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REVIEW ARTICLE
BIOLOGICAL ACTION OF ESSENTIAL OILS (TERPENES)

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ABSTRACT

Essential oils are chemically terpenes that are one of the largest groups of plant secondary metabolites. Terpenoids are multi cyclic structures that differ from one another not only in their functional groups but also in their basic carbon skeletons. They play a pivotal role in oriental herbal medicines and are currently under investigation for their pharmacological activities. Mostly plant derived essential oils consist of chemical components such as terpenoids including monoterpenes, sesquiterpenes and their oxygenated derivatives. These compounds have the ability to easily diffuse across cell membrane to induce biological reactions. A large number of terpenoids exhibited cytotoxicity against a variety of tumor cells and also showed cancer preventive as well as anticancer efficacy in preclinical animal models. Gastropods especially terrestrial snails and slugs, aquatic snails are major pests of agricultural plants and carrier of most devastating diseases fasciolosis in cattle/ human population. Plant derived molluscicides are found that most of them are biodegradable in nature and are considered to be bio rational, species specific, non- toxic to the non-target animals and of natural occurrence, thus generating less damage to the environment.

1. Introduction

Essential oils are chemically terpenes that are one of the largest group of plant secondary metabolites [1]. Phenolic acids such as thymol, eugenol and carvacrol are secondary plant metabolites that account for the antimicrobial activity of essential oils such as oregano, cinnamon, and clove [2]. The concentration of eugenol in clove oil is 79.2% [3]. Mittal et al. [4] reported that the inhibitory activity of clove is due to the presence of several constituents, mainly eugenol, eugenyl acetate,beta-caryophyllene, 2-heptanone. Terpenoids (or isoprenoids) are multi cyclic structures that differ from one another not only in their functional groups but also in their basic carbon skeletons [5]. They play a pivotal role in oriental herbal medicines and are currently under investigation for their antimicrobial activities [6]. Terpenoids contribute to the scent of the cinnamon, clove, eucalyptus, and ginger, the yellow color of sunflowers, and the red color of tomatoes [7]. They are volatile, limpid, colored and are soluble in lipids and organic solvents that have a lower density than water [7]. Miguel [8] reported that they may be present in all plant organs of specific plant families, including buds, flowers, leaves, seeds, twigs, stems, flowers, fruits, roots, wood or bark and are generally stored by the plant in secretory cells, cavities, canals, glandular trichomes or epidermal cells. Terpenes are synthesized in cannabis in secretory cells inside glandular trichomes, and production is increased with light exposure [8]. Sharma et al. [9] reported that terpenes also play an incredibly important role by providing the plant with natural protection from bacteria and fungus, insects and other environmental stresses. Mostly plant derived essential oils consist of chemical components such as terpenoids including monoterpenes, sesquiterpenes and their oxygenated derivatives [10]. These compounds have the ability to easily diffuse across cell membrane to induce biological reactions. These molecules can be naturally present in their active form in the plant or can be activated by specific enzymes when the plant is subjected to particular biotic or abiotic stress [11]. The presence of complex chemical structures constituted of several groups, such as terpenes and terpenoids, aromatic and aliphatic constituents, all characterized by low molecular weight, may explain their successful bacteriostatic and bactericidal action [12]. Terpenoids, also known as isoprenoids, are the most numerous and structurally diverse natural products found in many plants [13]. The diverse collection of terpenoid structures and functions has provoked increased interest in their commercial use resulting in some with established medical applications being registered as drugs on the market [13]. Terpenoids represent the most widespread group of natural products and can be found in all classes of living things. Many defensive compounds include sesquiterpenoids and diterpenoids from angiosperm species [12]. Sulsen et al. [14] reported that several terpenoids are biologically active and are exploited in the fight against cancer, malaria, inflammation, and a variety of infectious diseases.

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CHEMICAL COMPOSITION

Essential oils (EOs) are volatile, natural, complex compounds characterized by a string odor and are formed as PSMs by aromatic plants [15]. These chemical volatiles have functions in chemical defence, acting as insecticides, acaricides, avoiding bacterial or fungi phytopathogen colonization, attracting natural enemies of herbivores [16]. Yadava et al. [12] reported that terpenes form structurally and functionally different classes of compounds that are formed by coupling different numbers of isoprene units (5-carbon-base; C5), while terpenoids represent terpenes containing oxygen and the main structural classes of the terpenes are: monoterpenes (C10), sesquiterpenes (C15), hemiterpenes (C5), diterpenes (C20), triterpenes (C30), tetraterpenes (C40). Although hundreds of limonoids have been isolated from various plants, their occurrence in the plant kingdom is confined to plant families of the order Rutales and more abundantly in the families Meliaceae and Rutaceae, and less frequently in Cneoraceae and Harrisonia sp. of Simaroubaceae [16]. Of the 300 limonoids known today, about one third is obtained from Meliaceae species (Azadirachta indica and Melia azedarach), also known as meliacins [17]. Fang et al. [18] reported that the structural variations of limonoids found in Rutaceae are less than in Meliaceae and are generally limited to the modification of A and B rings. The limonoids of Meliaceae are more complex with very high degree of oxidation and rearrangement exhibited in the parent limonoid structure [17]. Most work has been focused on azadirachtin, a limonoid PSM (C35H44016, a tetranortriterpenoid) of the Indian Neem tree (Azadirachta indica L., Meliaceae). Azadirachtin is the mostly ever studied tetra nor-tri-terpenoid, which chemical structure required 18 years to solve and its total synthesis took almost 22 years [19]. The mode of action of azadirachtin lays on (i) deterrent effects on chemoreceptors resulting in antifeedancy (ii) effects on ecdysteroid and juvenile hormone titres through a blockage of morphogenetic peptide hormone release (e.g. PTTH; allatotropins) and (iii) direct effects on tissues resulting in an overall loss of fitness of the insect [16]. Besides limonoids, also the quassinoids and saponins fall in the PSMs'category of triterpenoids, being though much less studied. Quassinoids, the bitter principles of the Simaroubaceae family (Quassia amara, Cassia camara and Picrasma exelca), are a group of structurally complex and highly oxygenated degraded triterpenes [20].

BIOLOGICAL ACTIVITIES OF TERPENOIDS

The terpenoids present in Cannabis display a wide range of biological activities that may be involved in regulating the effects of THC as well as producing their own unique pharmacological effects [21]. Libro et al. [22] reported that THC is known to cause acetylcholine deficits in the hippocampus, which may lead to short-term memory loss. This effect can be alleviated in rats by administering tacrine, an alkaloid that inhibits acetylcholine esterase, the primary enzyme involved in the breakdown of acetylcholine in cholinergic receptors. Booth et al. [23] reported that Indeed, tacrine has blocked THC-induced memory loss behavior in rats. Interestingly, many of the terpenoids present in Cannabis display similar acetylcholine esterase inhibition, including pulegone, limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l- and d-carvone, 1,8-cineole, p-cymene, fenchone, and pulegone-1,2-epoxide. For this reason, terpenoids are investigated for the treatment of Alzheimer's disease. Cservenka et al. (2018) reported that limonene is a common component of Cannabis essential oil, and it was shown to have a strong antidepressant effect by inhibiting the secretion of hypothalamic–pituitary–adrenal (HPA) stress hormones and normalization of CD4:CD8 ratios. Andre et al. [21] reported that limonene is also under investigation as an antimutagenic compound because of its multiple anti-carcinogensis mechanisms. These effects may reduce some of carcinogenic effects of compounds present in Cannabis smoke.

MODE OF ACTION

Essential oils affect several targets at the same time, because of their great number of constituents; this fact decreases the target organisms' resistance or adaptation [25]. Also, EOs induce cytotoxicity, damage the cellular and organelle membranes, act as prooxidants on proteins and DNA and produce reactive oxygen species (ROS) [26]. Bakkali et al. [27] reported that in some cases when photoactive molecules such as furocoumarins, are exposed to activating light, they penetrate the cell without damaging the membranes, proteins and DNA, and then produce radical reactions and oxygen singlet. In some cases essential oils and their components have demonstrated nuclear and cytoplasmic mutagenicity, acting on mitochondria and the respiratory system [27]. Castro et al. [28] reported that the biological activity of EOs and their components on pest insects comprise behaviour and feeding detterance effects, fumigant toxicity, knockdown activity and lethal toxicity via contact. While these substances are generally active against a broad spectrum of pests, interspecific toxicity of individual oils and compounds is highly idiosyncratic [29]. Perhaps the most attractive aspect of using EOs and their constituents in pest management is their favourable mammalian toxicity and their nonpersistance in the environment, for which reason they are exempted from the usual data requirements for registration in the USA [29]. Limonoids are metabolically altered triterpenes and have a prototypical structure either containing or deriving from a precursor with a 4,4,8-trimethyl- 17-furanylsteroid skeleton [17]. Thymol, a plant-derived antimicrobial agent, caused rapid efflux of intracellular constituents of Porphyromonas gingivalis, Selenomonas artemidis and Streptococcus sobrinus. The thymol-induced decline of intracellular ATP in S. sobrinus and it appears to be entirely attributable to leakage, whereas in P. gingivalis thymol may also inhibit ATP-generating pathways. Relative changes in the transmembrane potential of resting cells of S. sobrinus pulsed with glucose are as sensitive to thymol as is leakage from this organism. The effects of thymol on transmembrane potential are probably secondary to those arising from leakage of intracellular substances [30]. Antibacterial effects of three terpene alcohols on Staphylococcus aureus , revealed that terpene alcohols, namely, farnesol, nerolidol and plaunotol might act on cell membranes. The antibacterial activity reflected the initial rate of leakage of K+ ions,

suggesting that damage to cell membranes might be one of the major modes of action of these terpene alcohols. The results also demonstrated that the initial rate of leakage and the amount of leaked K+ ions are useful as indices of the antibacterial activities of hydrophobic compounds [31]. It has been proved that carvacrol interacts with the membranes of bacteria such as B. cereus by changing its permeability for cations like H(+) and K(+). The dissipation of ion gradients leads to impairment of essential processes in the cell and finally to cell death [31]. The structural requirements for the activity of carvacrol were determined by comparison to structurally related (nonessential oil) compounds. Removal of the aliphatic ring substituents of carvacrol slightly decreased the antimicrobial activity [32]. Sugathi and Manpal [33] reported that the effect of the hydroxyl group of carvacrol on activity could not be determined by simply comparing it to p-cymene, because this compound is immiscible with water; therefore, 2-amino-p-cymene, the amino analogue of carvacrol, which has a similar hydrophobicity and structural characteristics, was used. 2-Amino-p-cymene had similar membrane disruption and bacterial killing characteristics as carvacrol showing that, contrary to previous reports, the hydroxyl group of carvacrol itself is not essential for the antimicrobial activity. However, the observed 3-fold lower activity for 2-amino-p-cymene as compared to carvacrol indicates special features in the antimicrobial mode of action of carvacrol due to the hydroxyl group [34].

ANTICANCEROUS ACTIVITY

Terpenoids, the largest group of phytochemicals, traditionally used for medicinal purposes in India and China, are currently being explored as anticancer agents in clinical trials [35]. Saleh et al. [36] shown that terpenoids in plants increase tumor latency and decrease tumor multiplicity. Terpenoids in various herbs possess strong antioxidant activities. The isoprenoids are useful cancer chemopreventive agents as they suppress tumor growth by inhibiting HMG-CoA reductase. A large number of terpenoids exhibited cytotoxicity against a variety of tumor cells and also showed cancer preventive as well as anticancer efficacy in preclinical animal models [37]. Epidemiological and experimental studies propose that monoterpenes may be helpful in the prevention and therapy of several cancers, including mammary, skin, lung, forestomach, colon, pancreatic, and prostate carcinomas[38]. A large number of tri- terpenoids have been shown to curb the growth of a variety of cancer cells without exerting any toxicity in normal cells. Numerous preclinical efficacy studies have provided widespread indication that both naturally occurring and synthetic derivatives of tri-terpenoids possess chemo-preventive and therapeutic effects against colon, breast, prostate, and skin cancers [39]. These tri-terpenoids and their derivatives act at various stages of tumor development; inhibit initiation and promotion of carcinogenesis; induce tumor cell differentiation and apoptosis; and suppress tumor angiogenesis, invasion, and metastasis through regulation of various transcription and growth factors as well as intracellular signaling mechanisms [40]. Terpenoids are chemicals that basically consist of isoprene (C5) units. Despite this similarity in basic units, terpenoids are extremely diverse in their structures and biological activities and include a large number of chemicals; at least 15 000 terpenoids are found in plants. Because of this diversity, terpenoids are divided into several groups according to their structures and biological functions [41] For example, monoterpenoids (C10) include volatile terpenoids rich in conifer resins, essential oil, and exudates of glandular trichome such as α-pinene, β-pinene, limonene, and menthol and confer defense on plants [23]. Iridoids are also included in monoterpenoids. Sesquiterpenoids (C15) include sesquiterpene lactones, phytojuvenile hormones, and others; diterpenoids (C20) include clerodanes, tiglianes, daphnanes, and others; and triterpenoids (C30) include cardenolides, cucurbitacins, limonoids, phytoecdysteroids, saponins, and others. As it is not possible to describe all these diverse terpenoids, some characteristic groups of terpenoids are briefly described here [42] .

MOLLUSCICIDAL ACTIVITY

Gastropods especially terrestrial snails and slugs, aquatic snails are major pests of agricultural/ horticultural plants and carrier of most devastating diseases fasciolosis/ schistosomiasis in cattle/ human population [43]. Control of these gastropods is one of most neglected field in pest control measures. Initial control of these snails was performed by biological/ mechanical methods. Simultaneously, chemical control was also very effective in control of pestiferous gastropods. In late nineties it was realized that although chemical control by different synthetic molluscicides yet, they are not safe to the environment. In continuation of this study use of plant products against gastropods pests were advocated by different researcher working in this field. Radwan and El-zemity [44] tested ten naturally occurring compounds for molluscicidal activity against the fresh water snail, Biomphalaria alexandrina and the white garden snail, Theba pisana. The role of the synergist, piperonyl butoxide (PB) in improving the efficacy of these chemicals was also investigated. The results showed that thymol (terpenoids) was the most effective against B. alexandrina snails, followed by trans - anethole, pulegone and cinnamyl aldehyde. In case of T. pisana snails, thymol was found to be the most effective compound followed by eugenol and pulegone. B. alexandrina snails were more susceptible to the tested chemicals than T. pisana. PB enhanced the toxicity of some of the tested chemicals, particularly against B. alexandrina. The toxic effect of these chemicals alone against the two tested snails was less active than the standard molluscicides. However, the mixture of thymol, eugenol or benzyl alcohol with PB notably increased the molluscicidal activity over methiocarb against T. pisana snails. Ferreira et al. [45] reported that the Influence of Caffeine and Thymol (terpenoids) on the survival , growth and reproduction of Subulina octona, a terrestrial snail which serves as an agricultural pest. He assessed, during 120 days, the effects of caffeine and thymol at 2.5 g/L and 5 g/L on the hatchability, survival after hatching, growth and reproduction of S. octona under the laboratory conditions. A total of 240 eggs, 240 juveniles aged 10-day-old, and 240 aged 30-day-old were tested. The results showed that thymol (at 2.5 g/L and 5 g/L) and caffeine (at 5 g/L) acted as ovicides. In the 10-day-old juveniles, caffeine at 5 g/L caused 25% mortality and at 2.5

g/L it caused 30% mortality. Thymol at 2.5 and 5 g/L caused 20 and 22.5% mortality, respectively. Ferreira et al. [46] reported that Bradybaena similaris commonly known as the Asian tramp snail, is a terrestrial snail native to Asia, acts as an intermediate host for parasites and is a difficult-to-control agricultural pest as well, causing great losses to crops and ornamental plant cultivation. Thymol (terpenoids) is a substance of plant origin which has bactericidal, fungicidal and anti-inflammatory properties and has been presented as a promissory biocide of mollusc species. He assessed the molluscicidal property of thymol in combination with DMSO against eggs and adults of B. similaris. During 120 days, we evaluated the effect of thymol+DMSO at different concentrations (2.5 g/L and 5 g/L) on the hatching success, hatchling survival, growth and reproduction of B. similaris under laboratory conditions. The results showed that thymol+DMSO (5 g/L and 2.5 g/L) affected hatching success, acting as an ovicide. The tests with 10-day-old juveniles showed that thymol+DMSO at 2.5 g/L and 5 g/L caused 90 and 100% of mortality, respectively. For the 30-day-old juveniles, thymol+DMSO caused 87.5% of mortality at 5 g/L, and 75% at 2.5 g/L. With regard to growth, the results were not significant. The 10-day-old individuals treated with thymol+DMSO showed only one reproductive event during the 120 days of the experiment. Thymol+DMSO showed molluscicidal and residual activity, which makes evident its potential for controlling snails, and consequently, snail-borne diseases. Salma et al. [47] reported that the molluscicidal and mosquitocidal activities of the essential oils of Thymus capitatus (Thymol) and Marrubium vulgare (carvacrol). The two oil samples appeared dominated by the oxygenated constituents (88.22% for T. capitatus and 57.50% for M. vulgare), composed of phenols, mainly carvacrol (32.98%) and thymol (32.82%) in essential oil of T. capitatus, and thymol (34.55%) in essential oil of M. vulgare. It was evaluated the molluscicidal activity of T. capitatus and M. vulgare essential oils on adult and eggs of Biomphalaria alexandrina as well as their mosquitocidal activity on Culex pipiens. The LC50 and LC90 of T. capitatus essential oil against adult snails was 200 and 400 ppm/3hrs, respectively, while for M. vulgare it was 50 and 100 ppm/3hrs, respectively. Moreover, M. vulgare showed LC100 ovicidal activity at 200 ppm/24 hrs while T. capitatus oil showed no ovicidal activity. It was verified mosquitocidal activity, with LC50 and LC90 of 100 and 200 ppm/12hrs respectively for larvae, and 200 and 400 ppm/12hrs respectively for pupae of C. pipiens. Kumar et al. [48] reported that Ferulic acid, umbelliferone (Ferula asafoetida), eugenol (terpenoids) and limonene (Carum carvi) are active molluscicidal components that inhibited the activity of alkaline phosphatase and acetylcholinesterase in in vivo and in vitro exposure of Lymnaea acuminata. It was observed that ferulic acid, umbelliferone and eugenol are competitive and limonene is a competitive–non-competitive inhibitor of alkaline phosphatase. Ferulic acid and umbelliferone are competitive, whereas eugenol and limonene are competitive–non-competitive and uncompetitive inhibitors of acetylcholinesterase, respectively. Kumar and Singh [49] reported that the molluscicidal activity of dried root latex powder of Ferula asafoetida, flower-bud powder of Syzygium aromaticum (terpenoids) and seed powder of Carum carvi against the snail Lymnaea acuminata was studied. The molluscicidal activity of all the three plant products was found to be both time and concentration dependent. The toxicity of S. aromaticum flower-bud powder (96 h LC50:51.98 mg/l) was more pronounced than that of root latex powder of F. asafoetida (96 h LC50:82.71 mg/l) and seed powder of C. carvi (96 h LC50:140.58 mg/l). Ethanol extract was more toxic than other organic extracts. The ethanol extract of S. aromaticum (24 h LC50:83.53 mg/l) was more effective than that of F. asafoetida (24 h LC50:132.31 mg/l) and C. carvi (24 h LC50:130.61 mg/l) in killing the test animals. The 96 h LC50 of column purified fraction of seed powder of C. carvi was 5.40 mg/l whereas those of flower-bud powder of S. aromaticum and dried root latex powder of F. asafoetida were 7.87 and 9.67 mg/l, respectively. The product of F. asafoetida, S. aromaticum and C. carvi may be used as potent molluscicides. Srivastava et al. [50] reported that feeding of baits containing sub-lethal concentration of eugenol (terpenoids) caused a significant reduction in fecundity, hatchability and survival of young snails. There was a significant ($P<0.05$) change in the endogenous level of protein, amino acid, DNA and RNA in the ovotestis of L. acuminata. Treatment of 80 % of 24h LC50 with eugenol in bait caused maximum reduction in protein (52.12% of control), amino acid (11.89% of control), DNA (30.90% of control) and RNA (13.12% of control) level. Simultaneous, inhibition in acetylcholinesterase (AChE) activity in nervous tissue was also noted. Maximum inhibition in AChE activity (36.19% of control) was observed in snail exposed to 80 % of 24h LC50 of eugenol. Srivastava and Singh [51] reported the action of bait containing Eugenol (terpenoids) on biochemical changes in fresh water snail Lymnaea acuminata and found that These baits caused maximum significant reduction in free amino acid, protein, DNA, RNA levels and AChE activity in the ovotestis/ nervous tissue of the snail in each month of the year Nov-2011- Oct-2012. Agrahari et al. [52] tested every month during the year 2010–2011, the 24 to 96 h LC50 values of molluscicide eugenol (terpenoids), in snail attractant pellets (SAP), against a snail Lymnaea acuminata, with concomitant determination of levels of temperature, pH, dissolved oxygen, carbon dioxide, and electrical conductivity in test water. On the basis of a 24 h toxicity assay, it was noted that LC50 values 2.55, 2.68, and 2.91% in SAP containing starch+eugenol and 2.67, 2.54, and 2.85% in SAP containing proline+eugenol during May, June, and July, respectively, were most effective treatments in killing the snails, while SAP containing starch or proline+eugenol were least effective in January when the 24 h LC50 was 10.73% and 7.14% for starch and proline, respectively. There was a significant positive correlation between LC50 of eugenol containing SAP and levels of dissolved O2 and pH of water in corresponding months. On the contrary, a negative correlation was observed between LC50 and dissolved CO2 and temperature of test water in the same months. A significant positive rank correlation occurred between AChE activities and the corresponding sublethal concentrations of eugenol in SAP. Moreover, there was a maximum inhibition of 58.96% of AChE in snails exposed to 80% of the 24 h LC50 of eugenol+starch in June. Kumar et al. [53] reported the sublethal treatment (20% and 60% of 24 hr LC50) of young snails (Lymnaea acuminata) with the active molluscicidal constituents ferulic acid and umbelliferone from Ferula asafoetida, eugenol from Syzygium aromaticum (terpenoids) and limonene from Carum carvi caused a significant reduction in the

fecundity, hatchability, and survival of the snails. Treatment with the constituents also increased the length of time to hatching of snails. Withdrawal of the snails from constituent treatments after 96 hr with movement to fresh water enabled a significant reproductive recovery in the snail. A 24 hr sublethal treatment with the ferulic acid, umbelliferone, eugenol, and limonene caused a significant ($p < 0.05$) reduction in protein, amino acid, DNA, and RNA levels in the ovotestis of treated snails.

CONCLUSION

Aromatic plants, their extracts and essential oils contain a variety of functional bioactive compounds, which have possible applications in the food, feed and pharmaceutical industries. The review of these work show that secondary metabolites (terpenoids) have molluscicidal, ovicidal and other pharmacological activity, affecting snail survival, reproduction and hatching success. These effects show the potential use of this substance for controlling terrestrial snails, and consequently, snail-borne diseases. Our review indicates positive potential for these chemicals of plant origin in the snail control. Such compound is promising as a lead towards maximizing the biological activity as pesticides for future potential efficient alternatives that are expected to be much safer than the synthetic conventional compounds now in use.

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