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Review article

Cedar leaf oil vapor in buildings and forests: Health benefits & mechanisms

Hudson, James B.

Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, Canada.

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***Corresponding Author: Hudson, James B,** 5344 Kenwill Drive, Nanaimo, British Columbia, Canada, V9T 5Z8.

Email: jbhudson@mail.ubc.ca
Tel: 1-250-756-2133

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Abstract

Many people today experience symptoms indicative of chronic stress, which is manifest as persistent or frequent inflammation in one or more parts of the body. These conditions may be the result of current lifestyles, including the buildings that they work or live in, a situation referred to as sick building syndrome (SBS). Relief may be obtained by incorporating cedar leaf oil vapor into ventilation (HVAC) systems, or by spending time in a forest containing cedar-like trees or similar conifers that exude volatile compounds (terpenes) from their leaves, an experience which often leads to an improvement in health parameters. This procedure is referred to as forest bathing, or nature therapy. Many studies recently have confirmed the beneficial effects of these leaf oils and their vapors, according to a variety of laboratory experiments and field trials. Thus the cedar leaf oil terpenes have been shown in various models to inactivate many viruses and microbes directly or indirectly through activation of natural killer cells. Furthermore the terpene mixtures, and some individual tepenes, can interfere in the production of pro-inflammatory cytokines and other inflammatory mediators. This review discusses the evidence and suggests a common mechanism to explain how the leaf oil compounds, the terpenes, could relieve the chronic inflammation and stress, and consequently lead to a restoration of homeostasis.

Introduction

Plant-derived oils have been used for centuries, in different parts of the world, for many pharmaceutical, food and cosmetic applications, pest control, and for the treatment and prevention of various diseases and their symptoms, as for example in aromatherapy. These have usually been applied on an individual basis, and often as vapors for controlling respiratory problems [1-5].

Recently there have been advances in the application of oil vapors derived from the leaves of cedar and related trees (see Table 1), targeting groups of individuals for the purpose of improving or optimizing health. Two such advances are discussed in this review, namely 1) alleviation of "sick building syndrome (SBS)" otherwise known as "built environment intolerance (BEI)" [6-11], and 2) "forest bathing" or "ShinrinYoku", a popular form of "nature therapy" [12-19].

Many people in current societies suffer chronic stress, involving persistent low- level inflammation, which leads to preventable diseases [20-23]. Consequently, scientists are searching for safe remedies that can alleviate the inflammatory responses. Several groups of investigators have carried out basic studies for the purpose of confirming previous anecdotal reports on the oil vapors obtained from different species of cedar-related trees, and understanding possible mechanisms of action. These studies have revealed potent antimicrobial and antiviral activities, as well as significant immune-related activities, including anti-inflammatory activities, all of which together indicate potential beneficial effects of these oil vapors on physiological and mental health parameters. I will first discuss the results of these studies, and in the following general discussion I will attempt to present an overall mechanism to explain the benefits that may result from these treatments.

Table 1 summarizes taxonomy and common names of the Thuja and other species of "cedar – like trees" (members of the Cupressaceae, cypress family) used as sources for the oils referred to in this review. Most of the experimental work has been conducted with steam distilled leaf extracts that comprise typically 20-30 chemically discrete terpenes, although unfortunately some reports contain ambiguous information about their source materials, whether leaf, branches, stems or wood, fresh or old, and discarded foliage. These factors are likely to result in differences in composition of the major bioactive ingredients, the terpenes (sometimes referred to as the more generic term terpenoids).

Sick Building Syndrome (SBS)

Also known as "built environment intolerance (BEI)", this term was coined to describe the recently recognized health problem associated with living or working in buildings with limited air circulation, particularly large office buildings and apartment blocks. The air within

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these buildings, and the indoor surfaces exposed to this air, often contains potentially pathogenic micro-organisms (bacteria and fungi/molds and their spores and toxins) and viruses, some of which could cause or enhance chronic respiratory problems, especially in individuals with asthma, allergies, and similar predisposing factors [6, 8]. Some of these organisms may also produce biofilms that are difficult to remove by conventional means [24]. Other exogenous factors, such as humidity, can also play a role [11].

In addition, individuals vary considerably in their capacity to counteract the offending micro-organisms or other triggers of symptoms such as environmental toxins/stressors [22, 25]. Thus our immune network, which is in continuous communication with our metabolic and other body networks, as well as our individual microbiomes [26-28], may not always remain optimal, with the result that a particular individual could be chronically distressed by the classical symptoms of SBS, including headaches, nausea, fevers, and exacerbation of asthma and allergic reactions. Persistence of these states has been incriminated in long-term inflammatory diseases [20].

One approach to this problem would be the periodic removal or substantial reduction in the micro-organisms inhabiting ventilation ducts and surfaces by a broad spectrum antimicrobial agent. However most of the existing products available are relatively specific and are toxic, and can only be used safely in empty buildings.

Antimicrobial activities of CLO Vapor

Earlier studies, involving the use of small animals and cell cultures, were discussed in a 2005 review [29]. In spite of the uncertainty of some of the source materials, there were strong indications that CLO, in liquid form, could provide beneficial effects in the form of antimicrobial and positive immune effects.

Tsiri *et al* [30] reported a detailed study of the chemical composition and antimicrobial activities of two varieties of *Thuja plicata* and two varieties of *Thuja occidentalis* oils derived by steam distillation of the leaves obtained from trees grown in different parts of Poland. The principal components of the oils were generally similar to each other, comprising the terpenes, alpha and beta thujones, fenchone, sabinene and terpinen-4-ol, together with smaller amounts of many other terpenoids. This analysis corroborated other studies of compositions of oils from Thuja species [30 31].

These oils were evaluated quantitatively (MIC, minimum inhibitory concentration) for antimicrobial activities against 6 bacteria, two gram-positives and four gram-negatives (see Table 2). All of them were susceptible to all four oils. In addition three species of Candida yeasts were tested by the same methodology and were found to be susceptible [30], (Table 2).

Based on anecdotal evidence and limited field trials conducted in British Columbia, we decided to investigate the oil and oil vapor, CLO and CLO-vapor, derived from Western red-cedar leaves [8, *Thuja plicata*]. The terpene content of the oil was qualitatively typical for Thuja species, with approximately 75% thujones alpha and beta. Several gram–positive and gram-negative bacteria, including potential environmental pathogens, were readily killed by exposure to the oil (CLO). The results are summarized in Table 2. Of particular note is the finding that CLO vapor was also effective against these same organisms, although longer times of exposure were required. Different quantities of bacteria were susceptible, and time course studies showed significant but slight differences in susceptibility. But in general these activities indicated potencies comparable to many other essential oils (e.g. tea-tree oil, [4, 8]). Tests indicated that the activities of CLO were bactericidal rather than bacteriostatic.

The possibility of photosensitivity was also evaluated, as many other herbal extracts, including oils, have been reported to be photoactive [3, 32]. However, the potency of CLO was not affected by the presence or absence of light [8].

Purified spores of *Bacillus subtilis* were also susceptible to CLO, but longer exposure to the oil was required in this case, a result comparable to studies with various other antimicrobial compounds [33, 34]. This may be a reflection of the more complex nature of spore walls in comparison with the vegetative bacteria [34].

Two fungi, *Candida albicans* and *Aspergillus niger*, were evaluated by techniques analogous to antibacterial MIC. Both organisms were susceptible, although *Aspergillus* was less sensitive and required longer exposure times [8]. CLO vapor was also effective against these fungal organisms, although longer exposure was required in comparison to the liquid oil.

Manoharan *et al* [24] found that CLO derived from *Cedrus libani* (Cedar of Lebanon) was a very effective agent against biofilm formation by the medically important yeast *Candida albicans*, and this was attributed to its inhibition of the hyphal growth, although the oil was not so effective at controlling growth of the planktonic (yeast) cells of the organism. Gene expression studies revealed that several proteins associated with hyphal growth and adhesion were affected by the treatment, thus explaining the inhibition of biofilm formation.

I should point out that other studies have described antimicrobial activities of oils obtained from cedar wood [35]. These not surprisingly contain some of the terpenoids found in the leaf oil, but they also contain additional compounds, including potentially toxic ones not usually found in the leaf oil.

Table 1. Cedar-like Trees (Cupressaceae-cypress family) discussed in this review. (Ref. 19 and Wikipedia, cypress family; Thuja species 2019).

Official Name	Common Names
Thuja plicata Don ex D. Don	Western red cedar; arborvitae; giant cedar
Thuja occidentalis L.	Northern/eastern white cedar; American/eastern arborvitae
Thuja koraiensis Nakai	-
Thuja standishii (Gordon) Carriere	-
Thuja sutchuensis Franch	-
Cryptomeria japonica D. Don	Sugi; Japanese cedar/redwood
Chamaecyparis obtusa	Korean/Japanese Hinoki
Cedrus libani (Cedar family)	Cedar of Lebanon

Table 2. Summary of Bioactivities of CLOs. (See text for details).

Source of CLO	Bioactivities	Relative potency (++, +)
Thuja species	Antibacterial:	
	Gram negative	++
	Gram positive	++
	Bacterial spores	+
Thuja sp	Antifungal	+ to ++
Thuja sp	Microbial biofilms	++
Thuja sp	Antiviral	++
Thuja sp	Anti-cytokine IL-6	+
Thuja plicata wood oil	inflammatory markers	Inhibited
Chamaecyparis obtusa *Cryptomeria japonica*	Inflammatory markers: NFkB, NO synthase, Cox-2	Inhibited
Different species	cytotoxicity	Not detected
Different sp	NK cell bioactivities	Increased
Different sp	insecticidal	++
Individual terpenes	Various activities re: cytokines, inflammatory mediators, NFkB, neurotransmitters, ion channels	- to ++

Antiviral activities

Viruses in general have often been incriminated as causes or triggers of the respiratory problems that initiate SBS and similar syndromes. Respiratory viruses such as various strains of influenza virus, respiratory syncytial virus, corona viruses, and rhinoviruses (common cold viruses), are frequent inhabitants of indoor air along with the microbes discussed above [36, 37]. But dozens of additional viruses are known to infect respiratory tracts of humans; consequently it has been a challenge to come up with a satisfactory "antiviral" approach for such an environment [38].

Nevertheless, the realization that essential oils could be a solution to this problem prompted us to study the potential of CLO vapor as a safe generic antiviral that could be administered through the HVAC (heating ventilation and air conditioning) system of a building. This rationale is supported by the knowledge that most known respiratory viruses contain a relatively simple but essential membrane that should be sensitive to an agent that can also kill microbes with more complex cell walls.

In quantitative tests (plaque assays, analogous to MICs for microbes), several strains of influenza virus and herpes viruses were readily killed by as little as a few minutes exposure to CLO vapor (*Thuja plicata*) [38]. Even rhinovirus and adenovirus, which are respiratory viruses without membranes, were also susceptible to CLO vapor, although in these cases somewhat longer exposures were required. In the case of influenza virus, the vital membrane protein hemagglutinin (HA) was a target for CLO, which could explain how the virus lost its infectivity.

Interestingly, two of the individual Thuja terpenes by themselves, alpha thujone and alpha pinene, failed to kill the influenza virus, suggesting that the antiviral activity of CLO vapor was due to the combined effect of many of the volatile constituents [38].

The fact that the vapor of CLO was capable of acting as a potent antiviral with a broad range of targets, is a major advantage over oils that need to be used in liquid form. I shall return to this point in the general discussion.

Insecticidal activities

Keita *et al* [31] evaluated the ability of *Thujaoccidentalis* leaf vapors to kill cowpea weevil adults (bruchids, responsible for ruining stored food products). 100% mortality was achieved at oil concentrations significantly lower than those used with traditional oil insecticides. A recent review discussed the prospects for control of insect pests by means of individual terpenes, based on QSAR (quantitative structure-activity relationship) analysis, against several insects relevant to human health [5]. Activities varied considerably according to chemical structures. However, a previous study [39] of *Salvia lavandulaefolia* essential oil and some of its individual terpenes indicated that the whole oil was more effective, in an enzyme inhibitory assay against acetyl cholinesterase, than isolated single terpenes. This should not be surprising since It is well known that the bioactivities of medicinal plant extracts are often more potent than their individual components [40, 41].

Anti-inflammatory cytokines

In our laboratory we established a model system for the detection and measurement of rhinovirus-induced inflammatory responses in human lung epithelial cells. In this system the pro-inflammatory cytokine IL-6 was secreted in substantial quantities, but in infected cells exposed for 60 minutes to CLO vapor the amount of IL-6 was decreased by more than 60% [38]. Since IL-6 is often produced in respiratory infections, and is usually considered as a pro-inflammatory cytokine, then this anti-inflammatory property of CLO vapor could be significant. In addition, exposure of control cells to the vapor did not cause any cytotoxic effects.

Forest bathing-experimental analyses

The concept of forest bathing (a translation from the Japanese *Shinrin Yoku*, [16]) as a natural and healthy approach to relieving the stress associated with urban lifestyles has been discussed in many popular sources, and in recent scientific reviews. It may be considered as a type of Nature Therapy, which has become very popular in many parts of the world that are still endowed with forested areas, eg. parts of Japan, Korea, coastal British Columbia [16, 19]. Accordingly, many reports have been published claiming improvement in certain physiological and psychological parameters following exposure, short or prolonged, to forest environments. The latter have been explained by the presence of volatile components, so-called "phytoncides", especially terpenoids, in the ambient air.

However, a number of recent reviews have criticized some of the earlier studies of this phenomenon because of inadequate scientific analysis, including too much reliance on subjective questionnaires and inadequate statistical significance. Consequently I will focus on studies that have been accompanied by acceptable laboratory evaluations. These typically compare blood samples from exposed and non-exposed subjects for specific parameters of immune function, such as natural killer cells (NK cells) and cytokines, accompanied by measurements of standard blood and urine parameters for stress indicators.

Immune parameters: NK (Natural Killer) cells

Li and co-workers carried out many field tests on subjects exposed to local forest environments, in which the most abundant trees were cedar – related, such as Japanese cedar (Sugi, or *Cryptomeria*), and Hinoki (*Chamaecyparis obtusa*), and known to contain many volatile terpenoids. Subjects were tested for several blood and urinary parameters, NK cell activity, and stress-related hormones, cortisol, adrenaline and noradrenaline [16, 17].

NK cells (natural killer cells) were chosen because they were known to be vital components of the innate immune defenses, and have properties associated with killing tumor cells and virus-infected cells, in addition to other possible roles. The mechanisms involve a variety of different molecular interactions between the NK cells and membrane proteins of the target cells, depending on the exact virus or type of tumor cell [42]. Following the initial interactions, the NK cells secrete cytolytic proteins including perforin, which damages the target cell membrane, and accompanying proteins such as granzymes, which program the target cells to proceed through apoptosis and death. Standard assays for NK cell activity in blood include measurement of the amount of cell killing by the test sample against a certain human lymphocyte cell line, as well as specific assays for perforin and granzymes [42-44].

Exposure of test subjects to the forest environment resulted in increases in the various NK cell parameters, and small decreases in the stress hormone levels [43, 44]. These results were confirmed in experiments in which subjects spent several nights in a hotel room, during which they were exposed to vaporizers containing "stem-oil" derived from *Chamaecyparis obtusa* [45].

However most of the changes in parameters tested were relatively small and in some cases of questionable significance. In addition in cases where individual subject data were plotted, there appeared to be quite different responses among the individuals. This could be a reflection of well-known findings in studies on physiological and psychological effects of natural phenomena, in which grouped data tend to be heavily influenced by individual high or low responders. Thus certain individuals could be strongly affected by the

forest exposure, or vapor exposure, whereas others may be unaffected.

Immune Parameters: Anti-inflammatory effects

A comprehensive study was recently reported by Raha *et al* [45], which included a detailed analysis of the mechanism of a significant anti-inflammatory effect in experimental rats, and in human lung cells following treatment with CLO. The rats were continuously exposed to vapors from Korean hinoki leaf oil (*Chamaecyparis obtusa*). Lung tissues from the treated and control rats were subsequently examined histologically. No toxic effects were seen in the treated animals, but their alveolar capacity had been improved by the exposure.

An in vitro model system of inflammation was established by treating cultures of WI38 cells (a standard cell line originating from human lung fibroblasts) with a microbial lipopolysaccharide preparation (LPS). In this system molecular markers of inflammation were seen, such as induction of nitric oxide synthase, activation of cyclooxygenase-2 (Cox-2), and inhibition of NF-kB, which is an important protein transcription factor that can control many other intracellular pathways involved in inflammatory responses (see below). These changes were reversed however by pre-treatment of the WI38 cells with exposure to the leaf oil. In other words, the oil, which was verified to contain the typical terpene composition expected, acted as an anti-inflammatory [45].

In a different approach to the subject of inflammation, Han and Parker [46] used a preparation of oil distilled from the heartwood of *Thuja plicata*, which has a chemical profile distinct from CLO, being rich in methyl thujate, methyl myrtenate, and terpinen-4-ol. This product, which has been used in the treatment of various skin conditions, was diluted and incubated with a commercial human skin cell model that had been cultured with a collection of known inflammatory mediators. They found that a non-toxic concentration of the oil decreased the level of several proteins associated with inflammation. They also investigated the effects of the oil on gene expression and protein production of a panel of more than 20,000 genes. There were numerous significant changes in 200 or so genes, many of which coded for proteins involved in inflammatory and wound repair pathways.

Thus the oil acted as an anti-inflammatory, or inflammation regulator. The significance of these results will be discussed below, in relation to other bioactivities of CLOs.

Bioactivities of individual terpenes

In addition to the individual studies mentioned above, there have been many reports of specific activities of individual terpenes in laboratory cell culture models and animals, many of them having the objective of finding suitable replacements of existing drugs by safe "natural" products. The targets for these tests were usually specific cytokines, inflammatory mediators, transcription factors such as NFkB, neurotransmitters, or ion channels. Some terpenes showed multiple stimulatory or inhibitory activities in certain tests, while others showed no evident activity [47-54]. It is not clear to what extent these results are relevant to the applications of total CLOs and their vapors.

Discussion & mechanisms

It might appear that I have been reviewing experimental results pertaining to two separate situations, namely: sick building syndrome on the one hand, and forest bathing, otherwise known as forest therapy or nature therapy, on the other. But in fact these situations are similar in that they consist of individuals exposing themselves to the volatile components from the leaves of cedar-like trees, which I have conveniently designated as CLO vapor, for the purpose of improving their health and reducing stress. In practice only certain parts of the body are exposed directly to the components of the CLO vapor, namely skin and respiratory surfaces, so we need to invoke a holistic role for the various body networks in their attempts to restore and maintain homeostasis as the need arises. Thus improvements in physiological functions associated with heart, lungs, blood, mental health, and stress indicators, as well as antiviral and antimicrobial responses, must be considered as parts of the overall effects of the terpenes in the oil vapors. Therefore we need a common mechanism of action.

How do people become "stressed out" and depressed? Many scientists and health advisors would agree that our current lifestyles, in urban and rural societies, in contrast to pre-industrial age lifestyles, are full of stressful stimuli, including environmental stressors that did not exist centuries ago, such as multiple toxins, and novel types of radiation from our many electronic devices [20]. Increasingly these situations are likely to lead to inflammatory responses that could become chronic and give rise to depression and possibly other abnormal mental states. In effect, stress at the cellular level is amplified by our body networks to produce physiological and mental stress [21-23]. Thus the inhabitants of inadequately ventilated buildings (poor HVAC systems), and those who deliberately expose themselves to forest essential oils, are all seeking restoration of health (homeostasis).

So how can a collection of approximately 20-30 terpenes from a specific species of conifer manage to accomplish this? This is even more of a challenge to explain when we consider that a forest is not a plantation, but a mixture of tree species, each with its own characteristic collection of terpenes, although usually these comprise just a few dominant terpenes with a larger number of minor compounds. Consequently at any time the ambient air

could be full of hundreds of different terpenes. But is it possible that certain individual terpenes work just as well? Studies referred to above indicated that a few individual terpenes are bioactive according to laboratory tests with model systems. How does this relate to exposure to CLO vapor?

Plants in general synthesize tens of thousands of different terpenes, by means of a common pathway from isoprenoid units, with various additional side chains that give each terpene a different chemical structure yet retain some common basic properties, such as a hydrocarbon chain that is responsible for their strong lipophilic nature. This property allows them easy access to and penetration through skin epithelia, and some of them have been advocated as adjuvants to help certain drugs to penetrate the skin [55]. Other properties of the terpenes are due to their various side chains, which explains why they do not all have the same physiological effects on humans. Although some individual terpenes possess multiple bioactivities, it is likely that the more widespread activities are a property of a particular mixture of terpenes, possibly in synergistic relationship between different compounds. Synergism is a property found frequently in extracts of medicinal plants, and can sometimes explain why they often possess properties different from individual constituents [37, 40, 41].

Viruses, especially the respiratory viruses, are a continuous threat to the health of humans everywhere, including many of the buildings we inhabit [36, 37]. Because of their variety and their frequency of mutations, the concept of specific antiviral drugs is impractical. However, in terms of chemical structures viruses are relatively simple, comprising RNA or DNA genes in association with one or more viral specific proteins and often surrounded by a lipoprotein membrane. Consequently they should afford easy targets for multiple terpenes. The results summarized above confirm this in the case of CLO liquid and vapor (Table 2). When viruses infect cells they often induce signaling pathways that result in the production of interferons and other cytokines that are excreted and may affect neighboring cells. Influenza virus for example has often been implicated in "cytokine storms", which can lead to severe inflammatory responses in cases of bronchitis and pneumonia [37, 56]. Several respiratory viruses have also been shown to enhance the presence of bacterial receptors, which in turn lead to secondary bacterial infections and more serious lung disease [56].

Many viruses, as exemplified by herpes viruses, establish chronic or latent infections following resolution of the initial acute infection, and may give rise to recurrent disease months or years later. Herpes simplex (cold sores, genital sores) and Herpes zoster (shingles) are common examples. Such chronic infections may act as persistent stressors with consequent low grade but significant inflammation. Thus viruses continue to pose threats to health throughout life.

Bacteria and fungi (molds) are larger and more complex organisms, usually with cell walls, but are also vulnerable to CLO liquid and vapor. Certain individual terpenes can show antibiotic effects, and this property seems to depend on the chemical nature of their side chains. Even biofilms composed of bacteria or fungi can be inactivated (Table 2). In all these cases one or more terpenes could be responsible for binding to or modifying various chemical target molecules or rendering them dysfunctional, and this could result in growth inhibition or death of the virus or microbe.

In several of the studies described above, cultured human cells were found not to be adversely affected by exposure to CLO vapor, or by incubation of the oil itself in low concentrations, according to microscopic appearance and cell viability tests. In other words CLO vapor was not cytotoxic.

In terms of indirect effects of CLO vapor on human cells, the relative ease of access and permeation of a mix of terpenes to skin tissues could enable binding of terpenes to a multitude of important receptor molecules that are prevalent on and inside cell membranes, and which are components of numerous signaling networks. For example epithelial cells, and several types of lymphoid cells, such as NK cells (natural killer cells), as well as monocytes or macrophages, inhabit the epidermis and respiratory mucosa, and many of these cells carry different types of ion channels, hormone receptors, neurotransmitters, and other protein or lipoprotein receptors in their membranes. These are all potential target molecules for terpenes. In addition some of these surface receptors also link up with the intracellular components of additional signaling pathways and their transcription factors such as NFkB that ultimately control important elements of the inflammatory and cytokine responses. I will use an example to illustrate how this scheme could work.

A common factor in numerous signaling pathways is the NFkB complex of proteins and the associated inhibitory IkB complex, both of which comprise several individual proteins. A variety of natural products, including some terpenes tested, can affect the function of different proteins in these complexes and consequently could modulate signaling pathways, including inflammatory responses.

Thus, the terpenes could likely find a variety of proteins or lipoproteins (the receptors), for which they have chemical affinity, in the cell membranes. This would trigger a set of programmed responses within the cell, involving adaptor proteins and binding to sites in the NFkB protein complex, which itself is normally inhibited, or held in check, by another cluster of proteins referred to as the IkB. If the terpene or other molecule can catalyze the phosphorylation of one of the proteins in the IkB

complex, the IkB is removed and degraded, thus allowing the NFkB to become "active". The latter is then translocated to the nucleus of the cell, where it finds and stimulates appropriate DNA binding sequences on various genes involve in inflammatory responses, such as cytokines and other inflammatory mediators [49].

Studies with individual pure terpenes have revealed a variety of reactions with different parts of this pathway, including binding with IkB proteins and interference in the DNA binding steps. But there are also many terpenes that appear not to influence this pathway [as discussed above]. The consequences of these terpene - protein interactions would likely impact most of the internal organs and tissues of the body indirectly since they are all interconnected by the various networks of communication molecules, such as cytokines, chemokines and neuro-endocrines [58] (see Figure 1).

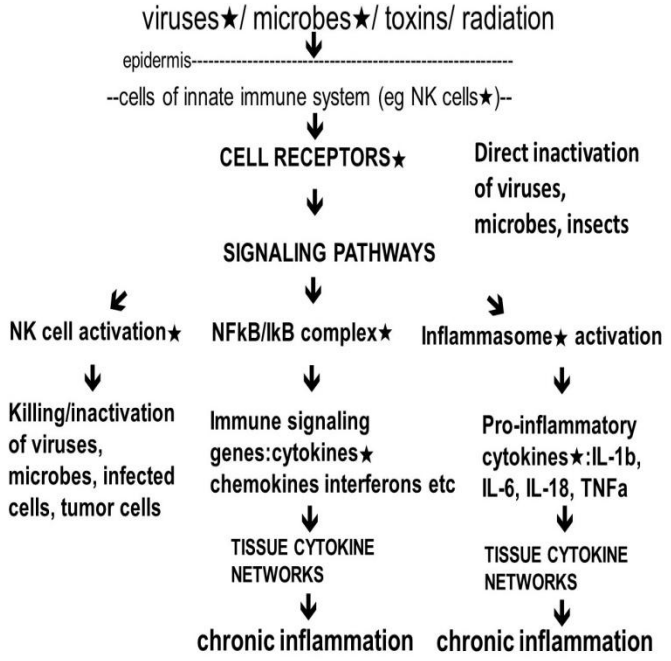


Figure 1. Scheme showing pathways leading to chronic inflammation.
—star (★) indicates known targets for CLO terpenes.

Among the cells that the terpenes would encounter on first contact with the epithelial surfaces are the Natural Killer cells (NK cells) that I discussed above.

These cells are activated by various cytokines and are ready to respond to foreign or modified proteins, ie-non-self proteins, in tumor cells and virus-infected cells, as well as some microbial cells [25].

We can think of stress at the cellular level, where any cell that is exposed to a potential pathogen (virus or microbe), or radiation, or a noxious chemical or particle, triggers a response (acts as a "stressor") to counteract this threat to its integrity. There are also intracellular stressors that have to be dealt with during the course of individual cell maintenance. Numerous recent studies have elucidated some of the signaling pathways involved in stress at the cellular level (various pattern recognition receptors, PRRs; damage associated molecular patterns, DAMPs; pathogen or microbe associated molecular patterns, PAMPs or MAMPs, [25]). Internal and external triggers induce the activation of different pathways that attempt to restore cell integrity, or sacrifice the cell by means of programmed cell death cascades.

Many of these responses go through NFkB or similar pathways and can result in the activation of a complex of cellular proteins referred to as an inflammasome, which has the primary objective of producing substantial amounts of the important pro-inflammatory cytokines such as IL-1 beta, IL-6, IL-18, and TNF alpha. This mature inflammasome is then transported to the cell membrane and the cytokines excreted into the extracellular milieu, possibly within exosomes (microvesicles), where they can circulate and influence other cells [25, 59]. Many other signaling pathways in neighboring cells amplify this response, and the result is a condition of inflammation, which could spread throughout the body by the manifold pro-inflammatory mediators, including additional cytokines and chemokines. Other tissues and organs may be involved, including the brain, by virtue of interactive neurotransmitter and endocrine signaling pathways in various cells. In this way, cellular stress can be translated into physiological and even psychological stress [21, 60-63]. Recent studies have illustrated how inflammatory cytokines can lead to numerous disturbances and pathology in the CNS including brain [61, 62].

In view of the ubiquitous nature of the inflammasome and its capacity to produce large amounts of pro-inflammatory cytokines and consequent stressful conditions, a potentially useful form of treatment could involve the use of inhibitory molecules capable of reversing the maturation or function of inflammasomes. Although some recent studies have found that certain plant derived compounds or extracts can inhibit the production of the pro-inflammatory inhibitors, terpenes have not yet been examined in this regard [63]. Nevertheless the studies referred to above in connection with cedar oils and anti-inflammatory activities suggest that terpenes might explain how forest-bathing/nature therapy, as well as CLO vapor in HVAC systems, may work by alleviating stress at cellular and body levels, and restore and maintain optimal health.

According to this concept, a stressed individual would inhale or absorb the terpene mixture, which would then penetrate the skin and mucosal layers, where they would encounter NK cells, which need to be activated, and numerous epithelial cells, which would be stressed from the various endogenous and exogenous triggers and consequently be in a state of inflammation resulting from the inflammasome pathways. Some terpenes could then inhibit the inflammasomes and consequently stop the

production and excretion of excess IL-1 beta, IL-6, and other inflammatory mediators. This could then result in cross-talk with other signaling pathways, including those involved in cortisol, adrenaline and noradrenaline production, and dispersal throughout the body. They could also affect the production and fate of exosomes (terpenes are lipophilic) responsible for communicating with other cells. The outcome would be restoration of non-stressed organs and tissues, including the brain, i.e. homeostasis, at least temporarily.

According to this scheme the terpenes may not have to gain direct access to all the tissues, only sites where inflammasomes are produced and excreted, for example in the epidermal tissues that are rich in many cells of the immune system. The networks of signaling pathways would do the rest. In addition the circulation transports exosomes around the body. These are small extracellular vesicles that are under intensive study from the aspect of informational or messenger molecules that are excreted and received by and from tumor cells, and possibly the products of the inflammasomes [60].

Thus in contrast to acute inflammation, in which the various inflammatory mediators would find their way to the site of the initial injury or infection and attract a variety of healing factors (such as anti-inflammatory cytokines) to control the situation, chronic inflammation could result from an inability to remove the initial trigger, or inability to dampen the level of inflammation produced. In practice many of us are probably in a state of low level inflammation, resulting in stress somewhere in the body, including the brain, and this could in turn result in damage to certain tissues (Alzheimer's or Parkinson's disease), or clinical states like depression [20-23].

Conclusions

Many recent studies have shown that the terpenes in cedar-leaf, or similar conifer leaf oils, can inactivate viruses and microbes, and activate NK (natural killer) cell activities. These bioactivities could be beneficial in counteracting the symptoms often found in people suffering from SBS, or inadequate HVAC systems. In addition terpenes were found to reduce levels of pro-inflammatory cytokines, in various model systems, thus providing evidence to corroborate the field studies indicating health benefits of forest bathing.

These results can be explained by a model in which the terpene mixtures interact with specific cellular proteins and consequently control cytokine levels and reduce inflammation at the cellular and tissue levels. In turn this could result in a significant reduction in stress and its many psychological and clinical manifestations.

Conflicts of interest

There were no conflicts of interest.

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