes to the inflammatory process resulting in central and peripheral hyperalgesia. Moreover, the α-T's anti-nociceptive activity indicated that the development of this mechanical hypernociception is inhibited by pre-systemic treatment with α-T at doses of 25, 50 or 100 mg/kg. i.p. A similar action was also noticed upon prostaglandin E_2 (PGE_2) and dopamine (DA) administration, where it was observed that α-T was able to maintain the baseline nociceptive threshold and significantly inhibited the neutrophil-influx in the pleurisy model [28]. These results may conclude that the synthesis of compounds, such as eicosanoids which are correlated with the inflammatory process, is inhibited by α-T possibly by means of suppressing NF-κB signaling [5]. α-T (1, 10 and 100 μg/mL) also significantly reduced ($p<0.01$) nitric oxide (NO) production in macrophages stimulated by lipopolysaccharides (LPS) *in vitro* [28].

In summary, the data collected so far provide information about the anti-nociceptive and anti-inflammatory properties of α-T which attract great pharmaceutical interest in developing new clinical drugs which can be useful in managing and controlling painful and/or inflammatory disease [28,32].

2.5 Antiulcer activity

"Peptic ulcer is one of the most common gastrointestinal diseases. Gastric ulcers are generally caused by a disruption in the balance between aggressive factors (pepsin and hydrochloric acid) and mucosal defensive factors, such as blood flow, mucus, and bicarbonate secretion. In recent years, a widespread search has been launched to identify new anti-ulcer drugs from natural sources" [41].

As α-T is an isomer of the monoterpene alcohol terpinen-4-ol (T-4-ol) which possesses anti-ulcer activity [42], it was also of interest to evaluate and present the anti-ulcer activity of α-T- in the present review. The gastroprotective activity of α-T was determined in the two ethanol-and indomethacin-induced ulcer models in rats. In the ethanol-induced ulcer model the oral administration of α-T furnished a gastroprotective activity, by reduction of the gastric lesions. Stimulation of defense mechanisms (cytoprotective effect) is the suggested mechanism of drug action showing gastroprotective activity against ethanol-induced gastric lesions, rather than the inhibition of aggressive ones (anti-secretory effect). The indomethacin-induced gastric lesions were also decreased by means of an oral treatment with α-T, but a considerable inhibition ($p<0.01$) was noticed only at concentrations of 30 mg/kg and 50 mg/kg. This result shows that α-T exerted its gastroprotective action in a dose-dependent manner [41]. Moreover, there is a relationship between gastric acid and the gastric lesion formation which was induced by indomethacin. Gerkens et al. proposed that the indomethacin-induced lesion formation was attributed to the decrease of gastric mucosal blood flow [43].

Pre-treatment with indomethacin (10 mg/kg) did not inhibit the gastroprotective action of α-T on ethanol-induced ulcers. Based on this result, an increase in prostaglandin synthesis is not believed to be involved in the gastroprotective action of α-T at a concentration 50 mg/kg. On the other hand, the secretion of gastric acid can be inhibited by either proton pump inhibitors and/or histamine H_2 receptor antagonists, which represent the currently used drugs in order to treat ulcers. However, α-T has not changed proton concentration values, pH, and the gastric volume after pylorus ligation, indicating that its gastroprotective action is not suggested to be due to gastric secretion inhibition. On this basis of such evidence, α-T exerts its gastroprotective effect probably by means of cytoprotective mechanisms which need further investigations to be more explained [41].

2.6 Anticonvulsant and sedative activity

Around 450 million people worldwide suffer from many problems during their lives, such as neurological, mental or behavioral disturbance [44]. Epilepsy can be defined as a disorder accompanied by recurrent spontaneous seizures, caused by several complex mechanisms including different neurotransmitter systems as GABA (γ-aminobutyric acid) and cholinergic system. Despite using more efficient and modern anticonvulsant drugs to treat epilepsy patients worldwide, seizures are still considered to be unmanageable in more than 20% of the cases. Furthermore, most of the currently used antiepileptic drugs are obtained by means of chemical syntheses, such

as benzodiazepines and succinimides [45]. Therefore, recent studies on monoterpene compounds such as α-T have been performed to examine their pharmacological aspects to develop new anticonvulsant drugs with lower side effects and more advantages than that of the currently used pharmaceutical drugs [45].

De Sousa et al. investigated the anticonvulsant activity of α-T. The results of this study indicated that the latency to pentylenetetrazole-induced convulsions is increased by treatment with α-T at concentrations of 100 and 200 mg/kg and the incidence of hind-limb extension produced by MES (maximal electroshock seizure) is reduced at concentrations 200 and 400 mg/kg in a dose-dependent manner in mice [46]. Another study analyzed the therapeutic effect of α-T as a relaxing drug and tranquilizer. The data showed that α-T increased the sleep time of the mice indicating a sedative property, due to the suggested action on central mechanisms affecting the inhibition of the metabolism of pentobarbital or the regulation of sleep in mice. In other words, α-T exhibited a depressant effect on the pentobarbital-induced sleep test, indicating a sedative property [47].

2.7 Anti-bronchitis activity

"Chronic obstructive pulmonary disease (COPD) is a chronic obstructive lung disease and is frequently found in well-developed countries due to the issue of aging population. COPD can lead to the restriction of lung function" [48,49]. The current treatment options for COPD are very limited and their side effects of treatment frequently noted is Cushing Syndrome caused by long-term steroid use [50]. At the final state of severe COPD patients need lung transplants but still the survival outcome is poor [51]. Despite improvement with regard to pharmacy and drug invention the occurrence of COPD and mortality related to COPD continues to rise [52]. Clearly, efforts to stop smoking and to control pneumonia could be the appropriate prevention methods to limit deterioration in cases of COPD. However, there are no other useful ways to attempt to cure the COPD; thus it remains the leading cause of death throughout the world [53]. Therefore, prevention of the occurrence of COPD is the most important issue to address, but not only the above-mentioned methods but also by the inhibition of IκB-kinase beta (IKK2) which is linked to COPD occurrence [54,55].

Tsou et al. investigated the effect of α-T against COPD. The top three traditional Chinese medicine (TCM) compounds were found to be sinapic acid-4-*O*-sulphate, kaempferol and α-T belonging to the TCM herbs *Magnolia officinalis* (Magnoliaceae), *Bupleurum chinese* (Apiaceae), respectively [56]. α-T exerts an antimicrobial effect and in particular, prevents infections that originate from periodontopathic and carcinogenic bacteria [57]. As a result, it was indicated that the above mentioned TCM compounds can have an effect on IKK2 inhibition and prevent exacerbation and disease progression with regards to COPD [56].

2.8 Skin penetration enhancing activity

Over the last two to three decades, the skin has become an important route for the administration of drugs for topical, regional or systemic action. The skin has evolved as a physical and biochemical protective barrier which prevents the loss of water from the body, and guards against entry into the body of external toxic chemicals and infectious agents, thereby maintaining homeostasis. The role of the skin as a barrier to the external environment renders the absorption and transdermal delivery of most drugs problematic. The stratum corneum (SC) which is the outermost layer of the skin and comprised of keratin-rich cells embedded in multiple lipid bilayers has been considered the rate-determining structure governing percutaneous absorption of permeants. Therefore, most of the drugs are not able to penetrate the SC or to be delivered through it [58]. *"Many strategies have been employed to enhance dermal and transdermal delivery. These include the use of chemical penetration enhancers, preparation of supersaturated drug delivery systems, electrically driving molecules through the tissues by iontophoresis, and physically disrupting the skin structure by electroporation or sonophoresis"* [59].

Delivery of drugs via the skin has numerous advantages, like non-invasiveness, the potential for continuous or controlled delivery, and potential for delivery of certain classes of drugs that are not amenable for the administration via other routes of drug delivery. Various types of penetration enhancers with different modes of action have therefore frequently been used in the field of transdermal drug delivery research [58]. Transdermal delivery of drugs promises many advantages over oral or intravenous administration such as decreasing the side effects, improving patients compliance, first-pass effect elimination, sustained drug delivery and interruption of the drug treatment if required [60], though human skin provides an effective barrier to the permeation of most drugs in the form of SC [61,62]. Many factors have a great influence on the dermal absorption such as skin type, the origin (human, animal), environmental factors, as

well as the physicochemical activities with the dermal/transdermal absorption in humans. [63]. Transdermal therapeutic systems offer a more reliable mean of administering the drug through the skin by various physical, chemical, biochemical, supersaturation and bioconvertable prodrug enhancement strategies [64].

Out of these strategies, a popular technique is the use of chemical permeation enhancers, which reversibly alters the permeability barrier of the SC. α-T is considered one of these chemical enhancers, which is currently believed to improve solubility within the SC or increase lipid fluidity of the intracellular bilayers [58,64]. Many studies have reported that α-T appears to be acceptable as a promising skin penetration enhancer as indicated by following advantages [63]:

- high percutaneous enhancement ability,
- less toxic with low irritancy potential,
- reversible effect on the lipids of SC

Several studies suggest that the activity of α-T as an enhancer is a result of disrupting the intracellular lipid bilayers. Evidence from skin electrical conductivity measurements suggests that α-T may create polar pathways across the SC for ions and polar drug penetration. In addition, results from electron paramagnetic resonance have demonstrated that α-T can fluidize the SC lipids and weaken the hydrogen-bonded network of the polar interface of the SC [60,65,66]. The mechanism of action of α-T appears to be difficult, depending on the nature of permeants (e.g. hydrophilic or lipophilic). Furthermore, α-T is an alcoholic monoterpene with a high degree of unsaturation and appears to be a better candidate for enhancing the permeation of hydrophilic drugs such as e.g. 5-fluorouracil by increasing the diffusion of the drug in the SC [58,64]. *"The interaction of α-T with SC lipids and keratin can be elucidated with instrumental methods such as Fourier transform infrared spectroscopy (FT-IR) and differential scanning colorimetry (DSC). The FT-IR provides the information about the molecular and conformational changes of lipids and proteins, whereas the DSC provides information about their thermotropic behavior"* [60].

As skin penetration enhancer, α-T has been employed directly or in combination with co-solvents such as propylene glycol or ethanol. Synergistic activity has been reported between α-T and propylene glycol as well as between α-T and ethanol [60,65]. It was reported that the *in vitro* permeation of haloperidol (HP), an antipsychotic drug, is increased through human skin by using α-T at a concentration of 5% w/v in 100% propylene glycol (PG). Haloperidol is a lipophilic drug and may play an important role in developing the transdermal dosage form. Since HP is clinically needed to be found in a long-acting formulation to avoid psychosis relapse, it was required to use as a skin penetration enhancer α-T and as co-solvent PG to increase the permeation of HD [60].

Narishetty et al. investigated the effect of this monoterpene alcohol and other various oxygen-containing monoterpenes, such as 1,8-cineole, menthol, menthone, pulegone and carvone for the *ex vivo* permeation of zidovudine (AZT), the first approved and wide clinically used anti-HIV substance, in a solution of 66.6 % ethanol in water across rat skin. Based on the result of this study, it was indicated that a hydrogen bonding interaction is formed by α-T with the ceramide head group of SC lipids and a subsequent reduction in the skin barrier property occurred [65].

According to many skin penetration studies using the skin of hairless mice and excised animal skin, it was found that α-T was effective in enhancing the skin penetration of model permeants, such as caffeine [67] and 5-Fluorouracil [68], respectively. α-T exerted an effective penetration enhancing activity for hydrocortisone percutaneously and also increased the permeation between 3.9-fold and 5-fold, and α-T was the most active compound among several other compounds to increase the delivery of triamcinolone acetonide [63,67].

The use of local anaesthetics in combination with penetration enhancers could overcome the barrier properties of the skin to epicutaneous penetration of local anesthetic drugs. Lidocaine is a topical anaesthetic agent with low skin permeability which cannot adequately penetrate the intact skin. On the other hand, the ideal topical anaesthetic agent is one that provides 100 % anaesthesia in a short period of time, is further effective on the intact skin without systemic side effects, and invokes neither pain nor discomfort [69]. The authors of that study investigated the effects of some permeability enhancers such as polysorbate 80, polysorbate 20, dimethylsulfoxide (DMSO), tert-butyl cyclohexanol (TBCH), and α-T in different concentrations on the percutaneous permeation of lidocaine. According to that literature review, α-T showed the best permeability-enhancing effects on the lidocaine penetration through the skin. Since α-T is a relatively safe compound, it can be recommended to incorporate it into local anaesthetic cream formulations at low concentrations. α-T exerts the best effect at a concentration of 2.5%, as it is believed that it can produce eutectic mixtures with lidocaine and increase the thermodynamic activity of lidocaine in the relevant formulation [69].

Interestingly, Fang et al. found that the best method to enhance the curcumin permeation is the pre-treatment

of rat skin with 5% α-T in an ethanolic solution for 1 h [70]. Curcumin exhibits various biological properties such as anticancer and anti-inflammatory. Therefore, it can be used in the treatment of several disorders, such as tumors and pro-inflammatory chronic diseases [71-73]. Because of the insufficient aqueous solubility and bioavailability of curcumin, it is not widely used in the clinical field for treatment of cancer and other diseases [74]. In another study, three terpenes, α-T, 1,8-cineole, and limonene, were used to compose an oil phase of the microemulsions. They provide another promising alternative for the dermal and transdermal delivery of both hydrophilic and lipophilic drugs [59]. Their effects on curcumin skin delivery were evaluated using neonatal pig skin mounted on a Franz diffusion cell. The results indicated that curcumin retained in the skin increased in the order limonene > α-T > 1,8-cineole [59]. Additionally, it was reported that α-T was used as a transdermal enhancer for buspirone hydrochloride, an anxiolytic, in hairless mouse skin [75]. Moreover, Jain et al. showed the effect of α-T on imipramine hydrochloride (IMH) permeation in the ethanol (EtOH): W (2:1) system. By means of unjacketed Franz diffusion cells, permeation studies of IMH were performed through rat skin. Based on the results of this literature [76], it was found that α-T is an effective permeation enhancer for IMH.

2.9 Insecticidal activity

"Some facts indicate that the use of synthetic chemicals to control insects and arthropods raises several concerns as to the environment and human health. So, there is a growing demand for alternative repellents or natural products. These products possess good efficacy and are environmentally friendly. Essential oils from plants belonging to several species have been extensively tested to assess their repellent and even insecticidal properties as valuable natural resources" [18]. Searching for novel and effective natural products which are based on biopesticides, terpenoids have shown promising insecticidal activities [77-79]. *Aedes aegypti* L. is the principal vector of dengue, Zika and chikungunya, and the use of repellents is one of the approaches to prevent these diseases. Scientists at the Center for Medical, Agricultural and Veterinary Entomology (Gainesville, Florida, U.S.) evaluated several natural terpenes for the discovery of safe and potential repellents against the female *Ae. aegypti*. They found that (-)-α-T was a repellent at a minimum effective dosage (MED) of 0.039 ± 0.008 mg/cm^2 compared to positive control (*N,N*-diethyl-3-methylbenzamide, DEET) (MED= 0.014 ± 0.002 mg/cm^2) [79]. Campbell et al. also found that α-T showed prompt olfactory responses in *Ae. aegypti* antennae [80], however, α-T had a moderate repellent effect based on EAG responses against the stable fly *Stomoxys calcitrans* L. [81]. Mosquito larvae are important and attractive targets for pesticide management programs. Tabanca et al. reported that (-)-α-T did not show any mortality in the pre-screening bioassays at a concentration of 100 ppm against 1st instar *Ae. aegypti* [82].

The maize weevil, *Sitophilus zeamais* Motschulsky, causes yield losses in storage products like corn. Under laboratory conditions, α-T showed 100% mortality against *S. zeamais* adults after 96 h of exposure at the highest dose (30 μL/μg) [83].

Booklice, *Liposcelis bostrychophila* Badonnel, have a widespread distribution infesting domestic premises, manufacturing factories, raw material stores; they are also found in historical documents [84]. Due to the presence of more damaging post-harvest primary pests, they are often disregarded and are generally considered to be secondary pests. Liu et al. reported that α-T exhibited strong contact toxicity and repellent properties against booklice [85]. α-T was a major compound (37.2%) in *Artemisia rupestris* L. (Asteraceae) essential oil and this essential oil, can be a great potential for the development into natural insecticides or fumigants as well as repellents for the control of insects in stored grains [85]. α-T also demonstrated high fumigant toxicity against two-spotted spider mites *Tetranychus urticae* Koch [86].

Termites are the most damaging insect pests damaging wooden structures worldwide. There is an increasing interest in naturally occurring toxicants to Formosan subterranean (*Coptotermes formosanus*), invasive species of termites [87]. α-T was selected to test for its antitermitic activity against *C. formosanus* and showed slight toxicity at a dose of 2.5 mg g^{-1} after seven days. However, α-T demonstrated 100% termite mortality against *C. formosanus* at a dosage of 4 mg g^{-1} after 7 days [87].

Based on these above research results, we can conclude that α-T had responded to selective insects and dose-dependent activity. To discover, develop and understand the naturally based bio-pesticides, we need more scientific research on the insect diversity, and α-T is one of the natural compounds to be widely investigated.

3 Conclusion

α-T is a monocyclic monoterpene tertiary alcohol with a pleasant scent similar to lilac. Therefore, it is widely used in the manufacturing of perfumes, cosmetics, soaps, antiseptic agents and is considered one of the most

frequently used fragrant compounds [1]. In addition, α-T possesses a wide range of biological actions which attract a great interest in the medicinal field [4].

The cardiovascular and the antihypertensive effects of α-terpineol were investigated in several studies. These results indicated that the oral administration of α-T was able to reduce the mean arterial pressure and endothelium-independent vasodilatation. Moreover, α-T was able to restore enzymatic antioxidant in L-NAME-induced hypertensive [5,15].

Additionally, α-T showed an anti-proliferative (antioxidant) activity, which could be used in the prevention or even treatment of cancer, as it was found that α-T demonstrated a potential antioxidant capacity effect against different human cancer cell lines (breast, lung, prostate, ovarian and leukemia). α-T inhibits the growth and induction of cell death in tumor cells by means of an inhibition of NF-κB activity [9,20].

The anti-nociceptive activity is one of the most important biological actions correlated to α-T. It was indicated that α-T produced significant analgesic effects by reduction at the early and late phases of paw licking and reduced the acetic acid-induced writhing reflexes in mice (formalin and writhing tests, respectively). Those effects are probably in relation to the inhibition in the peritoneal fluid levels of PGE2 and PGF2α and to the release inhibition of substance P and other inflammatory molecules [32]. However, α-T exerted also a selective COX-2 inhibition (0.69mM), therefore, it is believed that α-T showed higher COX-2 activity inhibition than Aspirin® [36]. α-T might be potentially interesting in the development of new drugs for the management of painful and/or inflammatory diseases, as well as the development of novel therapies for COPD [56].

Several studies have reported that α-T also possesses antiulcer activity. The results suggested that it presented a gastro-protective activity by reducing the gastric lesions at the doses 10, 30 and 50 mg/kg without the involvement of gastric acid secretion inhibition or increase in prostaglandin synthesis [41,42]. Furthermore, α-T showed anticonvulsant and sedative activities via a depressant effect on the pentobarbital-induced sleep test [47]. In addition, it increased the latency to convulsions induced by pentylenetetrazole and decreased the incidence of hind limb extension produced by MES in a dose-related manner [46].

Another important biological activit of α-T was its promising effect as a chemical skin penetration enhancer, currently believed to improve the solubility within the stratum corneum (SC) or to increase the lipid fluidity of the intracellular bilayers [58,64]. In addition, the insecticidal activity of α-T attracted the interest of many scientists. Therefore, it is suggested that α-T may be a potential agent for the development into natural insecticides or fumigants, as well as repellents for control of insects [77-87].

Consequently, α-T has exhibited a potential satisfaction in certain activities due to its usage in pharmaceutical and agricultural industries. Encouraging results from these wide range of biological activities show that α-T is very promising candidate in pharmaceutical and agricultural applications.

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