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Unlocking the Therapeutic Potential of Terpenoids: A Roadmap for Future Medicine

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ABSTRACT

The naturally produced plant-derived compounds, known as phytochemicals, are biologically effective and incorporated to reduce the risk of numerous human illnesses. The utilization of phytochemicals for traditional medicine or functional nutrition has likely existed for as long as human history itself. Plants may gather phytochemicals in a variety of sections, including the roots, seeds as well as leaves and fruits. Among all the phytochemicals class, terpenoids are renowned for its proven biological activities and found in enormous capacity in medicinal plants. Several studies report the use of terpenoids in a wide range of diseases and infections. Different classes of terpenoids showed a variety of biological activities in chronic disorders and autoimmune diseases such as hypertension, diabetes, arthritis and cancer. These classes of compounds are also used against cancer and infectious diseases. In the present study we mainly highlight the use of terpenoids in different diseases and its availability in nature as different class. The role of terpenoids in developing new medications and enhancing current treatment methods is significant. However, thorough and detailed research is still warranted to entirely recognize the pharmacological effects of several terpenoids.

Keywords: Phytochemicals, Secondary Metabolites, Terpenoids, Terpenes.

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INTRODUCTION

In recent years, there has been a notable rise in the utilization of metabolites and dietary supplements sourced from plants. The utilization of medicinal plants as herbal remedies for preventing and treating severe ailments varies among different communities. The biological scientific communities have recently shown interest in traditionally employed medicinal plants. Ethnopharmacologists, botanists, microbiologists and natural-products chemists are collectively engaged in finding approaches to address infectious diseases.[1,2] Plants produce and amass a diverse array of small molecules or natural products essential for fundamental physiological and ecological processes. Throughout millennia, humans have harnessed the therapeutic potential of certain natural products, utilizing them in traditional herbal medicine. In the modern era, as our comprehension of their biosynthesis, regulation and functionality has expanded, natural products derived from plants have become valuable for various purposes, including therapeutics, flavors, fragrances, colorants and agents promoting health. Plant natural products can be categorized into distinct groups, such as terpenoids, alkaloids and phenolic compounds, based on their structure and biosynthetic origin.[3]

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PHYTOCHEMICALS

The emergence of multiple drug resistance has prompted the exploration of alternative sources for medicines, specifically those derived from plants, often referred to as phytochemicals.[4] These are naturally derived plant compounds with strong antioxidant properties, offering significant health advantages for humans.[5]

SECONDARY METABOLITES

Plants have the ability to produce various organic compounds known as secondary metabolites, characterized by distinct carbon skeleton structures. Secondary metabolites are not essential for the survival of a cell or organism; however, they contribute to the organism's interaction with its environment, thereby securing its continued existence within its ecosystems. They shield plants from various stresses, encompassing both biotic factors such as bacteria, fungi, nematodes, insects, or grazing by animals and abiotic factors like elevated temperature, increased moisture, shading, injury, or exposure to heavy metals. Secondary metabolites, due to their significant economic value, find application in various human uses, including the production of chemicals such as drugs, flavors, fragrances, insecticides and dyes. Within plants, secondary metabolites can be categorized into three groups (Terpenoids, Polyketides and Phenylpropanoids), distinguished by their origins in biosynthesis.[6] Terpenes are classified as simple hydrocarbons, while terpenoids represent a structurally modified category of terpenes characterized by the presence of various functional groups and the relocation or elimination of oxidized methyl groups at different positions.[7]

TERPENOIDS

Originally, "Terpene" denoted cyclic hydrocarbons with the molecular formula $C_{10}H_{16}$ extracted from plants' essential oils. Yet, its meaning has broadened to include a wider scope, encompassing various categories of plant secondary metabolites. These are naturally occurring hydrocarbons derived from isoprene units. When alterations occur in the structure, they are also known as terpenoids. This, along with steroids, forms the extensive group of secondary metabolites, collectively known as isoprenoids. While steroids and certain terpenoids share a biogenetic relationship, they are treated as distinct groups due to the independent development of their chemistry.[8] Terpenoids exist not only as terpene hydrocarbons but also predominantly in diverse oxygen-containing derivatives, encompassing alcohols, aldehydes, carboxylic acids, ketones, esters and glycosides. The MVA pathway and the 1-deoxy-D-Xylulose-5-Phosphate (DXP) pathway are both involved in the synthesis of terpenoids. Isopentenyl diphosphate serves as the primary metabolic intermediate in both pathways. The cytoplasm hosts the MVA pathway, primarily responsible for the production of secondary metabolites like sesquiterpenes, sterols, and triterpenes. On the other hand, the DXP pathway predominantly occurs in plastids and it is the main route for the synthesis of monoterpenes, diterpenes and tetraterpenes.[9]

Isoprene Rule

The basic molecular formulas of terpenes consist of multiples of (C_5H_8) n, where 'n' signifies the quantity of linked units of isoprene as shown in Figure 1. According to the Isoprene Rule, the molecules of terpenoid are created through the union of more than 2 isoprene units. Additionally, previous researcher proposed that units of isoprene in terpenoids are connected in a head to tail manner as shown in Figure 1.

Typically, three techniques exist for connecting units of isoprene

Head-to-Head,

Tail to Tail,

Head to Tail.

The extraction and purification methods of terpenes from plant matter rely on the chemical and physical properties of the terpenes. Broadly, the procedures encompass the subsequent stages: 1) disrupting plant cells to liberate their chemical components; 2) employing an appropriate solvent for extraction (or utilizing distillation or compound trapping methods); 3) isolating the targeted terpene from other unwanted elements in the extracts that might hinder analysis and quantification; and 4) employing a suitable analytical technique (such as Thin Layer Chromatography [TLC], Gas Chromatography [GC], or Liquid Chromatography [LC]).[12] As described in Figure 2.

Classification

Terpenes can be classified according to the number of units of isoprene within the molecule and the prefix indicates the required number of terpene units for its generation. Figures 3 and 4 describes the classification of terpenes.

Hemiterpenes composed of a one isoprene unit, which consists of five carbon atoms. Isoprene itself is considered the only true hemiterpene. However, it's worth noting that the terms "hemiterpene" and "hemiterpenoid" are sometimes used interchangeably and the distinction may not be strictly adhered to in all cases.

Hemiterpenoids, on the other hand, are derivatives of isoprene that contain additional functional groups, often oxygen-containing groups. Examples of hemiterpenoids include isovaleric acid and isoprenol, as you mentioned. These compounds have structures derived from isoprene but have undergone modifications, typically involving the introduction of oxygen atoms.

So, to summarize, isoprene is the primary example of a hemiterpene and when isoprene undergoes further modifications, the resulting compounds are referred to as hemiterpenoids.

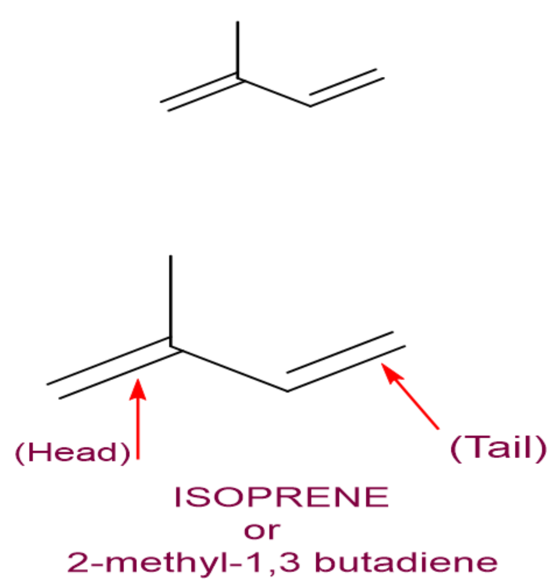

Figure 1: Structure of Isoprene Unit and combining of units of isoprene as described in method head to tail.[10]

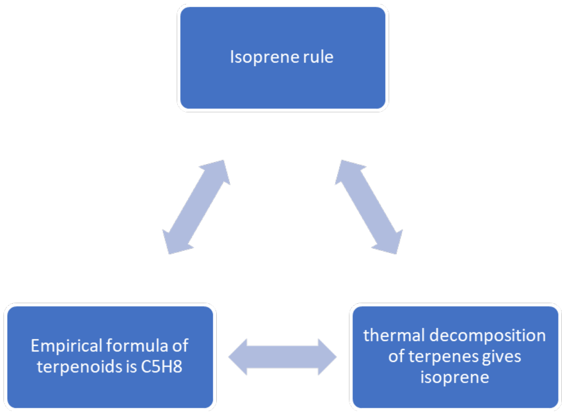

Figure 2: Illustrating empirical formula as well as thermal decomposition of terpenes.[11]

Monoterpenes are composed of two isoprene units and their general molecular formula is $C_{10}H_{16}$. Each isoprene unit contributes five carbon atoms, making a total of ten carbon atoms in the molecule. The structure of monoterpenes is often cyclic and they take part in a major role in the biosynthesis of various natural compounds, including essential oils found in many plants. Examples of monoterpenes include limonene, myrcene and pinene. Here's a brief overview of the mentioned monoterpenes and monoterpenoids:

Terpineol: Found in lilacs, terpineol is a monoterpene alcohol with a pleasant floral scent. It's commonly used in perfumes and cosmetics.

Geraniol: Present in the essential oils of various plants, geraniol has a rose-like scent. It is found in geraniums, roses and citronella.

Limonene: Occurring in the peels of citrus fruits such as lemons, oranges and grapefruits, limonene has a citrusy aroma. It is mostly used in the manufacturing of citrus-flavored stuffs, as a solvent.

Linalool: Found in lavender and many other flowers and spices, linalool has a floral and slightly spicy fragrance. It is used in the perfume and cosmetic industries.

Pinene: Present in pine trees, pinene is responsible for the characteristic scent of pine forests. It exists in two isomeric forms: alpha-pinene and beta-pinene.

Myrcene: Found in hops, myrcene contributes to the aroma of beer. It also occurs in other plants like cannabis and is responsible for some of the characteristic scents associated with these plants.

These compounds are not only responsible for the distinctive aromas of various plants but also have practical applications in industries such as perfumery, flavoring and pharmaceuticals.[13]

Sesquiterpenes, signified by the prefix "sesqui-" denoting 1.5, are created from three units of isoprene and possess $C_{15}H_{24}$ as its molecular formula of. Farnesol, humulene as well as farnesenes and their similar compounds are few examples of sesquiterpenes and sesquiterpenoids.

Diterpenes have $C_{20}H_{32}$ as its molecular formula and mainly composed of 4 units of isoprene. They are generated from a chemical named geranylgeranyl pyrophosphate. The components such as kahweol, cembrene, as well as taxadiene and cafestol are examples of diterpenes and diterpenoids. Additionally, the biologocal components such as phytol, retinol and also retinal are generated from diterpenes.

Sesterterpenes, characterized by twenty-five carbon atoms and 5 units of isoprene, are infrequent compared to terpenes of another dimension. Geranyl farnesol is an example of a sesterterpenoid. The prefix sester- denotes two plus half.

Triterpenes, ($C_{30}H_{48}$), are comprised of 6 units of isoprene. Squalene, a primary component of shark liver oil and a linear triterpene, is mainly produced by the reduction reaction of two molecules of farnesyl pyrophosphate. In the biosynthetic pathway, squalene undergoes further processing to produce one of the products such as cycloartenol and lanosterol, which serve as the structural predecessor for all steroids.

Sesquarterpenes ($C_{35}H_{56}$), consist of 7 units of isoprene. Sesquarterpenes generally originated from microbes. Tetraprenylcurcumene and ferrugicadiol are the example of sesquarterpenoids.

Tetraterpenes ($C_{40}H_{64}$) consists of 8 units of isoprene. The biological tetraterpenoids comprise of the monocyclic γ-carotene and the bicyclic β and α carotenes, also the acyclic lycopene.

Polyterpenes are mainly composed of elongated series containing multiple units of isoprene. Certain plants generate gutta-percha which is a polyisoprene composed of double bonds at trans position. Natural rubber is an example polyisoprene which contains cis double bonds.

Norisoprenoids, like C13-norisoprenoids discovered in Muscat of Alexandria leaves is an example of 3-oxo-α-ionol. The components such as 3-oxo-7,8-dihydro-α-ionol as well as megastigmane-3,9-diol which is found in wine is derivative of 7,8-dihydroionone. All of them may be generated through the action of fungal peroxidases or glycosidases.[14]

PHARMACOLOGICAL ACTIONS

In the Table 1 the examples of terpenoids along with their biological source and pharmacological activity is presented.

DISCUSSION

The medicinal attributes of herbs stem from their capacity to serve as potential drug sources, primarily due to the presence of secondary metabolites, particularly compounds like terpenoids.

Herbal remedies are crucial in the management and treatment of various diseases. Hence, the sole remedy to counteract the adverse effects of contemporary drugs is the utilization of natural,

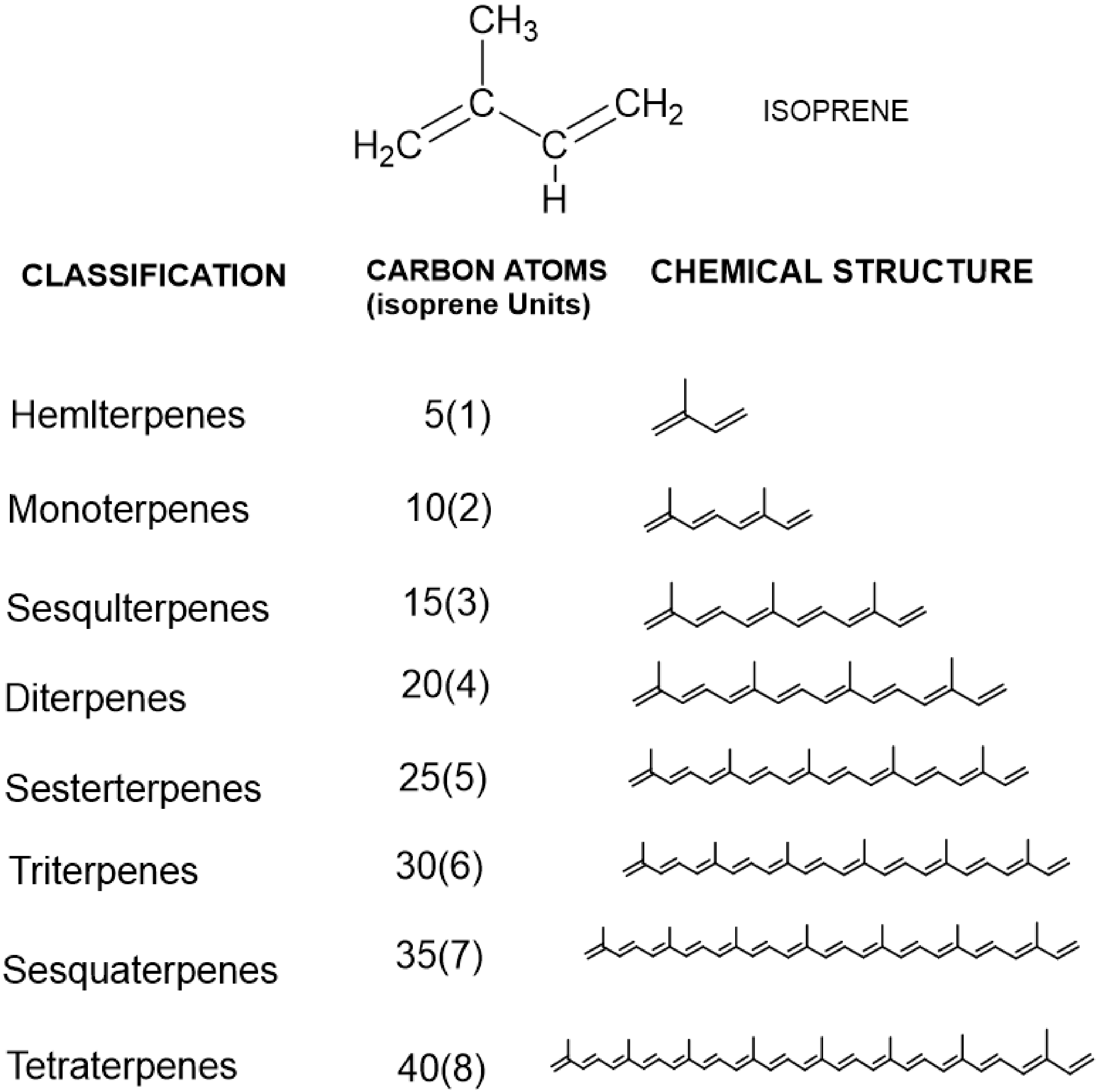

Figure 3: Chemical structure of isoprene and classification of terpenes according to the number of isoprene unit.[15,16]

plant-derived medication. This serves as a non-toxic alternative, aligning with social preferences, economic feasibility and sustainability, ultimately postponing or averting complications associated with neurological disorders.[60]

Within the realm of plant secondary compounds, terpenoids stand out as the most plentiful and varied category. Terpenoids are commonly present in plants found at elevated levels, typically synthesized in different parts of vegetable also in flowers and occasionally in roots. The wide array of terpenoids likely stems from their numerous natural biological functions, making them an extensively utilized source in both traditional and contemporary human endeavors.

Terpenoids found in nature offer fresh possibilities for uncovering medications with minimal adverse effects. Typically, they constitute the essential oils that hold economic significance in the form of flavors and fragrances. They are frequently employed as natural flavoring agents in the food industry.[54] Terpenoids play a crucial role in human nutrition and have significant

Table 1: Terpenoids and their examples with biological source and biological activity.

Sl. No.	Terpenoid	Examples	Biological source	Biological activity	References
1	Hemiterpenoids	Cibotiumbaroside B	*Cibotium barometz* (L.) J. Sm	Anti-inflammatory.	[17,18]
		1-O-caffeoyl-6-O-(4′-hydroxy-2′-me-thylene-butyroyl)-β-Dglucopyranose	*Spiraea prunifolia* leaves	Antioxidant	[19,20]
		Cibotiumbarosides F.	*Cibotium barometz* (L.) J. Sm	Hepatoprotective activity.	[21,18]
2	Monoterpenoids	Citronellol	Essential oil of plants of the genus *Cymbopogon*	Antifungal	[22,20]
		Thymol	*Thymus vulgaris* L.	Anticancer	[23,24]
		Carvacrol	Essential Oil of *Oregano*	Anti-inflammatory	[25,26]
		9-OH-isoegomaketone	*Perilla frutescens* leaves	Antioxidant	[27]
3	Sesquiterpenoids.	Tatridin A and Tanachin	*Oncosiphon piluliferum*	Antimalarial	[28-30]
		Laurebiphenyl	*Laurenciatristicha*	Cytotoxicity	[31,32]
		Polygodial	*Warburgia stuhlmannii* and *Warburgia ugandensis*.	Antifungal	[33,34]
		Epicubenol	*Juniperus sabina*	Protective effect on liver cells.	[35,36]
		Artefreynic acid C and Artefreynic acid G	*Artemisia freyniana*	Inhibit oxidation.	[37-39]
		Chrysanthemulide A	*Chrysanthemum indicum*	Effective against inflammation.	[40]
4	Diterpenoids.	Cephinoids derivative	*Cephalotaxus fortunei* var. *alpina* and *C. lanceolata*	Effective against inflammation and cancer.	[41,42]
		Nudiflopene F	*Callicarpa nudiflora*	-	[43,44]
		Eupheliotriol F and L	*Euphorbia helioscopia*	Cytotoxicity	[45-47]
		Genkwanin P and laurifolioside A	Buds of *Wikstroemia chamaedaphne*	Effective against hepatitis.	[48]
		Drechmerin B	Species of *Drechmeria* (fungus)	Effective against microbial infection.	[49]
5	Sesterterpenoids.	Cybastacines	Nostoc sp. Cyanobacterium	Antibiotic	[50]
		Scalarane	Mushroom species	Antiparasitic	[51]
6	Triterpenoids	Cyclocariols derivatives (A, B and H)	Leaves of *Cyclocarya paliurus*	Effective against tumour.	[52]
		Xuedanencins G, Xuedanencins H	*Hemsleya penxianensis*	Effective against cancer.	[53]
7	Tetraterpenoids	Lycopene	*Solanum lycopersicum* L.		[54,55]
		Canthaxanthin	Natural source	Anticancer	[54,56]
		Crocin	*Crocus sativus* L.	Anti-cancer	[54,57]
		β-carotene	Fruits such as Carrots, apricots, mangoes and vegetables such as red pepper, kale, spinach, broccoli.	Anticancer effect	[54,58]
		Lutein	Fruits, vegetables and egg yolk.		[54,59]

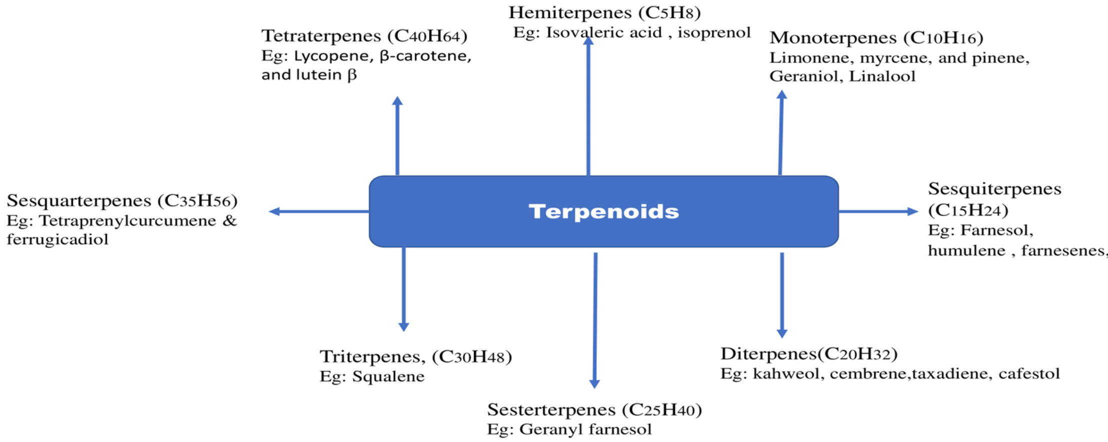

Figure 4: Classification of terpenoids and its examples.

economic potential in the fields of pharmaceuticals, aromatics and potential biofuels in the future. Metabolic engineering and synthetic biology projects are increasingly focusing on terpenoids as a primary objective. This phenomenon is propelled by the frequent shortage of these substances in nature and the requirement for innovative terpenoid configurations that provide novel or improved biological effects. A multitude of terpenoids, including those found in blood cells have been investigated for their potential as anti-inflammatory molecules. These analyses have been conducted in both *in vivo* animal models and carefully defined *ex vivo* cultures of inflammatory cells. The terpenoids are also capable of reducing inflammatory agents and thus reducing inflammation. Moreover, there is supporting evidence from the utilization of herbal extracts containing abundant terpenoids. This suggests the presence of potential candidates that could serve as potent anti-inflammatory medications. Previous studies have also reported that various types of terpenoids reduce disorders induced by oxidation. They are identified as potent agents that suppress oxidation, which is responsible for the development and progression of several disorders. The protective effect of terpenoids on liver cells is also reported in previous literature. Triterpenoids, diterpenoids as well as sesquiterpenoids possess protective effect on liver cells.

The biological scientist also reported the antifungal and cytotoxic activity of varied types of terpenoids. These biological compounds are reducing the colony of fungal growth and also having toxic effect on rapid growth of cells. In addition, the terpenoids are also reported as potent anticancer agents. Almost all types of terpenoids are having capability of suppressing the cell growth. They mainly affect the pathways such as cell cycle arrest, inhibition of differentiation of cancerous cell as well as stimulation of apoptosis. They are also capable of suppression of metastasis through targeting pathways of cell signals.

The plant kingdom presented a potential reservoir of such compounds. Numerous terpenoids function as plant hormones, overseeing distinct physiological functions such as gibberellins. Certain terpenoids act as secondary metabolites, safeguarding the host against potential pathogens in both plants and animals.[61-65]

The growing fascination with natural products has prompted the exploration of novel bioactive substances that might be tailored for particular therapeutic aims. Terpenoids, the primary category of secondary plant metabolites renowned for their anticancer properties, present themselves as promising options for pharmaceutical development.

CONCLUSION

Terpenoids are the only metabolites of plants which found in most abundant quantity also it is diversified class of phytoconstituents. Terpenoid is proved to be most wisely used phytochemicals in traditional system of medicines. Recent reviews have brought attention to numerous terpenoid compounds due to their promising pharmacological capabilities.[66,67] The terpenoids contains various pharmacological effects against diseases such as inflammation, cancer, arthritis, diabetes and hypertension. By employing sophisticated analytical methods, scientists have successfully isolated and identified a range of metabolites, laying the groundwork for drug development. The diverse pharmacological activities of terpenoids, makes them a potent future therapeutic agent as an alternative therapy for various illness and disorders. Currently there is an augment attention to use medicines originated from medicinal plants as an alternative therapy due to its lesser adverse effects. These newly discovered chemical structures hold great promise as potential treatments for diverse diseases. There is significant potential to leverage these metabolites in the creation of pharmaceuticals that are more cost-effective and environmentally sustainable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TLC: Thin layer chromatography; **GC:** Gas chromatography; **LC:** Liquid chromatography; **DXP:** 1-Deoxy-D-xylulose-5-phosphate; **MVA:** Mevalonate.

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