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Terpenoids from medicinal plants beneficial for human health care: Review

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Abstract
One of the group of natural products i.e. terpenoid mainly reported and found in all classes of living things. These terpenoids belongs to the group of secondary metabolites and these are naturally occurring hydrocarbons produced through a wide variety of plants, animals including microbes. Several terpenoids extracted from medicinal plant products and considered them as immunobiologically active molecules and used against various infectious diseases. Most of the bioactive terpenoids were identified with numbers of them having organ-protective effects while few are known for their nonbeneficial properties for humans. Since most of these terpenoid derivatives are reported in a very minute amount in nature but their massive harvesting in order to obtain higher amount of the drug applying various synthetic biological based techniques and metabolic engineering which mainly provides some innovative approaches pertaining to increase the production of terpenoids. In this review, we discuss about most common terpenoids reported from medicinal plant products and useful for human healthcare.

Keywords: terpenoid; medicinal plant; secondary metabolite; infectious

Introduction
The usage of metabolites including dietary supplements derived from plants have increased in the couple of years. The use of medicinal plants as herbal remedies to prevent and cure sever ailments differs from community to community. Traditionally used medicinal plants have recently caught the attention of the biological scientific communities. Ethno pharmacologists, botanists, microbiologists, and natural-products chemists are all working on developing ways to treat infectious diseases [1, 2]. Extraction of compounds from various natural sources such as plants, animals, microbes, insects, plant pathogens etc. These are known as secondary metabolites since they are formed due to the enzymatic resections of primary metabolites (amino acids, sugars, vitamins, etc.). This has involved in the isolation and identification of secondary metabolites produced by plants and their uses as an active principle in medicinal preparations [3]. While 50-60% of all pharmaceutical products are all derived from medicinal plant products (rich in a wide variety of secondary metabolites such as terpenoids, alkaloids and flavonoids) and showed immunopharmacological properties. One of the secondary metabolites i.e. terpenoids played crucial role with respect to human healthcare. The tremendous biosynthetic potential of any living organism, in particular the plants cannot be better explained other than by the presence of the secondary metabolites known as terpenoids [4, 6]. In general, the term terpenes is used to denote a compound containing an integral number of C5 units and chemically all terpenoids are said to be derived from the basic branched C5 unit i.e. isoprene (2-methyl-1,3-butadiene). Terpenes considered as one of them as simple hydrocarbons, whereas terpenoids are one of the structurally modified class of terpenes with different types of functional groups and oxidized methyl group moved or removed at various positions [7, 11]. According to number of C5 units present in the molecule Terpenoids are divided into monoterpenes, sesquiterpenes, diterpenes, sesterpenes and triterpenes having 2, 3, 4, 5 & 6 isoprenoid C5 unit respectively (Table 1). Most of the terpenoids extracted from medicinal plant products and showed immunobiologically properties and it may be applied worldwide especially for the treatment of various infectious diseases. In addition, some of the terpenoids are used as anticancer drugs such as Taxol and its derivatives [12, 14]. Many artificial flavors and nice fragrances mainly compromised of terpenes because of its nice aroma. In contrast, terpenoids are also used as antimalarial drugs such as artemisinin and related compounds. Meanwhile, they also play a diverse role in the field of foods, cosmetics, hormones, vitamins and so on [12, 14].

Table 1: Classification of terpenoids on the basis of isoprene units.

Terpenoids	No. of isoprene	Molecular formula
Hemiterpene or isoprene	1	C5H8
Monoterpenoids	2	C10H16
Sesquiterpenoids	3	C15H24
Diterpenoids	4	C20H32
Sesterterpenoids	5	C25H40
Triterpenoids	6	C30H48

Monoterpenes
Monoterpenes, class of terpenoids that consists of 10 carbon atoms with two isoprene units and its molecular formula $C_{10}H_{16}$. Monoterpenes may be linear (acrylic) or contain rings. These are naturally present in the essential oils of plants and related sources. The compounds belonging to this class usually have strong aroma and odor and are used in many pharmaceutical companies. In literature, combination of monoterpene-based oils in the form of mixture are used as fragrances for making perfumes and also applied in cosmetics as well. Most of the monoterpenes are biologically active with strong antibacterial activities. Many studies have shown *in vitro* and *in vivo* antitumor activity of many essential oils obtained from various medicinal plant products. The antitumor activity of various essential oils

extracted from many species of *Mangifera* species has been related to the presence of monoterpenes in their composition. One of the most familiar example of active monoterpenes and showed its activity as shown in Table 2. Modified terpenes such as those contain oxygen functionality or the ones that are missing methyl groups are known as monoterpenoids. Monoterpens and Monoterpenoids are different as they both have their own uses in the pharmaceutical, agriculture, cosmetic and food industries.

Table 2: Source and biological activity of monoterpene

Names	Plant Source	Activity	Ref
9-OH-isoegomaketone [(2*E*)-1-(3-furanyl)-4-OH-4-Me-2-penten-1-one	Leaves of *Perilla frutescens var. crispa*	Declining in nitric oxide (NO) production in lipopolysaccharide (LPS)-activated RAW264.7 cells with an IC_{50} value	[15]

Sesquiterpenes

Sesquiterpenes, class of secondary metabolites consisting of three isoprene units and having the formula $C_{15}H_{24}$. Like monoterpenes sesquiterpenes are found in linear, cyclic forms. Sesquiterpenes may also be present in the form of lactone ring (Table 3). Many of the latex-producing plants contain sesquiterpene, and these are potent antimicrobial and anti-insecticidal agent. Biochemical modifications such as oxidation or rearrangements results in the formation of Sesquiterpenoids.

Table 3: Source and biological activities of some sesquiterpenes

Names	Plant source	Activity	Ref
Arvestolides H and I	*Artemisia vestita*	Declining in NO production using BV-2 cells induced by LPS with IC_{50} values.	[16]
Drimenin	Canelo tree *Drimys winteri*	Reported as one of the molecular scaffolds for the development of potent type of inhibitors with higher selectivity (hα4β2 AChR).	[17]
Artefreynic acid B, C, and G	*Artemisia freyniana*	Inhibitory effects against LPS-stimulated NO production using RAW 264.7 macrophage cells with IC_{50} values.	[18]
Chrysanthemulide A	*Chrysanthemum indicum*	Potential anti-inflammatory activity (inhibition of LPS-induced NF-κB pathway and declining in MAPK activation.	[19]
14-*O*-Acetylinsulicolide A, 6β,9α-dihydroxy-14-p-nitrobenzoylcinnamolide, insulicolide A	Marine derived fungus i.e. *Aspergillus ochraceus*	Cytotoxic effect against cell lines (renal carcinoma) i.e. ACHN, OS-RC-2, and 786-O cells with IC_{50} values.	[20]

Diterpenes

Diterpenoids are generally defined as being hydrocarbons as they contain no heteroatoms, belonging to a class of chemical constituents found in different natural sources and having a molecular formula of $C_{20}H_{32}$ and four isoprene units. These diterpenes based compounds showed immunobiologically activities i.e. anti-inflammatory, antimicrobial, anticancer, and antifungal activities. Most of the familiar examples of diterpenes also showed cardiovascular activity i.e. grayanotoxin, forskolin, eleganolone, marrubenol, and 14-deoxyandrographolide (Table 4).

Table 4: Source and biological activities of some diterpenes.

Names	Plant Source	Activity	Ref
Genkwanine P and laurifolioside A	Buds of *Wikstroemia chamaedaphne*	Compounds exhibited HBsAg activities with IC_{50}.	[21]
Drechmerin B	Endophytic fungus Drechmeria sp.	Antimicrobial activity against *C. albicans* using MIC (minimum inhibitory concentration) value	[22]
Nicaeenin F	Latex of *Euphorbia nicaeensis*	Inhibition of P-glycoprotein (P-gp) activity using MDR cancer cells (NCI-H460/R and DLD1-TxR).	[23]
Eupheliotriol F and L	*Euphorbia helioscopia*	Cytotoxicity effect against MCF-7 and PANC-1 cell lines.	[24]

Sesterpenes

Sesterpenes i.e. terpene molecules consisting of 25 carbon atoms with 5 isoprene units and having a molecular formula of C25H40 which are rare among the terpene molecules. These are naturally present in the fungus (especially those from mangroves which include neomangicols A–C and mangicols A–G from the Bahamas mangrove fungus *Fusariam* sp.), marine organism, insects, sponges, lichens, and protective waxes of insects. These types of compounds are biologically active having anti-inflammatory, anticancer, antimicrobial, and antifungal activities (Table 5).

Table 5: Source and biological activity of sesterpene

Names	Plant Source	Activity	Ref
Scalarane sesterterpenes	Mushroom species, *P. ostreatus* and *S. areolatum*	Moderate activity against *P. falciparum* 3D7 and *T. cruzi Tulahuen* C4 parasites.	[25]

Triterpenes

Triterpenes, belongs to one of the major class of secondary metabolites and usually contains 30 carbon atoms consisting of 6 isoprene units and may be derived from the squalene biosynthetic pathway. In triterpenes, existence of several methyl groups were reported and these triterpenes oxidized

them into corresponding compounds in the form of alcohols, aldehydes and carboxylic acids. Triterpenes have many active sites for the process of glycosylation and helps them to converts into another big class of compounds, namely, saponins (triterpene glycoside). Herein, some of the active bioactive triterpenes as shown in Table 6.

Table 6: Source and activity of Triterpenes.

Names	Plant Source	Activity	Ref
Polyporenic acid B	*Fomitopsis palustris* (fruiting bodies)	Strong cytotoxicity against the HCT116, A549, and HepG2 cell lines	[26]
Pardinol B, E and F	*Tricholoma pardinum*	Cytotoxicity against HL-60 SMMC-7721 A-549 MCF-7 SW480.	[27]
Xuedanencins G and H	*Hemsleya penxianensis* (tubers)	Cytotoxic activity using Hela human cancer cell line	[28]
Cyclocariols A, B, and H	*Cyclocarya paliurus* (leaves)	Showing inhibition against human colon tumor (HCT-116) cell lines	[29]

Examples of terpenoids extracted from medicinal plant products that are currently under investigation

- Immunopharmacological studies were conducted on crude terpenoids extracted from *Emblica officinalis, Ficus racemosa* and *Strychnos nux-vomica* using leaves and evaluated its effect on human whole blood. According to these studies, it may indicate that crude terpenoids inhibited the percentage count of blood counts and also declining in antigen specific proliferation rate. Overall, crude terpenoids from these medicinal plants possess immunosuppressive activity and might be used for various therapeutic purposes [30].
- Immunopharmacological studies were conducted on human whole blood against specific antigen using crude terpenoids from *Mesua ferrea, Ficus benghalensis* and *Butea frondosa*. From these studies, the results showed that terpenoids showed decline in T cell proliferation rate and NO production. In short, crude terpenoids showed immunosuppressive activity and considered as one of the most promising source of medicinally important natural compound [31].
- Essential oils from *Cannabis* were reported and confirmed the presence of terpenoid content and showed *in vitro* (moderate level) and *in vivo* (without affecting tumor necrosis factor alpha serum levels) anti-inflammatory properties. The effect of these terpenoids may totally varied according to their composition [32].
- Terpenoids (i.e. one sesquiterpenoid and 2 triterpenoids), were reported using ethanolic extract, oleo-gum-resin from *Boswellia ovalifoliolata*. All these terpenoids were screened and significantly inhibited the production of tumor necrosis factor and also confirmed its declining in interleukin (IL-6 and IL-8) along with nitric oxide production. Overall, these terpenoids from *Boswellia ovalifoliolata* may showed anti-inflammatory potential [33].
- Diterpenoids were reported from *Euphorbia kopetdaghi* and showed immunosuppressive effect against T (phytohemagglutinin) cell mitogenic proliferative rate and also declining in interleukin-2 activity in mouse fibroblast cell-lines [34].

Conclusion

Medicinal plants showed enormous ability to synthesize diverse types of terpenoids using secondary metabolic pathways. In general, terpenoids mostly reported from various medicinal plant products and also reported in vegetables and fruit. In contrast, dietary terpenoids also may contribute declining in risk of metabolic syndrome. In short, terpenoids are reported in most of the herbal plants and several terpenoid derivatives have been shown to be available for pharmaceutical applications e.g. artemisinin and taxol as malaria and cancer medicines, respectively.

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