REVIEW

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Terpenes: substances useful in human healthcare

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Abstract

Terpenes are naturally occurring substances produced by a wide variety of plants and animals. A broad range of the biological properties of terpenoids is described, including cancer chemopreventive effects, antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, and antiparasitic activities. Terpenes are also presented as skin penetration enhancers and agents involved in the prevention and therapy of several inflammatory diseases. Moreover, a potential mechanism of their action against pathogens and their influence on skin permeability are discussed. The major conclusion is that larger-scale use of terpenoids in modern medicine should be taken into consideration.

Abbreviations: 5-FU – 5-fluorouracil, AKBA – acetyl-11-keto-β-boswellic acid, AZT – zidovudine, CoQ – coenzyme Q, COX-2 – cyclooxygenase 2, DMAPP – dimethylallyl pyrophosphate, HIV – human immunodeficiency virus, HSV – herpes simplex virus, iNOS – inducible nitric oxide synthetase, IPP – isopentenyl pyrophosphate, LPS – lipopolysaccharide, NF-κB – nuclear factor κB, NO – nitric oxide, PGE_2 – prostaglandin E_2, PLA_2 – phospholipase A_2, TGF-β – transforming growth factor β, TNF-α – tumor necrosis factor α.

Key words: terpenes, terpene activity, antitumor, antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, antiparasitic.

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INTRODUCTION

Terpenes occur widely in nature. They are a large and varied class of hydrocarbons which are produced by a wide variety of plants and by some animals. They are also abundantly found in fruits, vegetables, and flowers [28]. Their concentration is generally high in plant reproductive structures and foliage during and immediately following flowering [88]. Terpenes are also a major component of plant resins. In plants they function as infochemicals, attractants or repellents, as they are responsible for the typical fragrance of many plants [23, 88]. On the other hand, high concentrations of terpenes can be toxic and are thus an important weapon against herbivores and pathogens.

Animal cholesterol and steroids and the higher triterpenes and phytosterols of plants are directly involved in the stabilization of cell membranes and are regulators of permeability and enzymatic reactions [12]. Terpenes are biosynthetically derived from isoprene units with the molecular formula C_5H_8. The basic formula of all terpenes is $(C_5H_8)_n$, where n is the number of linked isoprene units [31]. Isoprene units may be linked "head to tail" to form linear chains or they may be arranged to form rings. Terpenes can exist as hydrocarbons or have oxygen-containing compounds such as hydroxyl, carbonyl, ketone, or aldehyde groups. After chemical modification of terpenes, the resulting compounds are referred to as terpenoids.

For a long time the mevalonate pathway was considered the universal source of the terpenoid C_5 precursors isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). In this pathway, three molecules of acetyl-CoA are condensed to 3-hydroxy-3-methylglutaryl-CoA with subsequent reduction to mevalonate, which is converted to IPP and DMAPP (Fig. 1). However, an mevalonate-independent pathway, "the Rohmer pathway" was recently discovered. The first intermediate, 1-deoxy-D-xylulose 5-phosphate, is assembled by condensation of glyceraldehyde 3-phos-

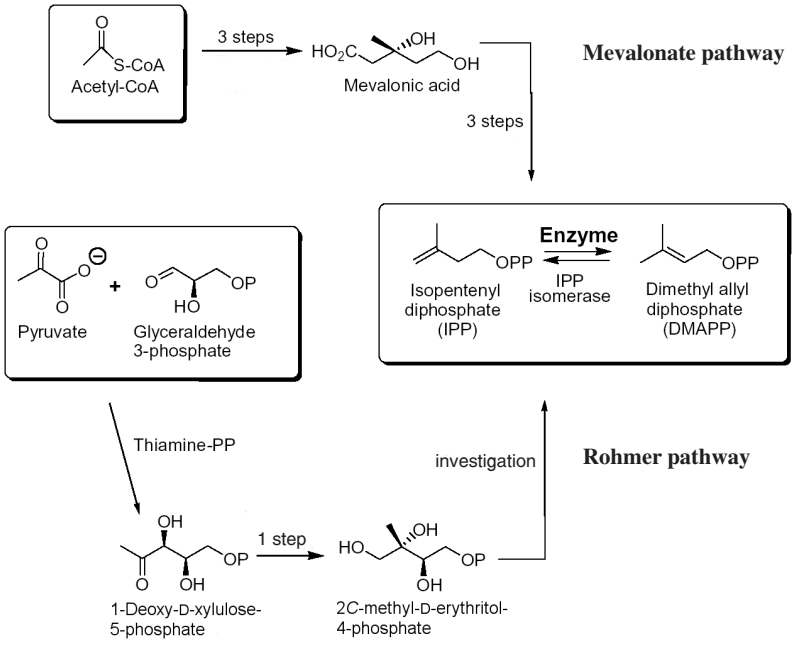

Fig. 1. Mevalonate and non-mevalonate pathways in the biosynthesis of terpenoids.

phate and pyruvate, as shown in Fig. 1. In the second step the product is converted into 2*C*-methyl-D-erythritol-4-phosphate which, by subsequent reactions, is converted into IPP and DMAPP (Fig. 1). *Archaea*, fungi, and animals use only the mevalonate pathway. In plants, the mevalonate pathway is utilized in the cytosolic compartment and the non-mevalonate pathway in plastids [82]. In the biochemical pathway of terpenoid synthesis, prenylotransferases participate in the condensation of activated forms of isoprene units. IPP is linked with an isopentenyl diphosphate isomer of DMAPP in a "head--to-tail" manner. The linear chains of prenyl diphosphates that are formed in the reaction may also be modified through dimerization or cyclization by terpene synthases, forming terpenoids with new functions. The resulting terpenes are classified in order of size into hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. Hemiterpenes consist of a single isoprene unit and are very often modified into oxygen-containing derivatives called hemiterpenoids (e.g. isovaleric acid). Monoterpenes consist of two isoprene units (C_{10}) and may be linear (myrcene, geraniol) or may contain rings (thymol, menthol, α-pinene). Sesquiterpenes consist of three isoprene units (C_{15}) and may be acyclic (farnesol) or contain rings, as well as many other modifications (δ-cadinene). Diterpenes consist of four isoprene units (C_{20}). Examples of diterpenes are cembrene and retinal, which is synthesized on the basis of the diterpene and is a fundamental chromophore involved in the transduction of light into visual signals. Triterpenes consist of six isoprene units (C_{30}). The linear triterpene squalene is a major constituent of shark-liver oil. Plant triterpenes and their derivatives are a large group of biologically active substances. Tetraterpenes contain eight isoprene units (C_{40}). Biologically important tetraterpenes include lycopene (tomatoes) and carotenes. Polyterpenes consist of a long chain of many isoprene units. Natural rubber is a polyisoprene with several *cis* double bonds.

The diverse array of terpenoid structures and functions has provoked increased interest in their commercial use. Terpenoids have been found to be useful in the prevention and therapy of several diseases, including cancer, and also to have antimicrobial, antifungal, antiparasitic, antiviral, anti-allergenic, antispasmodic, antihyperglycemic, anti-inflammatory, and immunomodulatory properties. They also act as natural insecticides and can be of use as protective substances in storing agriculture products [88].

ANTICANCER ACTIVITY

Epidemiological studies suggest that dietary monoterpenes may be helpful in the prevention and therapy of cancers [13, 80]. Among dietary monoterpenes, D-limonene and perillyl alcohol have been shown to possess chemopreventive and therapeutic properties against many human cancers [57] (Fig. 2). At present they are claimed to inhibit, in a dose-dependent manner, the development of mammary, liver, skin, lung, colon, fore-stomach, prostate, and pancreatic carcinomas [5, 24, 37]. D-limonene is a natural monocyclic monoterpene with chemopreventive and chemotherapeutic activities and low toxicity ascertained in pre-clinical studies [92]. There are multiple mechanisms of monoterpene chemopreventive actions. They may act during the initiation phase of carcinogenesis, preventing interaction of carcinogens with DNA, or during the promotion phase, inhibiting cancer cell development and migration. The chemopreventive and therapeutic activities of monoterpenes in later stages of carcinogenesis include induction

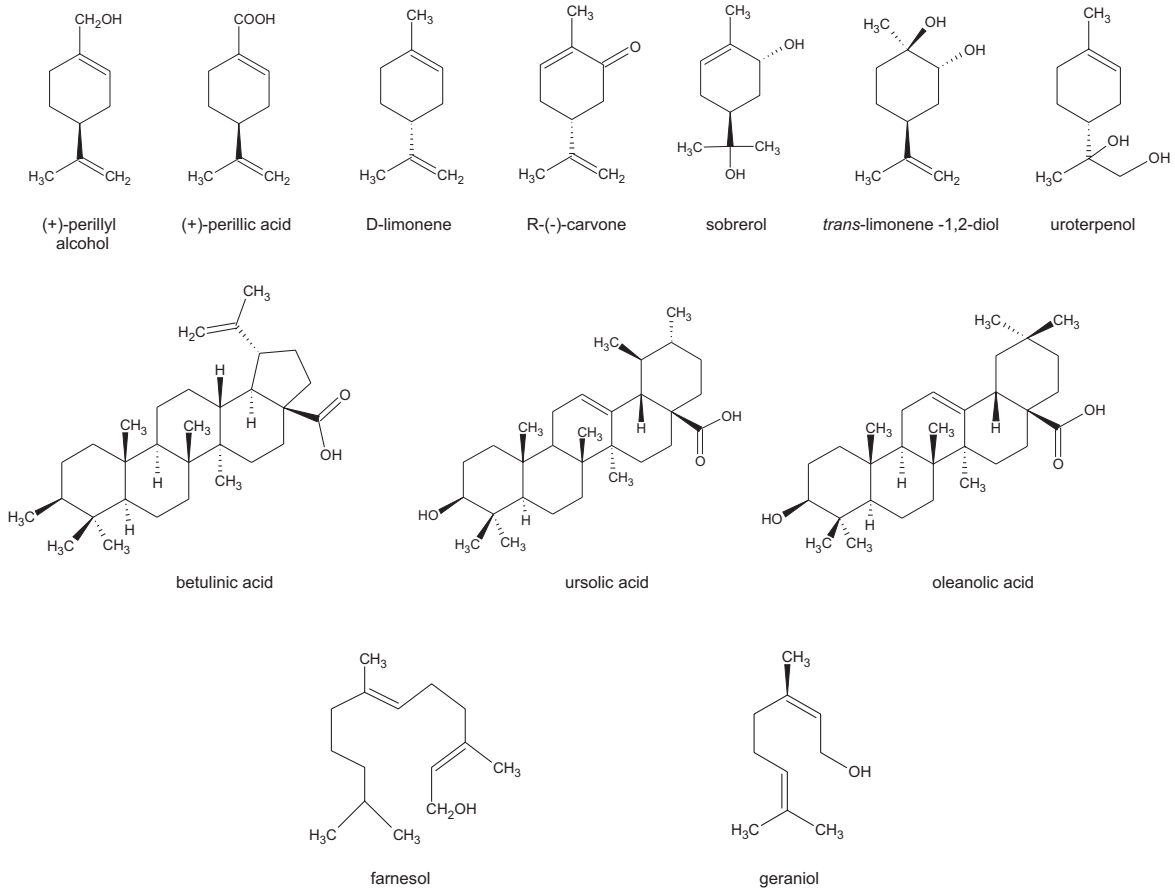

Fig. 2. Structures of selected terpenes with anticancer activity.

of cancer cell apoptosis, re-differentiation of tumor cells, and influence on molecular mechanisms regulating their functions. The most important mechanism that monoterpenes influence is post-translational isoprenylation of proteins regulating the growth of cells. In general, prenylated proteins regulate cell growth and transformation; therefore, disturbance of prenylation of one (especially Ras-regulated small GTP-binding proteins) or more of these proteins may be responsible for the antitumor activity of monoterpenes [23].

The activity of D-limonene and its oxygenated derivatives may be associated with selective inhibition of the post-translational isoprenylation oncoprotein $p21^{ras}$ regulating signal transduction and cell growth. This inhibition may also alter gene expression, leading to apoptosis, cellular re-differentiation and, consequently, tumor regression [25, 92]. In animal experiments the predominant blood-circulating metabolites of D-limonene were perillic acid, dihydroperillic acid, and limonene-1,2-diol. They were found to have greater pharmacological activity in inhibiting protein isoprenylation and cellular proliferation than the initial compound. These data suggest that the antitumor activity of D-limonene in *in vivo* conditions is not direct, but mediated via its metabolites [26, 92]. The most important advantage of D-limonene is its good tolerance in human volunteers at doses which may exhibit clinical activity. Moreover, its toxicity is reversible and does not lead to significant organ dysfunctions. For this reason, the activity, toxicity, and pharmacokinetics of D-limonene are currently in phase I clinical trials [92].

D-limonene serves as a precursor of other oxygenated monocyclic monoterpenes, e.g. perillyl alcohol and carvone, which have also been shown to have anticancer activities [23]. Perillyl alcohol is a naturally occurring monocyclic monoterpene which has preventive and therapeutic activity against a variety of pre-clinical tumor models. It has been shown that perillyl alcohol induces apoptosis in many kinds of cancer cells (pancreatic, mammary, colon, and liver) both in *in vitro* and *in vivo* tests. Its activity led to complete regression of chemically induced and animal transplanted tumors. Perillyl alcohol was also tested as an inhibitor of carcinogenesis induced by ultraviolet light. It was revealed that suntan lotions enriched with perillyl alcohol might limit melanoma induction. This monoterpene is, therefore, postulated to be an effective agent against skin carcinoma development [37]. The basis of the antitumor effects of perillyl alcohol, similarly to D-limonene, is the inhibition of posttranslational isoprenylation of small GTP-binding proteins. Another mechanism of the chemotherapeutic effects of perillyl alcohol is activation

of transforming growth factor (TGF)-β signaling. TGF-β is produced in a latent form, which needs to be activated. Perillyl alcohol mediates TGF-β activation and leads to increased mRNA synthesis encoding its receptors. Activation of TGF-β signaling by perillyl alcohol is closely associated with elevated synthesis of pro-apoptotic proteins (Bax, Bak, and Bad) without influencing p53 or Bcl-2 expression [2]. Moreover, through TGF-β, perillyl alcohol down-regulates the cell cycle, influencing the production of cyclin and cyclin-dependent kinases or their reciprocal interactions. In consequence, it leads to G1-phase arrest and cell apoptosis [2, 86]. Another mechanism of perillyl alcohol action on tumor cells is inhibition of the synthesis of coenzyme Q (CoQ) [2, 36], an important element of mitochondrial respiratory metabolism. In the plasma membrane, CoQ participates in the transmembrane electron transport to stabilize extracellular ascorbate [7]. The reduction of CoQ in cell membranes may, therefore, limit cellular signal transduction and metabolism and induce apoptosis of tumor cells.

During phase I clinical trials, perillyl alcohol at doses which may have clinical activity was well tolerated by patients and had relatively low normal-tissue and systemic toxicity [2, 5]. D-limonene and perillyl alcohol may therefore be considered as pharmaceuticals or pro-drugs, which after administration are converted in the organism into pharmacologically active derivatives with antitumor activity. However, it should be noted that enantiomeric derivatives of these monoterpenes do not influence the metabolism, growth, and differentiation of tumor cells [33]. Therefore, during the preparation of natural chemotherapeutic agents, their stereoisomeric configuration should be taken into consideration.

Chemotherapeutic activities towards human pancreatic cancers have also been shown for other terpenes, such as farnesol and geraniol [10]. Moreover, monoterpenes such as carveol, uroterpenol and sobrerol have been tested against mammary carcinomas. Additionally, carvone has been analyzed as an agent reducing pulmonary adenoma and fore-stomach tumor formation [13, 75, 93]. A stevioside mixture from *Stevia rebaudiana* was found to suppress the tumor-promotion effect of 12-*O*-tetradecanoylphorbol-13-acetate on skin tumor formation in mouse skin [34, 97]. Moreover, several plant triterpenes exhibited *in vitro* antitumor activity. Betulinic acid has been shown to induce apoptosis of several human tumor cells, among others melanoma and glioma. Apoptosis was induced via changes in the permeability transition potential in mitochondria and up-regulation of pro-apoptotic proteins (Bax) and decreasing bcl-2 expression. It was also shown that betulinic acid is an inhibitor of topoisomerase I, a nuclear enzyme that catalyses changes in DNA topology [18, 30] and, in consequence, leads to apoptosis of cells. Other plant triterpenes, such as ursolic acid and oleanolic acid, found in natural wax on apples and other fruits, reduced leukemia cell growth [19] and inhibited the proliferation of several transplantable tumors in animals by inducing nitric oxide (NO) and tumor necrosis factor (TNF) production [59, 70]. These triterpenoids and their derivatives act at various stages of tumor development, inhibiting initiation and promotion as well as inducing tumor cell differentiation and apoptosis. Moreover, they are effective inhibitors of angiogenesis, invasion, and metastasis of tumor cells [60].

Terpenes are easily available and make up a promising new class of agents which may be approved as supplementary drugs in contemporary oncology.

ANTIMICROBIAL AND ANTIFUNGAL ACTIVITIES

Many terpenes have been found to be active against a variety of microorganisms. Tests have been performed on Gram-positive and Gram-negative bacteria and also on fungi [90]. It has been shown that microorganisms express a differentiated sensitivity to plant-derived agents. In general, Gram-positive bacteria are more sensitive to terpenes than Gram-negative [54]. This is mainly determined by differences in the permeability, composition, and charge of the outer structures of the microorganisms. The mechanism of antimicrobial action of terpenes is closely associated with their lipophilic character. Monoterpenes preferentially influence membrane structures which increase membrane fluidity and permeability, changing the topology of membrane proteins and inducing disturbances in the respiration chain [90]. A mixture of terpinen-4-ol, α-terpineol, 1,8-cyneole, and linalool (monoterpenes) has been shown to possess antibacterial activity against Gram-positive and Gram-negative bacteria isolated from the oral cavity, skin, and respiratory tract (Fig. 3). Moreover, promising results were obtained in tests against the Gram-positive bacteria *Staphylococcus aureus*. The rank order of the antibacterial activities of terpenes against *S. aureus* was: farnesol>(+)-nerolidol>plaunotol>monoterpenes such as (–)-citronellol, geraniol, nerol, and linalool. Thymol and (+)-menthol (monoterpenes) also expressed high toxicity when analyzed with *S. aureus* and additionally (+)-menthol was toxic against *Escherichia coli* [39, 90].

Kubo et al. [58] suggested that the activity of terpenes against *S. aureus* may be closely dependent on the number of carbon atoms in the hydrophobic chain from hydrophilic hydroxyl groups. However, this suggestion has not been fully confirmed. Recently it was proposed that the antibacterial activity against *S. aureus* depends on the lengths of the aliphatic chains of terpene alcohols and the presence of double bonds [47]. In turn, the sesquiterpenoids nerolidol, farnesol, bisabolol, and apritone enhanced bacterial permeability and susceptibility to antibiotics [8]. The most important terpene that can be used in antimicrobial therapy is (4R)-(+)-carvone (monoterpene), which was effective against *Listeria monocytogenes* and showed activity towards *Enterococcus faecium* and *Escherichia coli* [13].

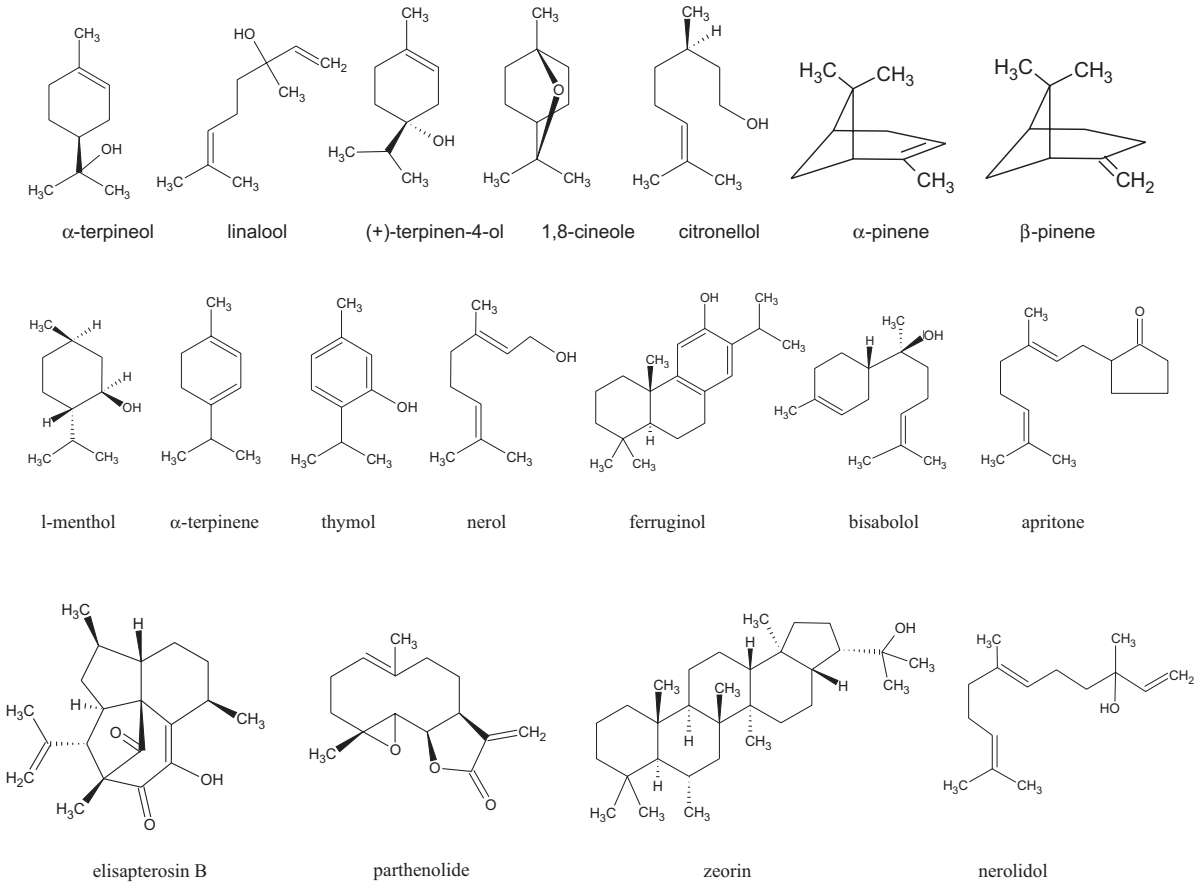

Fig. 3. Structures of selected terpenes with antimicrobial and antifungal activity.

Terpenoid derivatives have been reported to possess antimycobacterial activity, as well. Several metabolites have been tested, where the most active was ferruginol (diterpene), which exhibited inhibitory activity towards *Mycobacterium smegmatis*, *M. intracellulare*, and *M. chelonei*. On the other hand, benzoxazole-containing diterpenes, tetracyclic diterpene elisapterosin B, and triterpenoid zeorin were shown to reduce growth of *M. tuberculosis* [20]. An extensive array of sesquiterpenes and their lactones also revealed activity against *Mycobacteria*. Moreover, such sesquiterpene lactones as costunolide, parthenolide, and others exhibited antimycobaterial activity [20]. Among the triterpenes, oleanolic acid and ursolic acid were also active against *M. intracellulare* [20] and Gram-positive and Gram-negative bacteria [61].

Terpenes also display antifungal activity. Experiments have been performed in two groups of fungi: *Saccharomycetes* and mildew fungi, that are potentially pathogenic to humans. Both optical isomers of carvone were found to be active towards many kinds of human pathogenic fungi. Carvone and perillaldehyde inhibited the transformation of *Candida albicans* from the coccal to the filamentous form, which is responsible for the pathogenicity of the fungus [13]. The development of *C. albicans*, *C. krusei*, and *C. tropicalis* was also limited by a composition of monoterpenes, which included terpinen-4-ol, α-pinene, β-pinene, 1,8-cineole, linalool, and α-terpineol [40, 54]. They inhibited the development of dermatophytes such *Trichophyton mentagrophytes*, *T. rubrum*, and *Microsporum gypseum*, as well. α-terpinene also exhibited antifungal activity similar to that of commonly used antifungal drugs [69]. In general, antifungal therapy utilizing terpenes and their derivatives is very promising but may be difficult to apply because high doses of terpenes or terpenoids have to be used. For that reason, such therapy might result in serious side effects. These substances may nevertheless serve as supplementary agents that could improve standard, conventional antifungal therapies.

ANTIVIRAL ACTIVITY

Currently, the antiviral activity of terpenoids is rather poorly understood. Therefore, there is a lot of research aimed at discovering agents, also from natural sources, which could have potent antiviral activity. The new antiviral compounds should specifically inhibit viral functions and should not influence normal eukaryotic cell metabolism. The search for natural antiviral compounds has led to the isolation of isoborneol (Fig. 4).

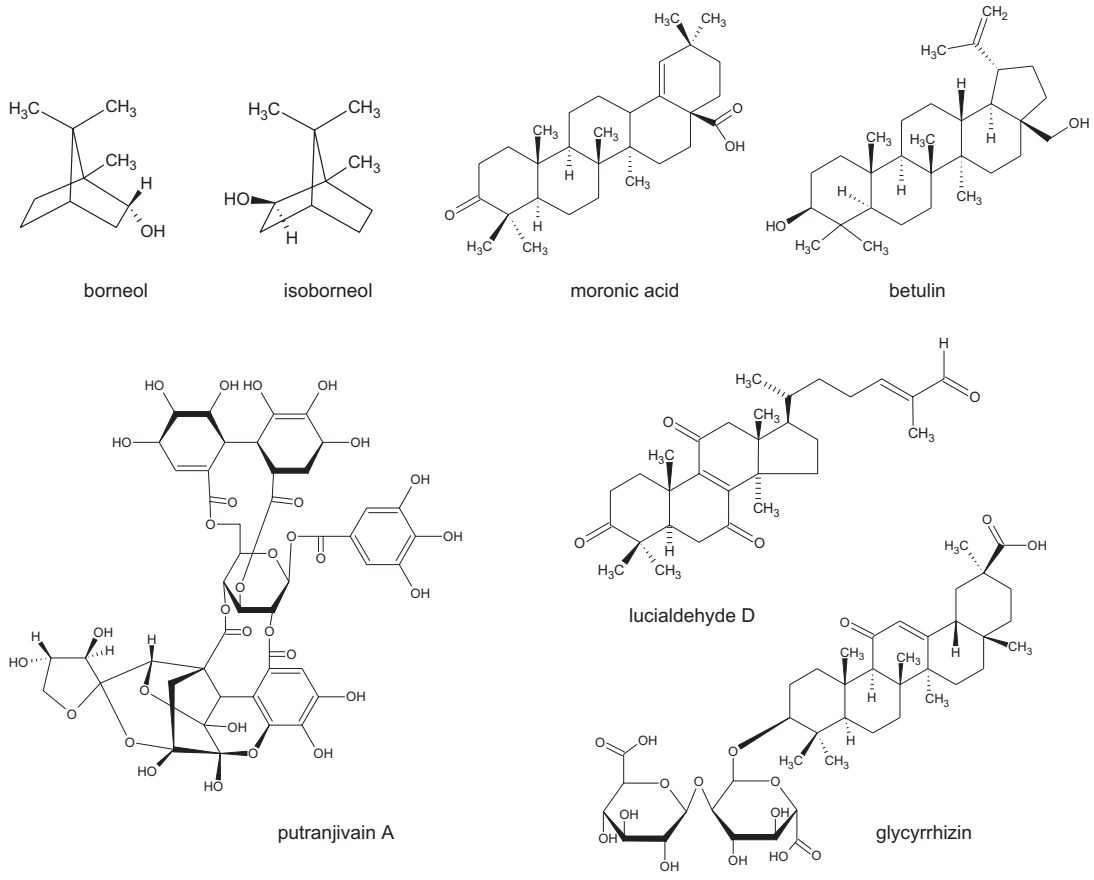

Fig. 4. Structures of selected terpenes with antiviral activity.

This monoterpene has been shown to exhibit low cytotoxicity and relatively strong anti-herpes simplex virus-1 (anti-HSV-1) action. The mechanism of isoborneol activity relies on interactions of its hydroxyl groups with virus envelope lipids. Furthermore, isoborneol may inhibit virus replication and the glycosylation of viral proteins. As a result, HSV-1 loses its infectivity [4]. Potent anti-HSV-1 activities have also been reported for monoterpenes such as cineol and borneol, a stereoisomer of isoborneol. Moreover, an analysis of diterpenes has revealed that putranjivain A, isolated from *Euphorbia jolkini* (*Euphorbiaceae*), may inhibit viral attachment and cell penetration and may also affect late stages of HSV-2 replication [55].

In a group of triterpenes, moronic acid from *Rhus javanica* and meliacine from *Melia azeolarch* exhibited anti-HSV-1 effects. They inhibited infected-cell polypeptides produced in late stages of infection or diminished viral DNA synthesis. Lupenone and its saponin also showed antiviral activities against HSV-1 and -2. They influenced HSV-1 DNA synthesis and exhibited inhibitory effects on viral plaque formation [55]. Triterpenoid saponins such as glycyrrhizin and oleanan-type triterpenoid saponins, including glycyrrhetic acid, had anti-HSV-1 activity. Interestingly, glycyrrhizin also effectively inhibited replication of severe acute respiratory syndrome-associated virus [46]. It also modulated the fluidity of human immunodeficiency virus (HIV) envelope [41]. In recent years, the antiviral activities of several triterpene compounds have also been described. Moronic and betulinic acids have been found to possess anti-HSV-1 activity. Moreover, betulin and betulinic acid, as well as several of their derivatives, have been described as very active anti-HIV agents affecting virus-cell fusion, reverse transcriptase activity, and virion assembly and/or budding. Betulin, betulinic acid, and oleanolic acid have also been shown to inhibit the replication of vesicular stomatitis virus and encephalomyocarditis virus [51]. The terpenoid constituents of *Ganoderma pfeifferi* oil lucialdehyde D and ganoderon A and C were also potent inhibitors of HSV [66]. To conclude, terpenoids are an interesting group of natural agents with both specific and wide-ranging antiviral activities that could be used to improve the therapeutic efficacy of standard antiviral therapy.

ANTIHYPERGLYCEMIC ACTIVITY

Type 2 diabetes mellitus is a chronic metabolic disorder that results from reduced first-phase insulin secretion, β cell dysfunction with relative glucagon excess, and defects in insulin action [48, 50]. Glucose is the most powerful physiological stimuli of the β cell. However,

chronic elevation of blood glucose concentration impairs β cell function. At early stages in type 2 diabetes, diet and exercise are sufficient to maintain glucose homeostasis [15]. With time, however, oral antidiabetic drugs and insulin replacement often become necessary. Long-time use of the oral hypoglycemic agents may, however, decrease their pharmacological action, a phenomenon described as desensitization [15, 16]. Therefore there is increasing scientific and clinical endorsement for the search and use of natural antidiabetic agents. Stevioside is a diterpene steviol glycoside extracted from leaves of the plant *Stevia rebaudiana* which possesses insulinotropic, glucagonostatic, and antihyperglycemic effects. It has been shown that stevioside and the aglucon steviol both potentiate insulin secretion from isolated mouse islets in a dose- and glucose-dependent way [49]. The antihyperglycemic action of stevioside and steviol may be associated in part with the induction of genes involved in glycolysis or inhibitory action on ATP phosphorylation and NADH-oxidase activity in liver mitochondria, leading to an increase in glycolysis and suppression of gluconeogenesis [17, 49].

Stevia leaves contain, beside stevioside, also other diterpene glycosides, such as rebaudioside A–F, steviolbioside, and dulcoside A, which all are responsible for the typical sweet taste [32]. Rebaudioside A, similarly to stevioside, possesses insulinotropic effects but does not cause a stimulation of insulin release at near-normal glucose levels [1].

Stevioside enjoys dual-positive effects by acting not only as an antihyperglycemic agent, but also as a blood pressure-lowering substance. It has been shown that stevioside induces blood pressure reduction and diuresis in rats. The antihypertensive effect of the plant glycoside is therefore closely associated with cardiovascular risk factor reduction, which appears through a calcium-antagonist mechanism [14, 45]. It has also been shown that isosteviol inhibits angiotensin-II-induced cell proliferation and endothelin-1 secretion. These results may suggest that isosteviol possesses substantial positive effects on the cardiovascular system [96].

ANTI-INFLAMMATORY ACTIVITY

Peana et al. [71, 72] have shown that (–)-linalool, a naturally occurring enantiomer, possesses anti-inflammatory activity. Moreover, (–)-linalool and its ester, linalyl acetate, demonstrated analgesic and edema-reducing effects [71] (Fig. 5). Arachidonic acid metabo-

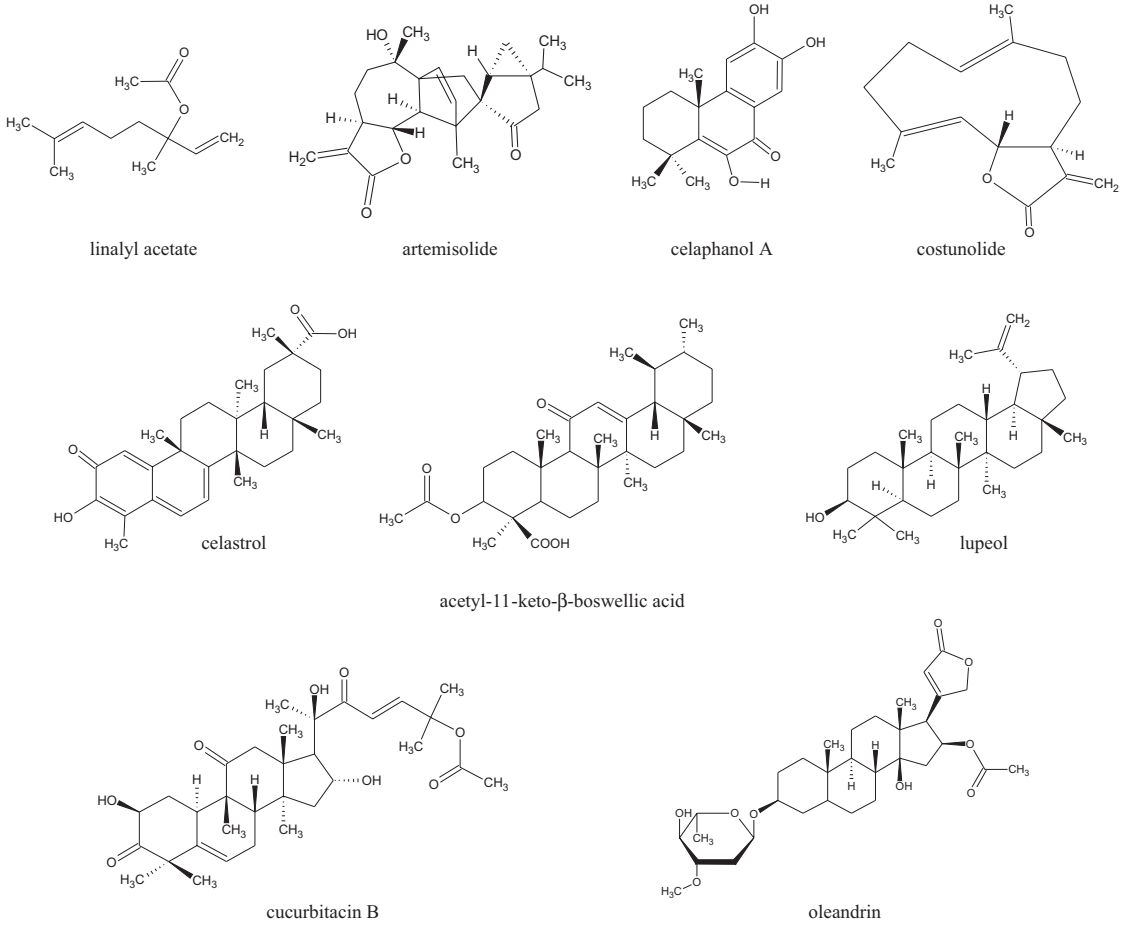

Fig. 5. Structures of selected terpenes with anti-inflammatory activity.

lism and pro-inflammatory cytokine production in activated human monocytes were suppressed by 1,8-cineole (eucalyptol), a monoterpene isolated from eucalyptus oil. 1,8-cineole was easily transported into tissues, but was rather slowly released into plasma. It also had a long terminal half-life, so it remained inside the tissues at high concentrations even after the dosing was over. Therefore, this monoterpene was found to be especially useful in curing chronic ailments such as *bronchitis sinusitis* and steroid-dependent asthma or as a preventive agent in returning respiratory infections [71]. The sesquiterpene-monoterpene lactone artemisolide, isolated from *Artemisia asiatica* (*Compositae*), was shown to be an nuclear factor (NF)-κB inhibitor. Artemisolide attenuated lipopolysaccharide (LPS)-induced production of prostaglandin E_2 (PGE_2) and NO in macrophages cultured *in vitro* [79]. Terpinen-4-ol, the main component of the oil of *Melaleuca alternifolia* (tea tree oil), and cineole derivatives present in many plant oils also suppressed the production of several proinflammatory substances such as PGE_2, TNF-α, and interleukin 1β [38, 42, 85]. Escandell et al. [29] have shown that cucurbitacin R reduce inducible nitric oxide synthetase (iNOS), cyclooxygenase 2 (COX-2), TNF-α, and PGE_2 in paw homogenates of rats with adjuvant-induced arthritis. Moreover, the naturally occurring diterpene pepluanone, isolated from *Euphorbia peplus*, was shown to reduce NO, PGE_2, and TNF-α production by inhibiting COX-2 and iNOS activity and down-regulating NF-κB [21]. NF-κB is a well-characterized protein responsible for the regulation of complex phenomena with a pivotal role in controlling cell signaling, especially the expression of gene-encoding pro-inflammatory cytokines, chemokines, adhesion molecules, growth factors, COX-2, and iNOS or immune receptors. All of these play critical roles in inflammatory processes. Naturally occurring NF-κB inhibitors have also been detected among the diterpenes (excisanin, kamebakaurin), triterpenes (avicin, oleandrin), sesquiterpenes and sesquiterpene lactones (costunolide, parthenolide), pentacyclic triterpenes (celastrol, celaphanol A), and pentacyclic triterpenes such as aglycones of saponins [64, 74, 83]. Among the pentacyclic terpenoids, acetyl-11-keto-β-boswellic acid (AKBA), isolated from *Boswellia serrata*, also exhibited pronounced anti-inflammatory activity. It causes selective blockade of the 5-lipooxygenase through a pentacyclic structure-binding site which is different from the substrate binding site. In consequence, AKBA is considered to be an anti-inflammatory remedy [62]. It is also an inhibitor of NF-κB function and has several biological effects, such as activation of cytokines production and enhancement of the activity of chemotherapeutic agents which induce apoptosis of tumor cells or suppress osteoclastogenesis. Therefore, AKBA may be active against a number of diseases, including cancer, arthritis, chronic colitis, ulcerative colitis, and bronchial asthma [3, 87]. NF-κB-activated genes are also involved in allergic reactions. It has been indicated that several tetranorterpenoids isolated from *Carapa guianensis* can be useful in attenuating allergen-induced eosinophilia [73]. Moreover, they inhibited NO and PGE_2 production in LPS-stimulated macrophages *in vitro* [52].

Other terpenes exhibiting *in vitro* and *in vivo* anti-inflammatory action, mainly by inhibition of phospholipase A_2 (PLA_2) activity, have also been detected. PLA_2 is strongly associated with the control and regulation of inflammatory processes involving arachidonic acid metabolism and phospholipids turnover. Among the most active, betulin and betulinic acid [6] and cucurbitacins isolated from *Cayaponia tayuya* [78] have been described. Also, PLA_2 was inhibited by oleanic and morolic acids [35] and a triterpene known as isomasticadienonalic acid and its derivative tirucallane-type lanostanoids (masticadienonic and masticadienolic acids), isolated from *Schinus molle* [98]. On the other hand, phospholipase Cβ was inhibited by several sesquiterpenes, among which petasin was the most active [89]. Betulin, betulinic acid, and ursolic acid isolated from *Diospyros leucomelas* also inhibited inflammation in the carrageenan and serotonin paw edema tests [76].

Several lupane, oleane, and ursane triterpenoids and their natural and synthetic derivatives exhibited anti-inflammatory effects *in vitro* and *in vivo* [77]. They inhibited NO production or interacted with PLA_2 or peroxisome proliferator-activated receptor γ, a regulator of the expression of genes expression involved in fatty-acid β-oxidation and energy homeostasis [27, 44, 59, 67, 94]. Moreover, oleanolic and ursolic acids at low doses exert an hepatoprotective effect which can be due to their anti-oxidant and anti-inflammatory actions. These triterpenoids are also effective inducers of metallothionein, a small cysteine-rich protein acting like glutathione in the body's defense against many natural and chemical insults that could induce liver injury [60]. A pentacyclic terpene, α-amarin, also exhibited anti-inflammatory activity *in vivo* (ear edema) and *in vitro* inhibiting pro-inflammatory cytokine production [68].

ANTIPARASITIC ACTIVITY

A variety of natural products have been described as antiparasitic agents with high efficacy and selectivity. The antiparasitic activity of terpenoids is explained by their interaction with heme and Fe(II) groups where free radicals are released and kill parasites. Clinically, their effects are rather immediate, but lead to a rapid reduction of parasitemia. In a group of monoterpenes, espintanol and piquerol A have been found to have some antiprotozoan parasite activity (Fig. 6). Thymol and its structural derivatives also possess an anti-leishmanial potential [81]. Menthol derivatives have, in turn, been described to possess trypanocidal activity [56]. Diterpenes and their lactones, e.g. dehydroabietinol isolated from *Hyptis suaveolens*, have been shown to have antimalarial activity [91, 99]. Diterpenes with a nor-abietane skeleton had leishmanicidal and antiplasmodial

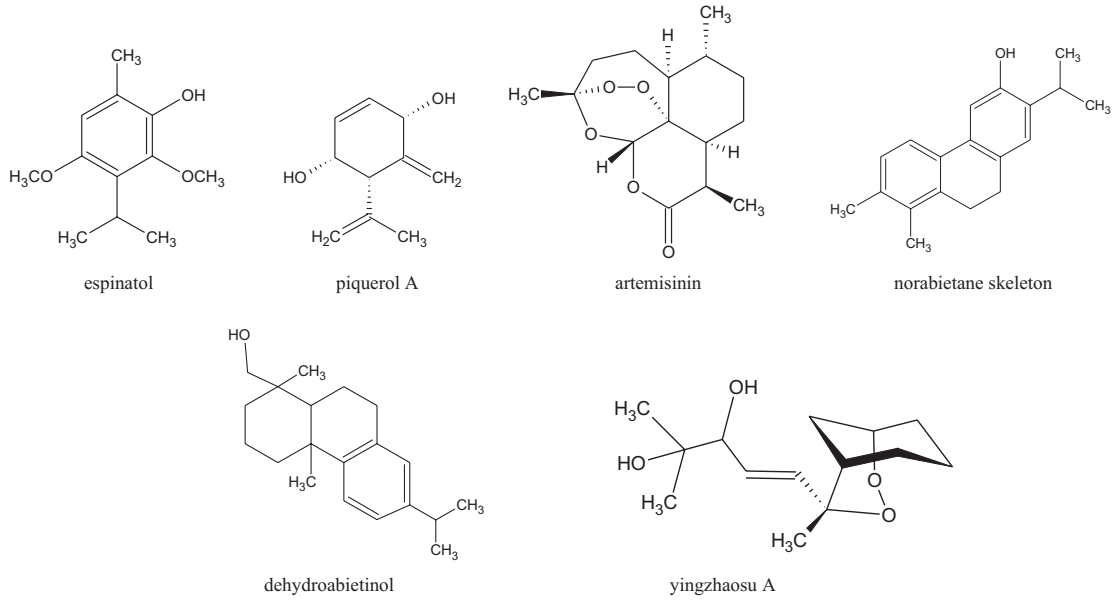

Fig. 6. Structures of selected terpenes with antiparasitic activity.

action [84]. Betulinic acid has been described to have antimalarial activity [9]. Among the sesquiterpenes, artemisinin and its derivatives, especially in combination with synthetic antimalarial substances, have been shown to be effective agents in the treatment of persons infected with drug-resistant *Plasmodium* [43]. Other sesquiterpene peroxides, such as yingzhaosu A and yingzhaosu C, also showed antiparasitic activity, especially against *Plasmodium berghei* [53].

TERPENOIDS AS SKIN PENETRATION ENHANCERS

Terpenes are used in numerous areas of medicine. There are many reports indicating that terpenes are skin penetration-enhancing agents. Currently, terpenes are being analyzed as supplementary agents in topical dermal preparations, cosmetics, and toiletries. Moreover, it has been demonstrated that the transdermal pathway may be suitable as an alternative route in, for example, antitumor drug administration. This is especially beneficial when relatively long-term therapy is required [31]. In anticancer therapy, terpenes may serve as safe and clinically acceptable accelerants for the application of drugs with both lipophilic and hydrophilic features [63]. In dermatology and cosmetology, lipophilic, hydrophilic, and multiphase vehicles are used. Among theses, hydrogel solutions and oil-in-water emulsions are often applied. The activity of terpenes as transdermal enhancers is based on a reversible disturbance of the lipid arrangement in the intercellular region of the stratum corneum [11]. The stratum corneum is the thin, outermost layer of the skin, which generally limits the amount of different agents, drugs among others, that can be administered transdermally. It has been suggested that skin penetration enhancers such as terpenes may increase the permeability of the stratum corneum through intercellular lipid disruption, interaction with proteins, or improved access of agents into the stratum corneum [63]. Such enhancers facilitate the diffusion of drugs through the skin, increasing their therapeutic value. Terpene compounds possess several advantages, such as good penetration-enhancing abilities, low skin irritation effects, and low systemic toxicity. The greatest enhancement activity has been shown for oxide terpenes and other terpenoids compared with hydrocarbon or even alcohol or ketone group-containing terpenes [95]. However, hydrocarbon terpenes, e.g. D-limonene, has already been approved as an active enhancer for steroids. Terpenes were also effective as skin permeability enhancers for the lipophilic molecule indomethacin and for hydrophilic diazepam and propranolol [95]. Moreover, monoterpenes such as linalool, carvone, and thymol were also demonstrated to enhance the permeability of a number of agents, e.g. 5-fluorouracil (5-FU), through skin and mucous membranes. Terpenes, however, vary in their enhancing activity towards 5-FU. It has been shown that D-limonene, nerolidol, and 1,8-cineole increase drug permeability 2-, 23-, and 95-fold, respectively [22]. Sesquiterpenes, larger terpene molecules, also function as skin penetration enhancers. It has been shown that nerolidol enhances the permeability of the hydrophilic drug 5-FU through human skin.

Terpenes have also been shown to significantly increase transdermal flux of zidovudine (AZT) compared with vehicle. AZT is the first anti-HIV compound approved for clinical use; however, its dose-dependent hematological toxicity limits its therapeutic effective-

ness. Therefore, to maintain a stable, non-toxic, and plasma-effective concentration of AZT, a route of administration other than the peroral route has to be found. AZT is a polar molecule, so its transdermal permeability is rather poor and its concentration in plasma after transdermal application is low. Therefore, enhancers allowing the drug molecule to pass through the skin, especially the stratum corneum barrier, should be applied. The effectiveness of terpenes' enhancement activity has been established as follows: cineole>menthol>menthone≈pulgeone≈α-terpineol>carvone>vehicle water [65]. Terpenes express low toxicity and are, therefore, regarded as safe agents, especially when used in humans with a weakened immunological system.

It is generally assumed that small terpene molecules are better enhancers than larger ones. However, it appears that non-polar terpenes such as D-limonene provide better enhancement for lipophilic agents than polar terpenes. On the other hand, terpenes containing polar groups, e.g. menthol and 1,8-cineole, enable hydrophobic permeants to traverse the human skin much more easily than terpenes without polar groups. This is the general mechanism on which the enhancing activities of terpenes are based [65].

CONCLUDING REMARKS

In this review, a wide spectrum of terpene activity was presented. Numerous terpenoids appear to possess beneficial healthcare effects. A variety of terpenoids have been shown to be effective in chemoprevention and chemotherapy and to express antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, and antiparasitic activities. Therefore, this group of substances should be further employed not only in ethnomedicine, but special attention should be paid to introducing them into modern therapies.

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