

Terpenoids as Natural Anti-Inflammatory Agents: A Review of their Biological Mechanisms

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ABSTRACT

Body's Immune system biological response also known as inflammation and it is stimulated by varied factors such as pathogenic organisms, ruptured cells and toxic components. The given factors can initiate inflammatory reactions may be acute or chronic in many vital organs of the body and causing cellular damage. This damage in-turn gives rise to pathways of inflammatory signals associated with mediators of inflammation. Inflammation associated diseases are rapidly growing worldwide. The treatment use to suppress inflammatory reactions in the body is also linked with serious adverse effects. In the current decade use of phytochemicals is increased heavily across the globe being advantageous of lesser side effects and better potential in reducing inflammatory reactions. Phytochemicals are not essential nutrients required for sustaining life, but they possess significant properties that help prevent or fight certain common diseases. Terpenoids are a vast and structurally diverse group of natural secondary metabolites found in plants, derived from isoprene units (C-5), and linked to a variety of biological properties such as anti-oxidant, anti-inflammatory and anticancer. The present review highlights the pharmacological aspects of terpenoids with reference to suppression of inflammation. The work also emphasizes on role of terpenoids at molecular level to reduce the signalling pathways of inflammation with certain examples. In addition, future perspective on the use of terpenoids as therapeutic agents is also overviewed.

Keywords: Anti-inflammatory, Phytochemicals, Terpenoids, Herbal Medicine.

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Received: 14-04-2025;

Revised: 09-06-2025;

Accepted: 25-08-2025.

INTRODUCTION

Inflammation

The term inflammation, which comes from the Latin word inflammation, refers to the body's tissues' biological reaction to harmful stimuli including infections, damaged cells, or irritants. Calor, dolor, rubor, tumor, and functio laesa are Latin for "heat," "pain," "redness," "swelling," as well as "loss of function." While adaptive immunity is unique to each disease, inflammation is a general response and is therefore regarded as an innate immunity mechanism. Immune cells, blood vessels, and chemical mediators are all part of the defensive response known as inflammation. The objective of inflammation is to eliminate the root source of cell damage, eliminate damaged cells and tissues, and initiate the process of tissue healing. Insufficient inflammation could put the organism's survival in danger by causing gradual tissue death from a harmful stimulus (like bacteria). On the

other hand, inflammation may be harmful.^[1] Atherosclerosis, osteoarthritis, periodontal disease, and hay fever are among the conditions that are associated with chronic inflammation, or excessive inflammation. Acute and chronic inflammation are both possible. Increased circulation migration of plasma and leukocytes, especially granulocytes, inside the injured tissues is a hallmark of acute inflammation, the body's first reaction to harmful stimuli. The local blood vascular system, the immune system, and many cells in the injured tissue are all involved in the series of biochemical processes that propagate and develop the inflammatory response.^[2] Long-term inflammation, sometimes referred to as chronic inflammation, results in tissue death and repair as well as a progressive change in the type of cells-such as mononuclear cells-that are present at the site of inflammation.^[3]

Causes

Chronic inflammation is covert, inconspicuous, and usually starts for no obvious reason. Inflammatory triggers abound in our modern society. These include substances found in our food, water, and air, cigarette smoke, gut microbiota, and psychological indicators like stress. Due to our environment and way of life, we now always have low levels of inflammatory signals "arming" our immune systems.^[4] Rather than producing the usual overt signs of inflammation, this quiet hazard exacerbates pre-existing



DOI: 10.5530/pres.20252308

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disease processes. Here are some instances of when chronic inflammation may arise: Exposure: Prolonged, low-level exposure to an irritant, such as smoke, air pollution, or industrial chemicals, can occasionally result in chronic inflammation. Sensitivity: The body experiences inflammation when it detects an abnormality.^[3] Allergies can be caused by hypersensitivity to an external trigger. Autoinflammatory diseases: Like Behçet's illness, a hereditary component influences how the immune system functions.^[1] Acute inflammation that persists: A person may occasionally not fully heal from acute inflammation. This can occasionally result in persistent inflammation. Many aspects, like progressive age, obesity, a diet rich in corrupt fats and extra sugars, smoking habit, low level of sex hormones, stress, and disturbed sleep, might raise the risk of chronic inflammation.

Pathophysiology

Most of the characteristics of short-term inflammation, like vasodilation (the expansion of blood vessels), permeability of capillaries, neutrophil migration through the wall of capillaries into the infected tissue, and diapedesis (an increase in blood flow), continue when the inflammation turns chronic. Nevertheless, white blood cell composition rapidly shifts, with lymphocytes and macrophages taking the place of the passing neutrophils.^[5] Therefore, principal proinflammatory cells like macrophages and lymphocytes as well as plasma cells secreting the tissue site and generation of cytokines of inflammatory reactions, growth factors, and enzymes are the hallmarks of chronic inflammation. This contributes to the development of secondary repair, including granuloma formation and fibrosis, as well as tissue damage. When exposed to self-antigens or foreign ones, tissue immune cells, such as dendritic cells and macrophages, release cytokines including TNF- α and IL-1.^[3] The given cytokines persuade the release of Selectins and Integrins by the endothelial cells at the site of injury, which in turn enable the chemotaxis reaction and diapedesis of leukocytes in circulation. Through the process of phagocytosis, release of cytokines, and presentation of antigen to lymphatic cells, the tissue macrophages and dendritic cells take part in the clearance of antigen in addition to recruitment of leukocytes. The macrophages and dendritic cells in turn release cytokines and chemokines as well that stimulate leukocytes of circulation as they reach the site of tissue damage. Leukocytes release more inflammatory mediators and cytokines when they are stimulated. In the inflammatory acute stage, neutrophils are the initial and utmost predominant cells.^[2] The lysosomal enzyme, matrix metalloproteinases as well as myeloperoxidase enriched granules which originate in neutrophils are unconfined upon the external or self-antigen, therefore abolishing it. Through phagocytosis process, neutrophils abolish the antigen, releasing cytokines which include TNF- α , IL-1 and IL-6 as well as reactive oxygen species. As the next line of defense, lymphocytes-including T- and B-lymphocytes-produce antibodies and immunological complexes, secrete cytokines, stimulate lymphocytes, and mediate

inflammation through a number of intricate processes.^[3] Through the process of platelet aggregation, formation of thrombus, and degranulation in which release of chemokines and inflammatory mediators takes place-thereby platelets in the circulation may be a participating aspect to inflammation. Two stages can be used to describe acute inflammation the phase named cellular after the vascular phase. At the time of vascular phase, there is an increment in the blood flow as the small blood capillaries subsequent to the injury side widens (vasodilate). To raise the permeability of the blood vessels barrier, the endothelial cells at first swell and after that they contract to produce extra space between them. There are chemical mediators that control this process. Fluid exudation causes oedema, or tumor, by causing a net loss of fluid from the vascular space into the interstitial space. Because of the enhanced vascular permeability, the fluid that is present is known as an "exudate" and is characterized by a high protein concentration. Upsurge tissue fluid aids as a conduit for the relocation of inflammatory proteins, counting complement as well as immunoglobulins.^[1] With the aid of lymphatic drainage, it might also benefit in the elimination of infections as well as cell waste from the injury area. In acute inflammation phase the primary cell is the neutrophil. Chemotaxis reaction, which are intermediaries unconfined into the blood circulation soon after an insult, appeals them to the place of impairment. Neutrophil migration takes place in four phases. To form a margin, the cells bring into line themselves with the endothelium. Rolling: making intimate contact with the endothelium and moving along it. Attaching takes place to the wall of endothelium by adhesion. Migration of cells to the distressed site through the blood vessel wall by emigration. Once there, neutrophils identify the foreign object and begin the process of phagocytosis, which entails using a phagosome to engulf and contain the pathogen.^[4] Following that, the phagosome is removed using either oxygen-dependent (free radical generation) or oxygen-independent (lysozymes) techniques.^[3]

Prevention

(A) Nonsteroidal anti-inflammatory drugs

Aspirin and ibuprofen as well as naproxen are examples of Nonsteroidal Anti-Inflammatory medicines (NSAIDs) that have been linked to a decreased risk of cancer. Acetylsalicylic acid (ASA), also recognized as aspirin, is one of the utmost extensively cast-off drugs in the world, predominantly for the inhibition of cardiovascular diseases. Numerous clinical investigations have found that long-term aspirin use reduces the incidence and mortality of several cancer types by 20% to 25%. Colorectal, stomach, and oesophageal adenocarcinoma tumours demonstrated the most benefit, whereas breast, lung, and prostate malignancies demonstrated a less beneficial effect.^[6] Some conceivable descriptions for the linkage between NSAID and aspirin usage and cancer deterrence include inhibition of COX1/2, modulation of immune response, effect on signalling of PI3K,

specific proinflammatory mediators' inhibition, suppression of PR tumorigenic transcription factors, preservation of cancer stem cell homeostasis, and reduced rate of glycolytic in cancer cells.^[7] With the help of suppressing cyclooxygenase-2 and 5-LOX, the key active constituents in its seeds named as alpha-amyrins, possess anti-inflammatory and anti-cancer effects.^[8]

(B) Corticosteroids

The best anti-inflammatory medications for a variability of long-term inflammatory diseases are corticosteroids, which have also been revealed to have anticancer properties. They are utmost frequently cast-off medicines as anti-emetic to treat nausea and vomiting induced by chemotherapy.^[8] For instance, pre-treatment with dexamethasone amplified the efficacy of chemotherapy in xenograft and experimental tumour models of glioma, breast and lung as well as colon cancers.^[9] In Figure 1 the mechanism of corticosteroids as anti-inflammatory agents is represented.

(C) Diet and lifestyle modifications

Given that the relationship between weight, diet, and activity and systemic inflammation has been thoroughly studied in recent years, the advantages of these factors may not be shocking. Participants in both interventional groups also lost a significant amount of weight, which could be a significant confounding factor. Another RCT comparing diets low in calories and saturated fats with high versus low egg intake in those with prediabetes or Type 2 diabetes mellitus likewise found that overall inflammatory markers decreased from baseline, but not between groups.^[6] In Figure 2 role of dietary phytochemicals in suppression of inflammatory reactions is presented.

HERBAL DRUG

Complementary and alternate medicine, which has expanded acceptance newly worldwide and is steadily being included in the traditional systems of healthcare, revolves around Herbal Medicine (HM). In both industrialized and developing nations worldwide, HM is used across racial, social, and gender boundaries.^[10] Due to HM's increasing popularity, its annual sales are rapidly approaching US \$62 billion, and its local and international market stakes are rapidly growing. The main reasons for this rise in use and patronage are its low cost, widespread acceptability as a drug of natural origin with the benefits of reduced toxicity, effectiveness in some tough disorders, and adaptability in terms of accessibility, preparation, and administration.^[11]

In command to preserve wellbeing and treat a variety of ailments, HM denotes to the medicines of natural origin containing biologically active component that are regularly composed of herbal materials, though some recipes may also contain ash, shells, insects, animal parts, minerals (kaolin, bentonite), fungal and bee products, and more. While there are many advantages to HMs, some can also have drawbacks.^[12] Secondary metabolite

activity has been linked to the pharmacologic and hazardous effects produced by HMs. HMs have been used appropriately, improperly, and even misinterpreted in a variety of situations.^[11] While misapplication and mistake have been allied to an information breach on herbal drugs, predominantly as they are link to their aids and possible negatives among chief health care experts: physicians, pharmacists, nursing staff and the general community, the advantages of HMs as a healthcare tool rely heavily on accurate and sufficient knowledge and experiences.^[12] For a number of reasons, the popularity of herbal medicine will only increase worldwide, making it imperative that adequate and relevant information about HM be provided, especially on crucial subjects like advantageous, efficacy, safe use, toxic effects and research and development, process of formulation, regulation, methods of analysis, control of quality, significance for economy and much more.^[11]

Role of pharmacist care of herbal medicine

Approximately 80 percent of populace universally use herbal treatments. Their perceived safety, effectiveness, cultural acceptance, and less adverse effects than prescription medications are what make them appealing.^[12] They are also said to be easily accessible and reasonably priced. In recent years, herbal products have grown in popularity. The global market was worth \$5.6 billion by the end of 2006. It is anticipated to reach \$6.1 billion by 2011 at an average annual growth rate of 1.7%. Herbal remedies may be beneficial, but they may also have the same adverse effects and drug interactions as prescription drugs. Herbal remedies' ability to interact with prescription pharmaceuticals is particularly significant for medications with low therapeutic indices.^[11] It's critical to comprehend the safety as well as effectiveness of herbal remedies. In actuality, one of the biggest risks connected to herbal remedies is that many patients mistakenly believe that because herbs are derived from nature, they are entirely safe and have no negative effects.^[10]

Advantage of herbal medicines

Herbal Medicines (HM), which are specifically used for the prevention and treatment of disease, comprised of herbs, herbal resources, preparations of herbs and final herbal formulations which consist of active constituents from fragments of plants, materials of other herbs, or their mixes.^[11]

In modern times, HM is an important part of prime patient care in several rural areas of African as well as Asian populaces. This is an essential aspect as per tradition of various communities around the globe. Numerous herbs and preparations of herbal drugs have a extensive past of folklore and medicinal privileges. Technical study has revealed that HMs include multifaceted chemical components that are accountable for their effects pharmacologically, which correspond to the health aids and/or harmfulness they cause.^[10] HMs have been castoff to treat a wide

range of moderate to severe illnesses as well as prophylactics for the passive preservation of health.^[11]

HMs are produced and utilized in a variety of methods nowadays, which influences the effects of their activities. Herbal medicine dosage forms vary widely depending on a number of factors, including the patient, culture, philosophy, and the type of illness being treated.^[13]

HMs are regularly made from fresh or dehydrated herbs and used in hometowns and clinics of traditional medicine to prepare decoctions, poultices, infusions, powders to apply to open wounds, and to make native drinks, puddings, and other products. Capsules, powders and granules, as well as lotions and ointments are examples of traditional commercial HMs products.^[10] The performance of herbal drugs in medicinal formulation is foretold for the improvement of correct dosage and agreement by encouraging usage.^[12]

The safety and effectiveness of HMs are also important factors in their use and commercialization. The safety as well as effectiveness of the herbal drugs in respect to its inherent chemical constituents, the kind of impurities present, manufacturing process are the main factors influencing the quality of herbal goods.^[11] Numerous diseases, including HIV infection, malignancy, malaria, sickle cell disorder and added communicable illnesses and non-infectious diseases like hyperglycaemia, overweightness, infertility, and so forth, have been demonstrated to benefit from the chemical compounds present in herbal materials.^[12] Despite their widespread acceptance, advantages, and occasionally misunderstandings, HMs must be decisively controlled to

guarantee that the public and healthcare professionals always have access to sufficient and accurate information about herbal materials and products, especially when it comes to topics like HM identification, quality, safety, and efficacy.^[11]

Health benefits of herbal medicines

Like traditional drugs, folk HMs are used to treat a wide range of ailments and have many indications. Colds, pain, and superficial wounds are examples of minor health problems; psychosis, hyperglycaemia, malaria, sickle cell disorder, tuberculosis, tumours, increased blood pressure, infertility, and so on are examples of significant health problems. In certain regions, HM plays as a significant part in primary care. In actual fact, the majority of healthcare for up to 80% of rural Africans is provided by traditional herbal remedies.^[12]

HM, which is commonly administered at home, is the first line of treatment for 60% of children in Ghana, Mali, Nigeria, and Zambia who have high fevers brought on by malaria and other diseases. Traditional medicine in rural South Africa is heavily centred on HM.^[10] Approximately half of all health product utilization in China and India is attributed to HM. As HM gains more attention worldwide, the number of medicinal herbs and products increases along with their use rate, particularly in areas where conventional healthcare is easily accessible and widely available.^[11]

Additionally, almost 40% of adults in the US have experimented with herbal remedies. HM's sales output is rapidly growing in, Australia and Europe, particularly countries like Germany and France.^[12]

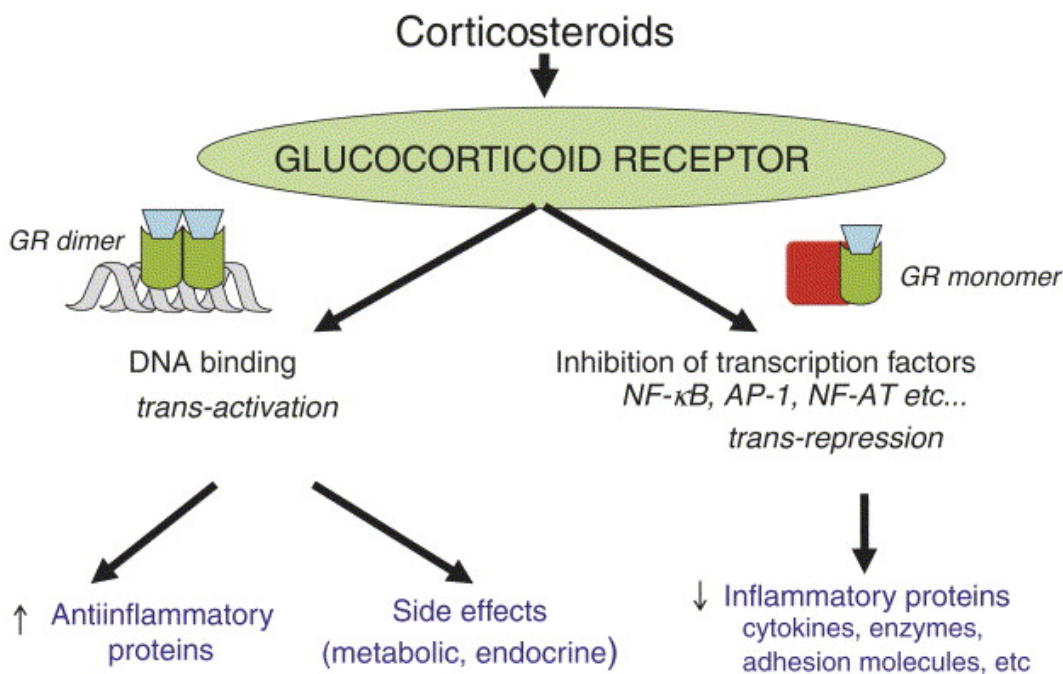


Figure 1: Mechanism of corticosteroids to reduce inflammation.^[9]

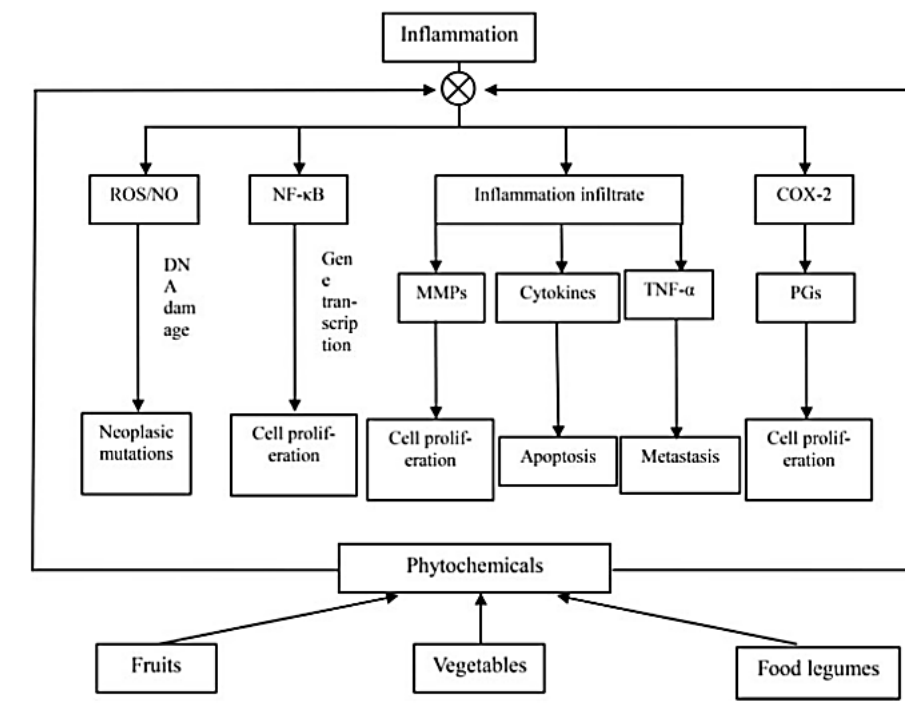


Figure 2: Role of phytochemicals in reducing inflammation.^[6]

Quality, safety, and scientific evidence

Herbal medicine has long been used to cure and prevent diseases, boost health, and improve life span and quality. However, there is no systematic approach to evaluating their safety and efficacy. Herbal therapy appeals to many people because of the holistic approach to healthcare, but because so many factors need to be taken into account, scientific evaluation becomes challenging. Although many people think that herbal treatments are harmless, they are often used in combination and are made from plant sources that differ in terms of species, growth circumstances, and biologically active substances.^[11]

Herbal extracts could be contaminated, tampered with, or contain dangerous ingredients. The safety and effectiveness of herbal medications are directly impacted by quality control. However, due to a lack of appropriate government regulations or laws, as well as a lack of a recognized or competent research methodology for assessing traditional medicines, there is a dearth of information regarding the quality and content of most herbal medicines.^[12]

A further problem is that, while though botanical dietary and herbal complements are quite widespread, few of the herbal goods in the market place are probably of substandard quality and have dubious effectiveness, even if the herb has remained to have an outcome in controlled studies with high-quality products. Since they are natural items, herbs are believed to be safe and effective in a range of dosages. Herbs may have adverse effects, but there is

no standard "doses," and interactions between herbs or between herbs and drugs may occur.^[11]

The fact that commercial herbal compounds are made from both cultivated and wild medicinal plants is another crucial factor to consider. The market for herbal products is expanding, which could lead to overharvesting and jeopardize biological diversity. Resources of natural origin may be worn-out and endangered plant species may become vanished as a result of poorly managed agricultural methods. An estimated 15 thousand of the seventy thousand species of remedial plants are in hazard of going extinct. The work of Botanic Gardens Conservation International is essential to maintaining plant populations and knowledge of the preparation and use of herbs for medicinal reasons.^[12]

PHYTOCHEMICALS

Phytochemicals, also referred to as plant chemicals, are substances that plants may produce that have biological properties; sources of phytochemicals include berries, root vegetable, whole grains, nutty fruits, seeds, shrubberies part, bark, florae, and other plant parts; biologically active phytoconstituents have been expansively studied in both *in vitro* and *in vivo* modules due to their massive potential for human consumption;^[14] they were commonly categorized into six main groups on the basis of their chemical assemblies and properties, including alkaloids, carbohydrates, lipids as well as phenolics, terpenoids and other nitrogen-containing compounds; similarly, microalgae are latent sources of a variety of natural bioactive constituents, such as pigments (e.g., phycocyanin, phycoerythrin, astaxanthin, and

others), polyunsaturated fatty acids, and the polysaccharide paramylon.^[15]

TERPENOIDS

The category of naturally occurring substances known as terpenoids is primarily found in plants, however some are derived from varied sources.^[16] They are also accountable for the smell of floras as well as plant parts. Frequently found in the leaves and fruits of citrus, eucalyptus, conifers, and higher plants. According to contemporary terminology: "Terpenoids are the plant that originated hydrocarbons of their oxygenated, hydrogenated and dehydrogenated derivatives".^[17] (C_5H_8) is the general formula. Their molecules are unsaturated and made up of interconnected isoprene units. Five carbons make up isoprene units. Another name for them is isoprenoids.^[18] Figure 3 signifies the role of terpenoids in suppression of inflammation.

Types

The typical formula for the mainstream of naturally happening terpenoid hydrocarbons is $(C_5H_8)_n$. They are categorized to the sum of carbon atoms in the assembly or the value of n .^[19] In the Table 1 terpenoids and their classification if presented as per the value of n .

It is further separated into subclasses conferring on the number of rings in the assembly. Terpenoids that are acyclic: They are consist of an exposed structure. One ring makes up the structure of monocyclic terpenoids. Two rings make up the structure of bicyclic terpenoids. Tricyclic Terpenoids: Their structure consists

of three rings. Tetracyclic Terpenoids: Their structure consists of four rings.^[20]

Monoterpenoids

Monoterpenes are a family of terpenes with the chemical formula $C_{10}H_{16}$ that are composed of two isoprene units. Monoterpenes can have rings or be linear (acyclic). Similar monoterpenoids are produced via biochemical changes including oxidation or rearrangement. Mono Terpenoids Acyclic monoterpenoids: Citral, Geraniol, and Myrcene Menthol, alpha-terpineol, and limonene are examples of monocyclic monoterpenoids. Alpha pinene and camphor are two examples of bicyclic monoterpenes.^[21]

Menthol (Monocyclic)

The main ingredient of *Mentha Piperita* is menthol. It has analgesic and antiseptic properties. The main component of peppermint oil, menthol (also known as peppermint camphor or mint camphor), gives it its Flavors and scent as well as its cooling effect when applied topically. Cold balms contain it as an ingredient. Menthol has the molecular formula $C_{10}H_{20}$ and is an optically active substance.^[17]

Limonene (Monocyclic)

At room temperature, a colourless liquid with a powerful orange scent. Cosmetics frequently include limonene. As the major odor element of citrus, D - limonene is employed in food manufacture and some medicines e.g., bitter alkaloids, as a flavouring. Additionally, it is employed as a botanical insecticide.^[22]

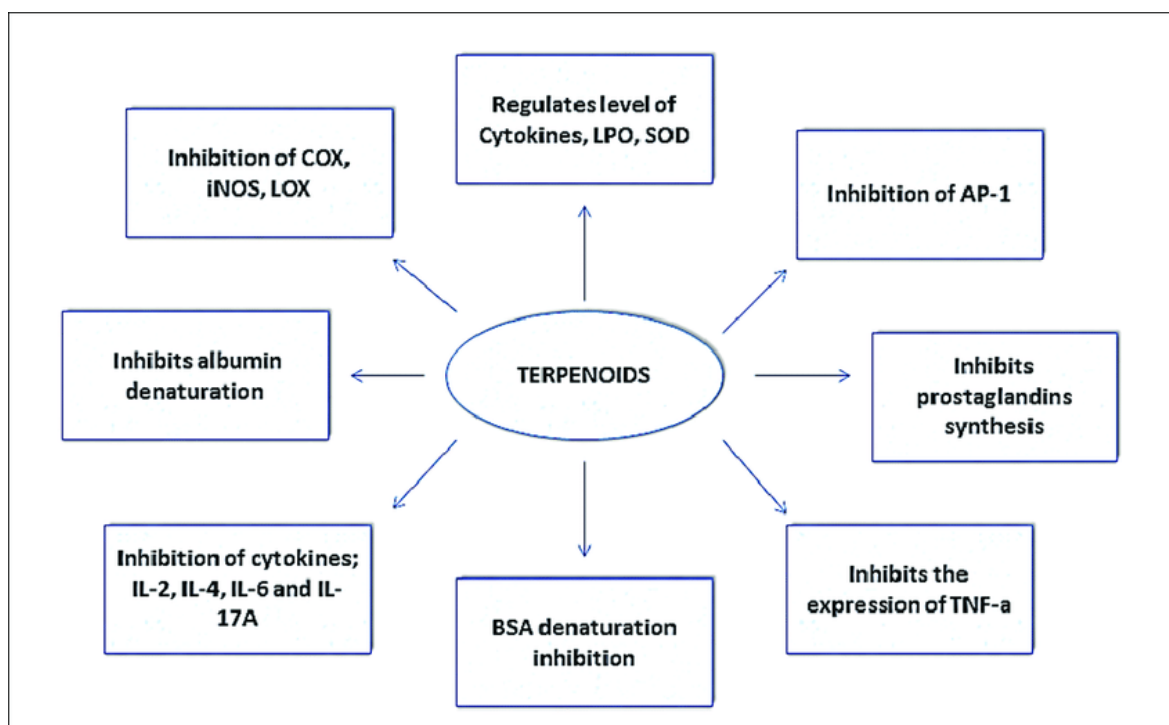


Figure 3: Role of terpenoids as anti-inflammatory agent.^[18]

Table 1: Terpenoids and their class based on the number of carbon atoms.^[19]

Number of carbon atoms	Value of n	Class
Ten	Two	Monoterpenoids
Fifteen	Three	Sesquiterpenoids
Twenty	Four	Diterpenoids
Twenty-Five	Five	Sesterpinoids
Thirty	Six	Triterpinoids
Forty	Eight	Tetraterpenoids
Less than forty	Less than eight	Polyterpenoids

Sesquiterpenoids

With the chemical formula $C_{15}H_{24}$, sesquiterpenes are a class of terpenes made up of three isoprene units. Sesquiterpenes come in a variety of unusual combinations and can be acyclic or ring-containing.^[1] [1] Farnesol is an Acyclic Sesquiterpenoids [2]. Zingiberene is one of the monocyclic Sesquiterpenoids. Cadinene is a bicyclic sesquiterpenoid.^[20]

Zingiberene

Zingiberene is a 2-Methylcyclohexa-1,3-diene in which a 6-methyl-hept-5-en-2-yl group replaces a hydrogen atom at position 5. It is the main component of ginger oil and is a monocyclic sesquiterpenoid. Up to 30% of the essential oils found in ginger rhizomes may come from it. This substance is what gives ginger its unique flavour.^[21]

Diterpenoids

Diterpenes have the chemical formula $C_{20}H_{32}$ and are made up of four isoprene units. [1] Phytol: Acyclic Diterpenoids [2] Vitamin A is a monocyclic diterpenoid [3]. Diterpenoids that are bicyclic: Andrographolide [4] Pimaric acid is one of the tricyclic diterpenoids. [5] Kaurene is a tetracyclic diterpene.^[17]

Phytol

Vitamins E and K 1 are precursors of this acyclic diterpene alcohol. Some cannabis strains and other plants, such green tea, contain the terpene phytol. All plants contain this extremely prevalent terpenoid, which is esterified to chlorophyll to give it lipid solubility. Petroleum sediments contain it.^[13]

Triterpenoids

Triterpenes have the chemical formula $C_{30}H_{48}$ and are composed of six isoprene units. Squalene is a linear triterpene. Squalene, an Acyclic Triterpenoid, Alpha and beta carotene are bicyclic triterpenoids.^[19]

Squalene

Shark liver oil's main ingredient. After that, squalene undergoes biosynthesis to produce either cycloartenol or lanosterol, which are the structural antecedents of all steroids. Despite the fact that impure samples appear yellow, the oil is colourless. In several vaccine adjuvants, squalene is a crucial component. Topical lubrication and skin protection are two functions of squalene.^[18] In the Table 2, terpenoids and their class as well as examples are tabulated.

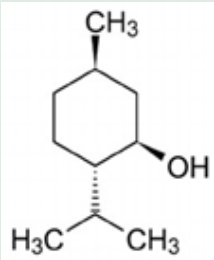
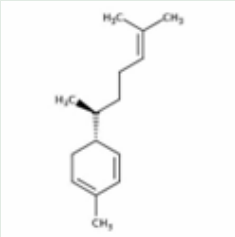
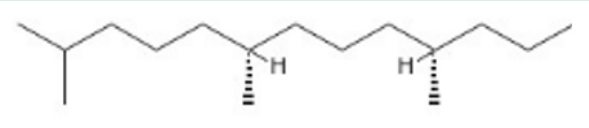
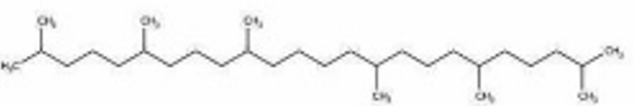
Role of Terpenoids and its Phytochemicals in Reducing Inflammation

A number of dynamic processes, including cellular and vascular activity as well as specific humoral secretions, are involved in the process of inflammation. Tissue damage can be severe or long-lasting in both acute and chronic inflammatory diseases.^[23] Studies over the last few decades have demonstrated that terpenes and terpenoids can reduce many inflammatory symptoms by blocking multiple inflammatory process stages. Figure, which displays the structures of terpenoids having anti-inflammatory properties.^[24] In the Figure 4 some commonly used different class of terpenoids with their chemical structure are showed having potential activity against inflammation.

A monoterpene glycoside named paeoniflorin was extracted from the root portion of *Paeonia lacriform* Pall. The mechanism of action and anti-inflammatory characteristics of certain monoterpenoids, such as 4-O-methyl and methylbenzoyl paeoniflorin, and derivatives of paeoniflorin, that are present in peonies. The results exhibited that utmost monoterpenes may hinder the construction of the inflammatory factors like Nitric Oxide (NO), Interleukin-6 (IL-6) as well as Tumour Necrosis Factor-alpha (TNF- α) that are produced by Lipopolysaccharide (LPS).^[25]

The traditional Chinese herbal treatment inula flower (*Inula japonica* Thumb.) is found in the genus Asteraceae. IVSE, a sesquiterpene lactone molecule found in inula flowers, has anti-inflammatory effects by inhibiting the generation of NO, which is triggered by LPS. By significantly lowering LPS-induced NO production, JEUD-38, a sesquiterpene lactone molecule present in inula flowers, has been demonstrated to prevent and treat inflammatory diseases.^[24] The findings of this study demonstrated that, in comparison to the blank group, the amount of NO rose by about 11 times when LPS was activated. The addition of JEUD-38 significantly decreased NO generation (the cells were reacted with manifold doses of JEUD-38), and the inhibitory effect was found to be significantly dose-dependent.^[23] Tripterygium Wilford has been used for hundreds of years in Traditional Chinese Medicine to treat immune system and inflammatory conditions. Triptolide Nol is the key bioactive constituent of Tripterygium Wilford.^[26] Numerous autoimmune and inflammation-related illnesses have been identified to be

Table 2: Terpenoids and their category with examples.^[18]

Sl. No.	Class	Example	Structure
1	Monoterpenoids	Menthol	
2	Sesquiterpenoids	Zingiberene	
3	Diterpenoids	Phytol	
4	Triterpenoids	Squalene	

efficiently treated by it, making it one of the utmost potent natural components for regulation of inflammation and immunological reactions. Its key mode of action is to halt the production of cytokines responsible for inflammation. Furthermore, research has exposed that triptolide, tripterpine as well as triptolide have certain effects against inflammatory reactions. One of the studies, revealed that triptolide and triptonide significantly suppress the signs of acute lung injury (ALI) in mice. Triptolide can advance the lung tissue's worsened stage in ALI mice. The generation of the chemokines induced by LPS can be significantly suppressed by triptolide.^[25]

The main component of ginseng, ginsenoside which is a traditional Chinese medicine, is. As study progresses, Ginsenoside-Rb1 (G-Rb1) has been identified as a potential anti-inflammatory agent, with the capacity to significantly inhibit NF- κ B activation, which is crucial for inflammation and regulates the production of TNF- α . Additionally, Ginsenoside-Rd (G-Rd) and Ginsenoside-Rb2 (G-Rb2) were found to have neuroprotective qualities.^[23]

Plentiful extracted bioactive terpenes complexes have revealed the potential to diminish the inflammation by wide mechanisms.^[24]

Pro-inflammatory mediators and its regulation

It has been publicized that the main way terpenes and terpenoids have anti-inflammatory effects is by lowering pro-inflammatory mediators viz. PGE2, NO and TNF- α , as well as interleukins.^[27] To evaluate the anti-inflammatory efficacy of terpenes these mediators of inflammatory reactions are used in numerous *in vitro* studies as biomarkers. With a range of terpenes pre-treatment including d-limonene, linalool and terpinolene as well as alpha-terpineol, the number of mediators of inflammatory reactions are suppressed which are generated by LPS.^[24] Terpenes anti-inflammatory qualities are also evaluated using a number of *in vivo* models of inflammatory illnesses. There is a suppression of production of mediators of inflammation induced by chemicals such as carrageenan and LPS in the lung injury models. Some of the examples of bioactive compounds for the given purpose are viz. alpha-phellandrene, borneol, 1,8-cineole as well as terpinen-4-ol. Furthermore, there is decrement in the levels certain cytokines which includes TNF- α and ILs by cineole a phytocompound, in the fluid obtained from bronchoalveolar lavage of animal models of asthma. Additionally, borneol decreased the rise in NO level as well as the upsurge in iNOS enzymatic activity in a model of ischemia.^[23]

Transcription factors regulation tangled in responses of inflammatory reactions

Typically, NF- κ B is observed as a mark of anti-inflammatory medicines since it is the main factor of transcription step that governs the production of mediators of inflammatory reactions. Numerous reports have steadily exposed that the different types of terpenes inhibited the production of intermediaries of inflammation and are facilitated by the reduced generation of NF- κ B.^[24] Maximum studies, however, have only exposed that treatment with terpene reduced the translocation of NF- κ B into the nucleus, I- κ B phosphorylation as well as decreased expression of NF- κ B level. Furthermore, a transcription factor recognized as nuclear factor erythroid 2-related factor 2 (Nrf2), tangled in cellular response which is due to oxidative damage and inflammation, the regulation takes place by several terpenes. Preceding findings also revealed that alpha-pinene, borneol,

beta-caryophyllene and cineole augmented activity of Nrf2 to guard the cells from oxidation reactions.^[25]

Function of terpene compounds against oxidative stress

An imbalance between the generation of ROS and its removal by defence systems leads to oxidative stress. Overproduction of ROS damages tissue and can trigger an inflammatory response. There are two ways that ROS can be generated: either spontaneously within the cell, where it regulates homeostasis and functions, or during cellular respiration process in oxidative metabolism of mitochondria. Proteins, lipids and DNA/RNA are the primary goals of oxidative damage; there is an advancement of harm due to mutagenesis and cell damage irreversibly through the changes in structure of these molecules, which can lead to necrotic and apoptotic cell death.^[28] Through a variety of antioxidant activity mechanisms, such as scavenging a broad spectrum of ROS and

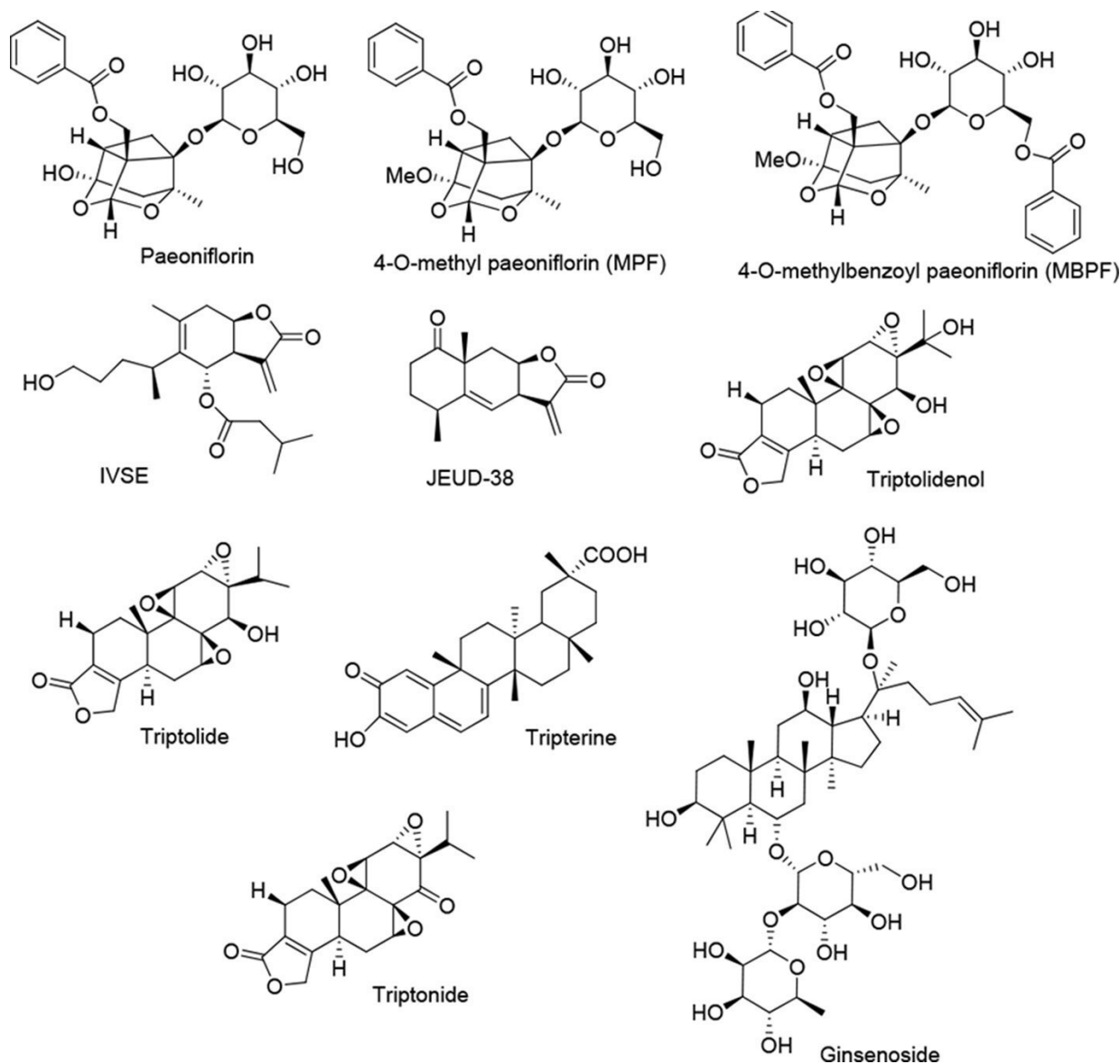


Figure 4: The chemical assemblies of commonly used terpenoids having anti-inflammatory potential.^[24]

having the ability to chelate metal ions, terpene compounds may prevent oxidative damage or decrease the catalytic enzymatic action intricate in formation of ROS. Terpene compounds may prevent impairment due to oxidation or decrease the catalytic action of enzymes which are tangled in ROS production through a range of antioxidant potential such as protecting a broad spectrum of ROS and possessing the volume to chelate metal ions.^[23] Several reports have confirmed the reducing capabilities to oxidative stress through volatile terpenes as well as terpenoids *in vitro* models.^[29,30] A monoterpene called D-limonene that has robust antioxidant possessions. The epithelial cells of lens are protected by D-limonene from the process of apoptosis which was induced by H₂O₂. The main action is by hindering construction of ROS, activation of caspase-3 and 9, phosphorylation of MAPK, also through ratio of Bcl-2/Bax mounting, signifying its potential for the cataract treatment.^[25]

Rat alveolar macrophages that have been exposed to tert-butyl hydroperoxide (c) have been utilized to investigate the antioxidant activity of camphene, another potent antioxidant. Camphene improved Glutathione (GSH) concentration and cell viability while decreasing ROS and NO generation and restoring mitochondrial membrane potential. Furthermore, compared to other terpenes, camphene has demonstrated significant scavenging capabilities against a variety of free radicals generated *in vitro*. However, it has been confirmed that α -phellandrene, which is extensively cast-off in the food and fragrance segments, causes apoptosis and changes the structure of cells. However, it's interesting to note that α -phellandrene has showed potential to decrease inflammation as well as oxidative stress *in vitro*, indicating that it has the opposite effect on wound healing.^[24]

Autophagy

Through autophagy, cells can adapt to a variety of stimuli by eliminating harmful or damaged components, allowing the cells to survive. Autophagy is crucial for the pathogenesis and development of inflammation and the immunological response, according to growing evidence.^[23] Limonene has been exposed to significantly upsurge autophagy and suppress growth of tumours both *in vitro* and *in vivo*. Limonene treatment increases LC3 lipidation by inhibiting formation of autophagosome and triggering autophagy process via ERK activation without inhibiting kinase enzyme specially mTOR.^[25] For the development of anti-tumour therapy terpene are utilized which are linked to activity of autophagy. Borneol promotes autophagy by increasing chemical permeability, especially to the brain. Nevertheless, ruthenium complexes and other novel and potent metal anti-tumour drugs can be made using p-cymene. These complexes exhibited no cytotoxicity *in vitro* or *in vivo* and successfully displayed anti-proliferative characteristics connected to a dual mechanism of autophagy and apoptosis.^[25]

Direct targets of terpene compounds and signal transduction

Interestingly, little study has observed the efficiency of terpenes on signal transduction, despite the fact that many signalling pathways regulate inflammatory responses. In a variety of experimental settings, it has been shown that many terpenes have anti-inflammatory properties and inhibit pathways of MAPK signal transduction. Remarkably, certain terpenes, such as borneol, camphor and linalool, triggers a family of transient receptors probably cation channels called Transient Receptor Potential Vanilloids (TRPVs). Given its strong association with inflammatory responses, TRPVs are most likely the cause of certain terpenes' anti-inflammatory properties. However, it is known that β -caryophyllene is an agonist functionally to the cannabinoid type 2 receptor.^[24] Likewise, in hypoxic cultured microglia, CB(2)R RNA interference removed β -caryophyllene's inhibitory effects on NF- κ B activation and inflammatory cytokine production, signifying that CB(2)R facilitates potential inflammation inhibitory action of β -caryophyllene.^[25]

Terpenes functions on other pathways

The anti-inflammatory capabilities of volatile terpene molecules have recently been shown to function in a variety of novel ways. For instance, injection of limonene suppressed stress of endoplasmic reticulum induced by methylglyoxal, which recruits signalling of inflammatory reactions in the cell line of murine preosteoclast, further to its autophagy as well as ROS-secreting characteristics. Current finding has also attentive on new mechanism of action allied to the influence of terpene complexes open inflammation of blood vessels or neurones. A ligand-dependent factor of transcription named as Peroxisome Proliferator-Activated Receptor gamma (PPAR γ) is that hinders the creation of cytokines of inflammatory one and guides the expansion of immunity cells in the direction of anti-inflammatory efficiency.^[25]

An enzyme involved in inflammatory reaction named 5-lipoxygenase, inhibitors of acetylcholinesterase enzyme is reported for decreasing the neurodegeneration after surgery in the cortex area and hippocampus region, as well as the pro-inflammatory response; therefore, further investigation in inflammatory diseases and memory deficit disorders, terpene components are suggested to be a best therapeutic agent in near future.^[23]

DISCUSSION

In current centuries, there is an increasing interest in natural substances with medicinal qualities. Remarkably, as this artefact discusses, a number of findings have presented that terpenes as well as terpenoids hold a great deal of promise as complementary therapies for inflammatory illnesses.^[22] Many targets on molecular basis, such as cytokines of pro-inflammatory reactions, factors of transcription process, autophagy machinery, ROS,

receptors of membrane, and further mediators of inflammation, are identified to be tangled in the anti-inflammatory activity of terpenes, even though not all of these processes have been fully characterized.^[31] As a result, terpenes may be more effective than some current treatments since they can work across many cell signalling pathways at the same time and have a pleiotropic effect on inflammatory illnesses.^[20]

However, it should be highlighted that there are numerous concentration-dependent negative effects, even with the strong evidence for terpenes' anti-inflammatory qualities.^[22] Therefore, in order to determine acceptable dosage levels, a significant amount of study will be warranted to assess their scientific efficiency and safety profile in clinical application. In this regard, *in vivo* observations and *in vitro* studies are not always compatible.^[32] Clinical studies particularly of controlled type will be necessary to ascertain the therapeutic efficacy of these medications because data derived from models of animal experimentation cannot continually be extrapolated to individuals because of notable interspecies variations. Last but not least, terpenes' limited solubility and instability may greatly limit their therapeutic advantages; for this reason, encapsulation in nanocarriers is a desirable substitute for existing medications.^[33-37]

CONCLUSION

Terpenes with anti-inflammatory qualities have drawn more attention in recent years. According to this study, a variety of goals, such as factors of transcription process and inflammatory mediators, are involved in the actions behind the anti-inflammatory potential of the terpenes. The targets at molecular level of terpenes are very tempting for generating anti-inflammatory medications of target oriented, even if the mechanisms of action of many of these compounds are yet unknown. Another strategy for treating inflammatory diseases may involve combination of terpenes which possess robust anti-inflammatory properties and well-established mode of action with currently prescribed medications.

In the near future, as more become available, terpenoid-based therapeutic drugs will become more and more significant in the treatment of human illnesses. Nevertheless, depending on the dosages examined, the reporting of several adverse effects of terpenes was done. Camphor and α -pinene have demonstrated cytotoxic effects in this review. According to the Food and Drug Administration the total percentage of camphor in herbal products is bound to eleven percent. The component such as camphor and α -pinene as well as myrcene have been associated to allergic dermatitis.

This problem emphasizes the need for more research on the safe terpene concentrations for medicinal applications. In this case, interacting with BVOCs while forest bathing might be less harmful but safer than ingesting them or applying them topically.

Together, these reviews highlight the use of forest-derived terpenes and terpenoids to treat a range of inflammatory conditions.

ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to Sumandeep Vidyapeeth (Deemed to be University), Vadodara, Gujarat for providing necessary support and resources in the preparation of this review article.

CONFLICT OF INTEREST

The authors declare that there is no Conflict of Interest.

ABBREVIATIONS

TNF- α : Tumor Necrosis Factor Alpha; **IL-1:** Interleukin-1; **IL-6-:** Interleukin-6; **NSAIDs:** Nonsteroidal anti-inflammatory medicines; **ASA:** Acetylsalicylic acid; **Cox 1/2 inhibitor:** Cyclooxygenase inhibitors; **PI3K:** Phosphoinositide-3-kinase; **5-LOX:** 5-lipoxygenase; **RCT:** Root Canal Treatment; **AP-1:** Activator Protein-1; **NF-AT:** Nuclear Factor of Activated T cells; **PGs:** Prostaglandins; **MMPs:** Matrix metalloproteinases; **HM:** Herbal medicine; **HIV:** Human immunodeficiency virus; **NO:** Nitric oxide; **LPS:** Lipopolysaccharide **IVSE:** Inula japonica sesquiterpene extract; **JEUD-38-1:** 1-oxo-4aH-eudesma-5(6),11(13)-dien-12,8 β -olide; **ALI:** Acute lung injury; **ginsenoside-Rb1:** RB transcriptional corepressor 1 or Retinoblastoma 1; **NF-KB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **G-Rd:** Ginsenoside Rd or Gypenoside VIII; **G-Rb2:** Growth Factor Receptor-bound Protein 2; **PGE2:** Prostaglandin E2; **I-KB:** Inhibitor of Nuclear Factor Kappa B; **Nrf2:** Nuclear factor E₂-related factor 2; **ROS:** Reactive Oxygen Species; **DNA:** Deoxy ribonucleic acid; **RNA:** Ribonucleic acid; **MAPK:** Mitogen-activated protein kinase; **Bcl-2/Bax B:** cell lymphoma 2, while Bax stands for Bcl-2-associated X; **GSH:** Glutathione; **LC3:** Microtubule-Associated Protein 1 Light Chain 3; **ERK:** Extracellular Signal-Regulated Kinase; **mTOR:** Mechanistic Target of Rapamycin; **TRPVs:** Transient receptor potential vanilloids; **CB(2)R:** Cannabinoid Receptor Type 2; **PPAR γ :** Peroxisome proliferator-activated receptor gamma; **BVOCs:** Biogenic Volatile Organic Compounds.

SUMMARY

In the current era phytochemicals from medicinal plants are utilized world wide due to their availability and less side effects. Various researchers also proved therapeutic beneficial of phytochemicals in the treatment of various disorders terpenoids among one of them. Terpenoids showed better therapeutic effects in the treatment of inflammation associated disorders. In this study we have showed the therapeutic potential of terpenoids in suppressing the inflammatory reactions with examples. The efficacy of terpenoids proved to be beneficial in all the

inflammatory linked pathways. Due to this reason terpenoids will be proved to be a better therapeutic agent against inflammatory disorders as per future perspectives.

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Cite this article: Parekh SS, Trivedi R, Kanojiya D, Baile SB, Nimeshkumar PR, Sakshiben M, et al. Terpenoids as Natural Anti-Inflammatory Agents: A Review of their Biological Mechanisms. *Pharmacog Res*. 2025;17(4):1104-15.