REVIEW ARTICLE

Plant origin anti-inflammatory and immunomodulatory agents and their mechanism of action: A review

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Abstract

This review article describes the anti-inflammatory and immunomodulatory activities of essential oils (EOs), gums, latex, and pigments. It also highlighted the numerous diseases curing potential of these phytochemicals from various species. These natural bio-organic ingredients induce the synthesis of inflammatory mediators which successfully work against inflammation. These phytochemicals can easily replace the use of steroidal drugs as anti-inflammatory agents which show multiple side effects. Phytochemicals representing the class of flavonoids, terpenoids, polyphenols, saponins, tannins, alkaloids, anthraquinones, chemical constituents of EOs, plant pigments, and gum components have been reported from more than 100 medicinal plants for the treatment of inflammatory diseases saponins, polysaccharides, and organosulfur compounds. These natural products showed promising anti-inflammatory activities to treat skin, liver, cardiovascular, joint, gastrointestinal, neurological, and lung inflammation diseases. These plant products accelerate the healing process by activating the immune system and inhibition or neutralization of inflammatory molecules. These plant-origin phytochemicals quickly heal the tissue damage and ultimately do the restoration of tissue function. These are novel, safer, and show lesser side effects agents. These healing agents could be used for longer duration for the treatment of various inflammatory health disorders.

Key words: Anti-inflammatory and immunomodulatory activities, essential oils, gums, inflammatory health disorders, latex, and pigments

INTRODUCTION

Inflammation is a natural process that occurs in response to tissue injury, cell death, cancer, ischemia, and degeneration. It is also evoked after the invasion of body cells by different pathogens and parasites. In response to an injury, various cellular events and glandular secretions try to heal the wound site. The body begins to make primary protection and activate both innate and adaptive immune defense for healing tissue injury. To counterattack the pathogens both systemic and local responses take place.[1] The innate immune response is maintained by involving various cells such as macrophages, mast cells, natural killer cells, and dendritic cells. The adaptive immune system is made up of more specialized cells such as B and T cells, which produce specific receptors and antibodies to eliminate invading pathogens and cancer cells. The adaptive immune response also involves leukocyte cells such as macrophages, neutrophils, and lymphocytes, also known as inflammatory cells. In expansion to its part in quick touchiness responses, histamine can apply H2-receptor-mediated anti-inflammatory movement counting restraint of human neutrophil lysosomal chemical discharge, restraint of IgE-mediated histamine discharge from fringe leukocytes, and enactment of silencer T-lymphocytes.

However, to respond to foreign antigens or tissue damage and mitigation of the impact of harmful inflammatory substances various inflammatory mediators are produced and released during the body's different inflammatory responses. These are categorized into two primary groups: Proinflammatory and anti-inflammatory mediators. Proinflammatory cytokines and other mediators are vital in the inflammation of the central

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nervous system, as they induce the production of chemokines and adhesion molecules, attract immune cells into the tissue, and activate both immune cells and endogenous glial cells.[2] Key mediators consist of interleukin (IL)-1, tumor necrosis factor (TNF), and thrombin, along with various cytokines and small molecule mediators that control these processes in both healthy and diseased conditions. These mediators also influence the biochemical pathways, helping to prevent the progression of diseases.

In reaction to the inflammatory process, damaged cells in the body release specific substances such as vasoactive amines and peptides, eicosanoids, proinflammatory cytokines, and acute-phase proteins, which facilitate the inflammatory response by protecting against further tissue damage, ultimately leading to healing and recovery of tissue function. Key proinflammatory mediators include various cytokines such as IL1-alpha, IL1-beta, IL6, TNF-alpha, and thrombin. These crucial regulators significantly affect the blood vessels and result in heightened vascular permeability.[3] In addition, they modify morphogenic responses of blood vessels, promote adhesion and migration of leukocytes, enhance procoagulant activities, and increase the adhesion and aggregation of platelets. These small molecule mediators control anti-inflammatory responses in both healthy and diseased conditions. Proinflammatory cytokines are produced and released as a reaction to oxidative stress and an overproduction of reactive oxygen species (ROS). Primary immune organs, such as IL-2, IL-1, and various cytokines, function as mediators to facilitate the healing process.[4] More specifically, IL-12 exhibits both proinflammatory and anti-inflammatory characteristics.[5] Inflammation is a complex underlying mechanism that contributes to the development of conditions such as diabetes, Alzheimer's, Parkinson's disease, cardiovascular issues, respiratory disorders, renal problems, liver disease, and cancer[2] [Figure 1].

Typically, non-steroidal or steroidal pharmaceutical agents are employed in the management of inflammatory conditions,[6] although these can lead to a variety of adverse effects in patients.[7] Various phytochemical compounds have been extracted from plant species, and their extensive pharmacological and biological properties have been documented. Numerous investigations have been conducted to evaluate the anti-inflammatory properties of extracts and/or isolated compounds from different plant species. These phytochemicals have been traditionally utilized worldwide for inflammation treatment.[8] They serve as superior alternatives to synthetic medications, which often have detrimental residual effects on bodily functions, a range of side effects, and high costs. Therefore, the discovery and evaluation of new compounds with minimal side effects that exhibit strong anti-inflammatory properties may be derived from local medicinal plants. This review intends to highlight the anti-inflammatory capabilities of specific various plant natural products to treat and alleviate inflammation from everyday life.

The body experiences inflammation because of the inflammatory agents' stimulation and activation of several cellular and vascular processes. Figure 1 illustrates how several proinflammatory substances cause inflammation and necrosis at the site of injury by stimulating cells. Activated

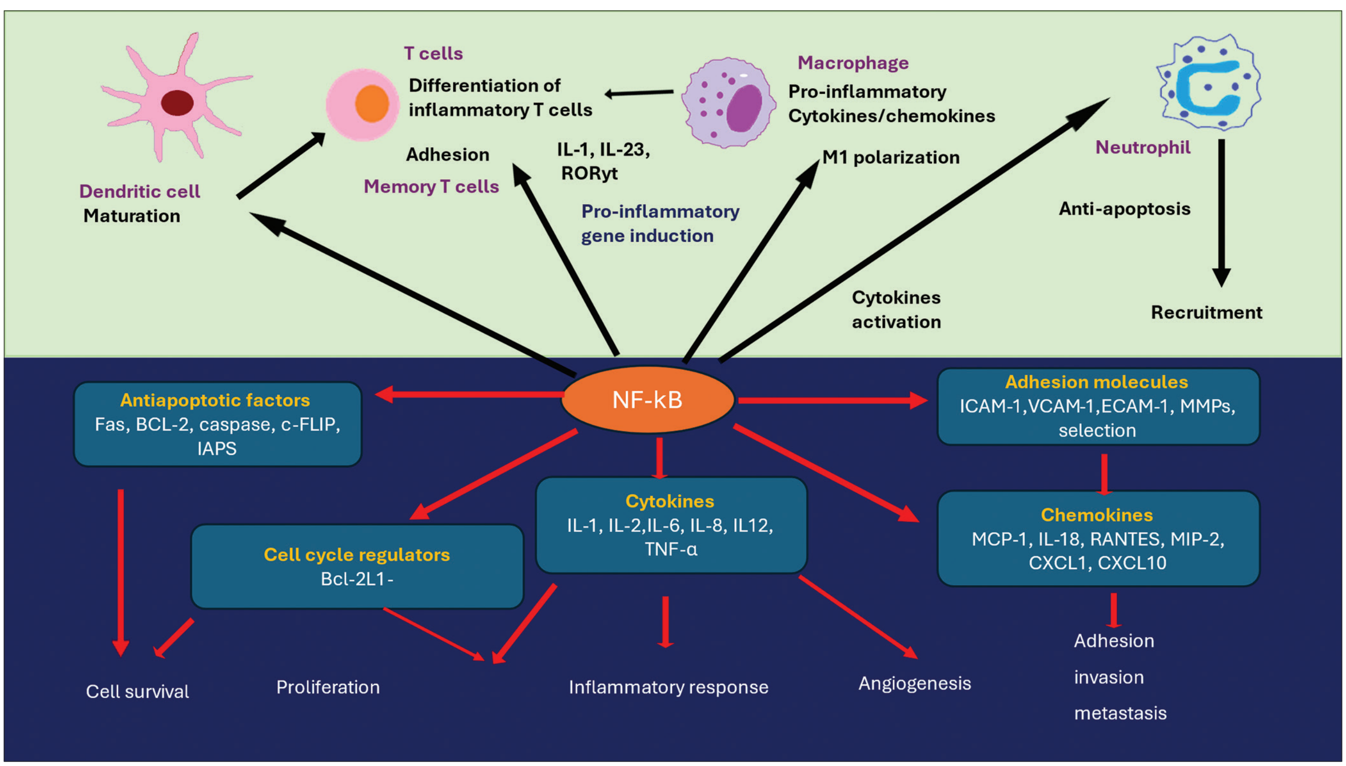

Figure 1: Role of various immune cells and molecules in the regulation of inflammatory response

phospholipase A2, for instance, activates the phospholipids on cell membranes to produce arachidonic acid, which causes vasodilation and an increase in blood flow by causing mast cells to degranulate and release histamine and serotonin. Tissue edema results from the vasoactive molecule's increase in vascular permeability, which allows fluids and proteins to flow from blood arteries to the tissue.[9] Three important proinflammatory cytokines include TNF-α, IL-1 beta (IL-1β), and IL-6[10] [Figure 1].

In addition, the arachidonic acid metabolic pathway causes the inflammatory tissue to release prostaglandins (PG) and leukotrienes (LT). Prostaglandin E2 (PGE2) contributes significantly to acute inflammation by inducing edema, intense discomfort, and vasodilation. LTB4 causes neutrophil activation, superoxide generation, and macrophage degranulation.[11] ROS can control how inflammation develops. Excessive ROS levels can harm tissue through oxidative stress and decrease T lymphocyte activation and proliferation. A vicious cycle of oxidative stress and inflammatory response is created when ROS attracts immune cells to the site of injury[12-14] [Figure 1].

ROLE OF PG E LT

PG and LT primarily function through certain G protein-coupled receptors, several of which have recently been cloned, allowing for the development of specialized receptor agonists and antagonists.[15] LT, thromboxanes (Tx), and PG are a class of derivatives of arachidonic acid that contribute to the inflammatory response. Eicosanoids play a role in immune cell recruitment into the vascular wall, vascular tone and permeability modulation, and more.[16] The phospholipase A2/cyclooxygenase (COX) pathway produces prostanoids, such as PG and Tx, whereas the 5-lipoxygenase pathway produces LT from arachidonic acid. Prostanoids belong to a family of lipid mediators produced by the action of COX on a 20-carbon unsaturated fatty acid, arachidonic acid [Figure 1].

Many anti-inflammatory substances that block the COX enzymes that convert arachidonic acid to PG are naturally produced by plants. Phospholipase-released arachidonic acid is the source of PG and LT, which are strong eicosanoid lipid mediators implicated in inflammation and a variety of homeostatic biological processes. LT modifiers, the more recent generation of coxibs (selective inhibitors of COX-2), and clinically important non-steroidal anti-inflammatory medications prevent their manufacture and activities. They are produced by COX isozymes and 5-lipoxygenase, respectively.

Histamine and bradykinin's effects on vascular permeability are amplified by vasodilator PG at physiological quantities, and LT plays a significant role in mediating leukocyte accumulation during acute inflammation. However, by preventing nuclear factor-kappaB (NF-κB) activation, PG metabolites such as cyclopentenone PG help to resolve acute inflammation. Thus, a range of activities that produce and reduce acute inflammation caused by bacterial infections are regulated by the oxygenation products of arachidonic acid[17] [Figure 1].

THE TRANSCRIPTION FACTOR NFκB

The control of inflammatory reactions is one of NF-κB's well-known roles. NF-κB controls the activation, differentiation, and effector function of inflammatory T cells in addition to controlling the expression of many proinflammatory genes in innate immune cells. A family of transcription factors known as NF-κB is essential for immunity, inflammation, cell division, proliferation, and survival. Phosphorylation-induced proteasomal degradation of the inhibitor of NF-κB proteins (IκBs), which keep dormant NF-κB dimers in the cytosol of unstimulated cells, is necessary for inducible NF-κB activation. The IκB kinase (IKK) complex, which is in charge of IκB phosphorylation and is necessary for signal transduction to NF-κB, is where most of the several signaling pathways that result in NF-κB activation converge.[18] The fundamental elements of the NF-κB signaling pathways undergo a variety of post-translational changes to further regulate NF-κB activity. Apart from the cytosolic changes of IKK and IκB proteins and other mediators specific to the route, the transcription factors undergo significant modifications as well. Over the past 20 years, significant strides have been achieved in deciphering the complex regulatory networks that govern the NF-κB response [Figure 1].

LITERATURE SEARCH AND STUDY SELECTION

For writing this comprehensive research review on "Anti-inflammatory and immune-modulatory effects of plant natural products" various databases were searched. For the collection of relevant information specific terms such as medical subject headings and keytext words, such as plant natural products "their anti-inflammatory and immune-modulatory effects" and its use in wound healing management control" published till 2024 were explored in MEDLINE. There are more than 200 plant species that synthesize bio-organic constituents that exhibit anti-inflammatory and immune-modulatory effects were collected. Most especially for retrieving all articles pertaining to the traditional uses of plant natural products/extracts/compounds for inflammatory and immune-modulatory effects in animal models were searched in, electronic bibliographic databases and abstracts of published studies with relevant information on the inflammatory and immune-modulatory effects were collected. Furthermore, references cited by the studies on the present topic were exhaustively searched. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporating recent knowledge, relevant research articles, books, conference proceedings, and public health organization survey reports were selected and collated based on the broader objective of the review. The present review aimed to systematically analyze published data on plant-origin contraceptives: Its use and side effects. This was achieved by searching databases, including SCOPUS, Web of Science, *EMBASE*, PubMed, Swiss-Prot, Google searches, and Cochrane Library, were searched. From this common methodology, discoveries and findings were identified and summarized in this final review.

BIOMARKERS OF INFLAMMATION

In response to pathogen invasion and severe injuries, specific inflammatory molecules are released in the affected organ systems, and their presence can be detected in the bloodstream. Inflammation is identified by specific biomarkers. For instance, intestinal inflammation associated with inflammatory bowel disease is indicated by various non-invasive biomarkers found in blood, stool, and urine, including serum C-reactive protein (CRP), fecal lactoferrin, and fecal calprotectin.[19] Likewise, in chronic liver disease, damage to hepatocytes triggers a pro-inflammatory response in both parenchymal and non-parenchymal hepatic cells. This condition is characterized by liver fibrosis, cirrhosis, portal hypertension, and liver failure. In liver disease, innate immune cells react to liver damage by activating cell-intrinsic inflammasomes through toll-like receptors and NF-κB and by secreting proinflammatory cytokines (such as IL-1β, IL-18, TNF-α, and IL-6). As a result, adaptive immune system cells are drawn in to exacerbate liver inflammation, whereas liver parenchymal cells may undergo gasdermin D-mediated programmed cell death, known as pyroptosis.[20]

In the context of colorectal cancer, inflammation-related prognostic biomarkers include the neutrophil-lymphocyte ratio, lymphocyte-CRP ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio, among others.[21] When a lung injury occurs, macrophages transition into proinflammatory M1 phenotypes and start to release proinflammatory cytokines (TNF-α, IL-6, and IL-1) and chemokines (IL-8, CCL7, and CCL2), which enhances the chemotactic response and leads to the accumulation of monocytes and neutrophils in the alveolar spaces.[22] Subsequently, neutrophils secrete a variety of inflammatory mediators, ROS, and proteinases, which damage surfactants, basal membranes, and the epithelial–endothelial barrier. Surfactant is a lipid-protein complex produced by alveolar epithelial type II cells.[23]

The pathophysiology of inflammatory diseases is affected by several factors, such as the levels of pro-inflammatory cytokines including IL-1, IL-6, and TNF-α, along with inflammatory mediators such as PGE2 and nitric oxide (NO) free radicals. Through a range of cellular and vascular processes, these substances play a role in both acute and chronic inflammation. They ultimately trigger, recruit, and enhance immune cell activity in response to pathogen invasion.[24] IL-6 is superior to CRP, and procalcitonin (PCT) serves as a significant biological marker of inflammation that rises early during the inflammatory response.[25] Additional inflammatory biomarkers include CRP, erythrocyte sedimentation rate (ESR), total white blood cell count, and neutrophil levels.[26]

While PCT is quite specific in differentiating between acute bacterial infection and illness flare in patients with autoimmune disorders, CRP is more sensitive and specific in identifying bacterial infection.[27] In addition, IL-6, CRP, PCT, ESR, and other markers linked to inflammation can be used to precisely track the course of inflammation and to detect and treat inflammatory disorders at an earlier stage.[28,29] The local inflammatory response Pin response is known to be amplified and upregulated in lupus due to the involvement of modified CRP (mCRP). Plasma and urinary levels of mCRP increased significantly in patients with lupus nephritis Lupus nephritis-derived immunoglobulin G could induce CRP production by HK2 cells.[30]

PLANT ESSENTIAL OILS (PEOs)

Natural products mainly PEOs are new therapeutic agents which are used for the treatment of inflammatory diseases. PEOs extracted from flowers, leaves, stems, fruits, flowers, buds, seeds, leaves, twigs, bark, herbs, wood, fruits, and roots contain terpenes, lipids, aldehydes, alcohols, and other compounds. These are derived blends of aromatic compounds and are used for the production of special fragrances or flavorings for food materials, perfumes, used as medicine, and cosmetics. Natural products mainly PEOs are new therapeutic agents which are used for the treatment of inflammatory diseases. These are derived blends of aromatic compounds and are used for the production of special fragrances or flavoring for food materials, and perfumes, used as medicine, and cosmetics, and in the treatment of human diseases. However, components of essential oil (EOs) such as carvacrol suppresses lipopolysaccharide (LPS)-induced proinflammatory activation in RAW 264.7 macrophages through ERK1/2 and NF-kB pathway.[31] These oils show anti-inflammatory effects by regulating different mechanisms and cellular pathways.[32]

There are a few prominent EOs-producing plant families, i.e., *Apiaceae*, *Asteraceae*, *Burseraceae*, *Boraginaceae*, *Cupressaceae*, *Euphorbiaceae*, *Fabaceae*, *Lamiaceae*, *Lauraceae*, *Myrtaceae*, *Piperaceae*, *Poaceae*, *Rutaceae*, *Verbenaceae*, and *Zingiberaceae* which are famous for their anti-inflammatory action and used in treatment of paw edema in animal models. PEOs show multiple biological activities, i.e., antibacterial, antifungal, antimutagenic, antiviral, antiprotozoal, antioxidant, and antidiabetic but these showed strong anti-inflammatory properties.[33,34] EOs and their components exhibit antioxidant and anti-inflammatory properties and are of great significance for human health. These act through certain inflammatory mediators, such as cytokines, COX-2 expression, the levels of PGE2, and NO, or evaluate the effect of EOs or their major compounds on inflammation response directly induced by inflammatory mediators[35] [Table 1 and Figure 2].

These are also used as natural preservatives for food items.[36] These are used to protect against mycotoxin contamination of food commodities,[37] and oxidative deterioration of agri-food commodities[38] and in ecofriendly pest control.[39] Plant-based products are gaining interest over the past few decades due to their environment friendliness and their effectiveness in controlling mosquitoes along with their lack

Table 1: Plant essential oils and their bioactive components and mechanisms of anti-inflammatory action

Plant species	Plant part	Essential oil components	Mechanism of action
Artemisia verlotorum	Leaves	Flavanoids, azuleues,	Potent inhibitory effect on NO production
Lavandula augustifolia	Flower	Sesquiterpenes	Inhibited microglial inflammation
Ocimum gratissimum	Leaves	ρ-cymene (28.08-53.82%), thymol (3.32 – 29.13%), γ-terpinene (1.11-10.91%), α-thujene (3.37–10.77%), and β-myrcene (4.24–8.28%) and almost no Eugenol].	Acts against oxidative stress and inflammatory processes immunomodulatory properties
Lippia alba	Leaves	Linalool	Cause downregulation of inflammatory mediators and MAPKs/NF-κB signaling.
Citrus limon	Fruit peel, Peel & Leaf	Limonene/beta piene/gamma Linalool/citronellal, Terpinene/ geranial/neral	α-terpineol exhibited a superior anti-inflammatory effects, inhibit the expression of the inflammatory mediators and proinflammatory cytokines in lipopolysaccharide-stimulated RAW 264.7 cells.
Satsumo mandarin	Peel & Leaf	linalyl acetate, Sabinene, N-methylanthranilate, limonene, limonene/gamma-Terpinene b- myrcene, a- myrcene p-cymene, b-pinene, Terpinolin, 3- carene	flavonoids and other antioxidants reduce inflammation in the body
Citrus natsudaidai	Peel & Leaf	Limonene, gama-terpinene, Myrene, alpha-pinene nonal, Peel	natsudaidai reduced P. acnes-induced secretion of IL-8 and TNF-α in THP-1 cells, indicating anti-inflammatory effects
(Hyata) Germacrene-D perillyl alcohol *Olea europea* Oleaceae	Leaves & Fruit	Hydroxytyrosol, Tyrosol, Phenolic Apigenin, Tuleolin, Elenolic acid Oleceropein, Ligtroside aglycons	Ameliorating almost all of the pro-inflammatory readouts (IL-1β, TNF-α, IL-8, ICAM, VCAM) and reducing the release of IL-6 in all the cellular models.
Syzigium aromaticum	Bud	Eugenol, sesquiterpenes, monoterpenes, hydrocarbon, and phenolic compounds. Eugenyl acetate, eugenol, and β-caryophyllen	Help decrease inflammation and alleviate pain.
Cinnamon zeylanicum	Leaves	Cinnmaldehyde and Eugenol	Increase Tristetraprolin mRNA and protein levels, anti-oxidant and free-radical scavenging properties
Allium sativus	Bulb	Allicin, diallylsulfide, alliin	Modulating the nuclear factor-kappa B (NF-κB) pathway. NF-κB is a transcription factor that regulates the expression of pro-inflammatory cytokines
Origanum vulgare	Leaves	γ-muurolene, linalool, carvacrol, and thymol, p-cymene, spathulenol, γ-terpinene, β-fenchyl alcohol, caryophyllene, germacrene D, and δ-terpineol in minor quantities	Tissue DNA damage from exposure to aflatoxin B1

(Contd...)

Table 1: *(Continued)*

Plant species	Plant part	Essential oil components	Mechanism of action
Verbena bonariensis	Leaves	Terpenoids, Monoterpenes, sequiterpenes Diterpenes	Anti-inflammatory and anthelmintic.
Cymbopogon martini	Leaves	Apinene, Beta pipene and camphor, rich in cyclic and acyclic monoterpenoids	Geraniol exerted an anti-inflammatory action by increasing IL-10 production.
Eucalyptus intertexta, Eucalyptus globules	Leaves & twigs	Myrtaceae Terpene-ol and a-pinene, D-limonene, Cineole, beta myrecene, 1,8-Cineole, n-piterie	Reduced anti-inflammatory effects, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine.
Juniperus communis	Fruit	a- pinene, b- pinene	Strong anti-inflammatory, immune modulatory, and wound healing
Mentha aquatica		sabinene, limonene, mircene	anti-inflammatory and antioxidant bioactivities.
Mentha longofolia, M. piperata	Leaves	1, 8-cineole, Menthone, isomenthone	Decreases mRNA expression of NF-κB gene in Tox-S treated Caco-2 cells.
Cestrum diurnum	Flowers	Stearic, oleic, linoleic acids	Downregulation of NF-κB p65 protein expression and/or inhibition of autacoids (histamine, serotonin, prostaglandin).
Headychium ceronarium	Rhizome	1, 8-cineole, b-pinene	Significant inhibition of paw oedema
Zingiber officinalis	Root & rhizome	gingerols, flavanoids,	Its anti-inflammatory mechanism is linked to Akt inhibition and NF-KB activation, triggering the release of anti-inflammatory cytokines while reducing proinflammatory cytokines.
Ginger *Ginger officinalis*	Rhizome	a-Zingiberene (30.06%), β-sesquiphellandrene (10.71%), E-E-a-farnesene (9.75), β-bisabolene (6.53%), y-curcumene (5.90%) and ar-curcumene (5.18%), phenolic secondary metabolites, the gingerols.	Nrf2 signaling pathway activation. Its anti-inflammatory mechanism is linked to Akt inhibition and NF-KB activation, triggering the release of anti-inflammatory cytokines while reducing proinflammatory cytokines.
Coriandrum sativum	Seeds	a-pinene, p-cymene, Linalool, nerol	Superoxide dismutase activity increased , increased respiratory burst and myeloperoxidase activities
Foeniculum vulgare	Seeds	a-pinene, limonene, Fenchone, E-anethole	anti-inflammatory activity by inhibiting the action of proteases
Thymus vulgare	Leaves	thymol, carvacrol, b-bisabolene, Camphene, g-terpinene, Camphor, borneole, menthol ,1,8—creole Terpenylacetate, borteol	Potent inhibitor of the synthesis of IL-6, IL-8, IL-β, and TNF-α
Rosemery *Origanum vulgare*	Leaves	α-pinene, 1,8-cineole and camphor, associated with variable amounts of camphene, limonene, borneol, verbenone, bornyl acetate, α-terpineol, etc.	efficacy in supporting and enhancing the cell motility. In IFN-γ and H treated cells, OEO displayed a significant reduction of ROS, ICAM-1, iNOS, COX-2, 8-OHdG, MMP-1, and MMP-12.
Artemisia viscose	Seeds and leaves	germacrene D (up to 18.9%), artemisia ketone (up to 68%), and 1,8 cineole (up to 51.5% α-bisabolol (45.4%), chamazulene (21.9%) and lavandulol (3.6%).	Inhibitory effect on lipopolysaccharide-induced nitric oxide (NO), prostaglandin E_2 (PGE_2), and proinflammatory cytokine (IL-1β , IL-6, and IL-10) production.

(Contd...)

Table 1: *(Continued)*

Plant species	Plant part	Essential oil components	Mechanism of action
Mentha piperata	Leaves	Menthol (38.3–69.1%), menthone (0.4–20.9%), menthyl acetate (3.5–4.5%), iso-menthone (0.8–8.8%), linalool (0.6–5.1%), and limonene (2.50–6.70%)	Inhibited the production of pro-inflammatory cytokines from LPS-stimulated porcine alveolar macrophages
Cymbopogon citratuts	Lemongrass essential	Citral (mixture of geranial and neral), isoneral, isogeranial, geraniol, geranyl acetate, citronellal, citronellol, germacrene-D, and elemol,	Polyphenols inhibited the cytokine production on human macrophages
Cola nut *Kola acuminata*	Seeds and nuts	5.8% moisture, 9.4% crude protein, 4.2% ash, 12.5% crude fibre, 15.8% crude protein and 52.2% total carbohydrate.	Exhibits its analgesic property through cholinergic pathway
Cinnamon *Cinnamon zeylanicum*	Bark	E)-cinnamaldehyde (71.50%), linalool (7.00%), β-caryophyllene (6.40%), eucalyptol (5.40%), and eugenol (4.60%)	Anti-inflammatory effects are mainly related to the reduction of TNF-α, IL-1β, IL-6, IL-18, IL-10, iNOS, MCP-1, and COX-2, and the inhibition of NF-κB, ERK1/2, p38, and JNK activation
Pumpkin oil *Cucurbita papo*	Seeds	Tocopherols, fatty acids, and phytosterols palmitic, oleic and linoleic acids, with a predominance of oleic acid	Wound healing and reduce inflammation
Ponderosa pine *Pinus pondenosa*	Wood	β-pinene (21.5–55.3%), methyl chavicol (8.5–41.5%), α-pinene (3.6–9.6%), δ-3-carene (3.6–6.2%), and α-terpineol (1.4–5.3%)	Decreased the expression of inflammatory-related genes (i.e., IL-4 and IL-13)
Juniper *Juniperous communis*	Leaves and branches	Monoterpene hydrocarbons α-pinene (51.4%), myrcene (8.3%), sabinene (5.8%), limonene (5.1%) and β-pinene (5.0%)	Antiproliferative ability against cancer cells and the ability to activate inductive hepato-, renal- and gastroprotective mechanisms.
Tea tree oil *Melaleuca alternafolia*	Leaves	40.3%. γ-Terpinene, 1,8-cineole, and *p*-cymene	Inhibited PBMC proliferation, as revealed by a reduction in IL-2 secretion by stimulated lymphocytes.
Cloves *Eugenia caryophyllata*	Flower buds	Phenylpropanoids such as carvacrol, thymol, eugenol and cinnamaldehyde.	Inhibited the increased production of several proinflammatory biomarkers such as vascular cell adhesion molecule-1 (VCAM-1), interferon γ-induced protein 10 (IP-10), monokine induced by γ interferon
Myrrh essential oils	Essential oils.	Volatile oil (2–8%), resin (23–40%), gum (40–60%) and bitter principles (10–25%)	Down-regulation of COX-2, TNF-α, IL-6 and NF-κB. Myrrh also blocks the production of inflammatory chemicals that can lead to swelling and pain
Hedychium coccineum rhizome essential oil	Essential oil	⁰*E*-nerolidol (40.5%), borneol acetate EO's main components were ⁰*E*-nerolidol (40.5%), borneol acetate (24.8%), spathulenol (4.5%), linalool (3.8%), elemol (3.5%), and borneol (3.4%).	In RAW264.7 cells stimulated by LPS, reduced inflammatory factor secretion in LPS-induced RAW264.7 cells.
Lavandula multifida	Lavender essential oil	Linalool, linalyl acetate, lavandulol, geraniol, or eucalyptol.	Potent inhibitor of the synthesis of four pro-inflammatory cytokines IL-6, IL-8, IL-β and TNFα of THP-1 cells.

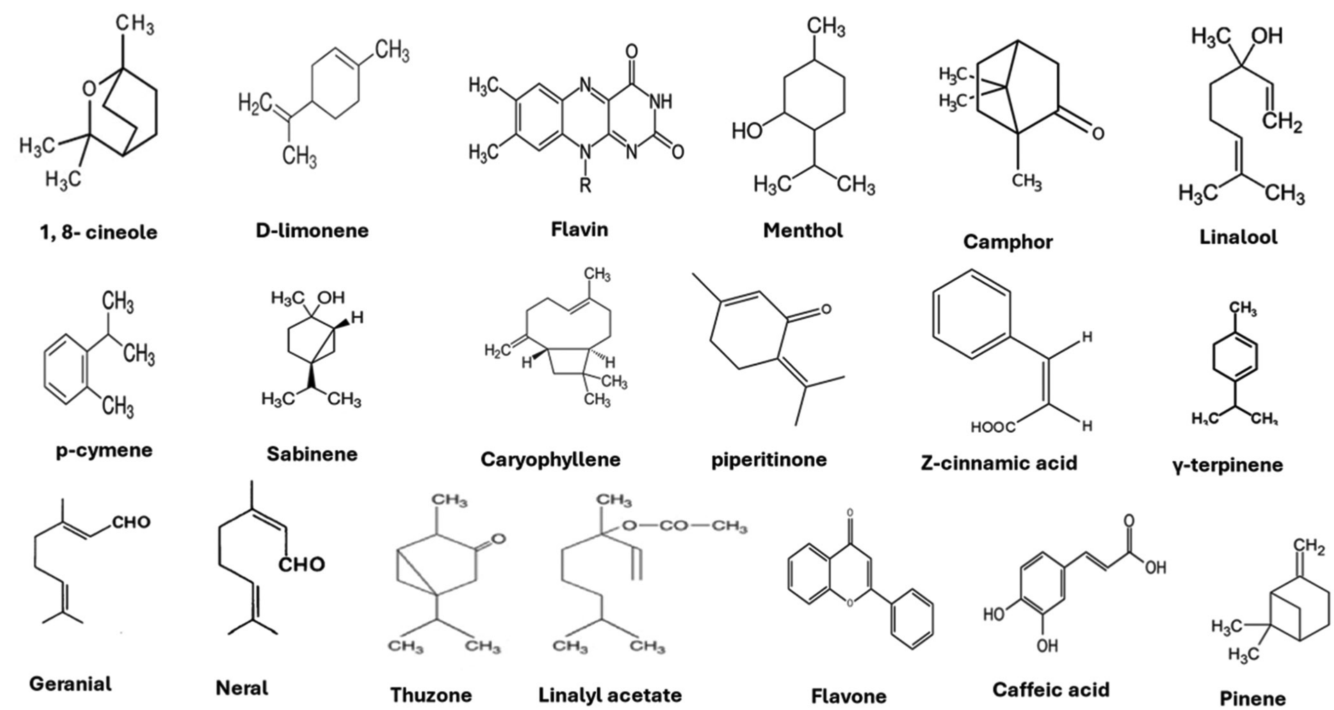

Figure 2: Major components of various plant essential oils

of toxicity[40] [Table 1 and Figure 2]. Few EO components such as phenylpropanoids and sesquiterpenes showed therapeutic potential of EOs with anti-inflammatory activity.[41] *Rosmarinus officinalis* essential contains 1,8-cineole, α-pinene, and camphor as major components, these mainly work through inhibition of NF-κB transcription and suppression of arachidonic acid cascade.[42] However, EOs, from sage (*Salvia officinalis*), coriander (*Coriandrum sativum*), rosemary (*R. officinalis*), black cumin (*Nigella sativa*), prickly juniper (*Juniperus oxycedrus*), geranium (*Pelargonium graveolens*), oregano (*Origanum vulgare*), and wormwood (*Artemisia herba-alba*), act on the inhibition of NF-κB activation at concentrations up to 0.25 μL/mL.[43] Similar activity is also reported in *A. herba-alba* EOs[44] [Table 1 and Figure 2].

PEOs coriander (*C. sativum*), geranium (*P. graveolens*), and wormwood (*A. herba-alba*) showed the capacity to inhibit NF-κB activation and display the potential to reduce the expression of IL-6, IL-1β, TNF-α, and COX-2 mRNA by over 50% in LPS-stimulated THP-1 macrophages. This anti-inflammatory effect is due to β-citronellol/geranium oil which does 40%/65% caspase-1 inhibition.[43] EOs from coriander, geranium, and wormwood inhibit both NF-κB and caspase-1 activation. The anti-inflammatory activity is due to the presence of linalool and β-citronellol, whereas α-thujone and camphor are thought to replicate the anti-inflammatory effects of wormwood EO.[45] Clove (*Syzygium aromaticum*) EOs contain volatile compounds, i.e., eugenol, β-caryophyllene, and α-humulene. Eugenol is the major compound, whereas eugenyl acetate, β-caryophyllene, and α-humulene are minor components.[46] These are strong antioxidants, antimicrobial, antioxidant, and insecticidal in nature. *Origanum*, *Citrus*, and *Pimpinella* genus EOs contain carvacrol and isoeugenol, which demonstrate significant anti-inflammatory activity[47] [Table 1 and Figure 2].

The EOs of coriander, geranium, and wormwood prevent the activation of caspase-1 and NF-κB. The Eos' anti-inflammatory qualities are explained by linalool and β-citronellol. Camphor and α-Thujone imitate wormwood EO's anti-inflammatory properties. However, in response to oxidative burst many blood cells, i.e., monocytes, neutrophils, eosinophils, and macrophages secrete mediators that make inflammatory responses. The most common is that EOs components can scavenge some free radicals and can also have anti-inflammatory effects. The extract from *Achillea* contains bisabolol, bisabolol oxide, menthol, and β-caryophyllene, all of which exhibit anti-inflammatory effects.[45] Furthermore, EOs from *Camellia japonica* and *Cucurbita maxima* have shown superior anti-inflammatory activities, effectively inhibiting the expression of inflammatory mediators and proinflammatory cytokines in LPS-stimulated RAW 264.7 cells.[48] These herbal natural extract products were found highly effective in the mitigation of inflammation and can be used for the development of therapeutic drugs for inflammatory diseases. Vanilla EOs combat free radical changes, promote restoration, it suppress depression, reduce stress and anxiety, and reverse the aging process. Most of the oils possess strong biologically active compounds which show anti-inflammatory and germ-killing properties [Table 1 and Figure 2].

PLANT GUMS

Plant-based gum contains C-glycosylated derivative (GG) and sulfated derivative (SGG), which have anti-inflammatory and cancer-chemo preventive properties. It was discovered that GG was a strong inhibitor of cytochrome P450 1A (CYP1A), an enzyme that activates cancer. In addition, it triggers the glutathione S-transferases (GSTs), which are carcinogen detoxification enzymes. Both GSTs and CYP1A were inhibited by SGG. Compared to GG, SGG was a more efficient radical scavenger against superoxide, peroxyl, and hydroxyl anion radicals. It was discovered that GG and SGG alter macrophage activity in an anti-inflammatory manner. Both substances significantly reduced the production of NO and the release of TNF-alpha in LPS-stimulated RAW macrophage 264.7, while also promoting macrophage proliferation and phagocytosis of fluorescein isothiocyanate-zymosan. Chewing gum has chemopreventive benefits and is an easy and efficient way to help cancer patients recover from surgery[49] [Table 2 and Figure 3].

C-glycosidic 2-propanol derivative (PE) and its sulfated derivative (SPE) were prepared by a straightforward chemical modification of the polysaccharides extract (E) obtained from *Leucaena leucocephala* seeds. While SPE may stimulate macrophage functions against pathogens, PE is a strong anti-inflammatory agent[50] Chewing gum increases bowel movement following colorectal cancer surgery. GL is an extract from the Indian Ayurvedic herb *Commiphora mukul* that primarily targets human prostate cancer cells with its anticancer properties. With an IC_{50} of 1 μM (24-h treatment), GL treatment markedly reduced the viability of the human prostate cancer cell line LNCaP (androgen-dependent) and its androgen-independent variant (C81). JNK, which operated upstream of Bax activation in the apoptotic response, was activated by the GL treatment. Moreover, the JNK signaling axis controls GL's ROS-dependent apoptosis[51] Xiao D. Inflammation, neurological conditions, hyperlipidemia, related cardiac conditions such as hypertension and ischemia, skin conditions, cancer, and urinary disorders are all treated with gum guggul.[52] In addition, it is used to treat intestinal worms, leucoderma (vitiligo), sinuses, edema, internal tumors, obesity, liver diseases, malignant sores and ulcers, urinary complaints, and sudden paralytic seizures[52] [Table 2 and Figure 3].

Oleo gum resin extracted by incision of the bark is a very complex mixture of gum, minerals, EOs, terpenes, sterols, ferrulates, flavanones, and sterones.[52] It is secreted by *C. mukul*, also known as gum guggul, and has been used widely as an Ayurvedic drug. Its active constituents are Z- and E-guggulsterones, which bind to nuclear receptors and modulate the expression of proteins involved in carcinogenic activities. Guggulsterone has been identified as one of the major active components of this gum resin.[53] Guggulsterones have also been reported to regulate gene expression by exhibiting control over other molecular targets including transcription factors such as NF-κB, signal transducer and activator of transcription (STAT), and steroid receptors. This steroid also binds to the farnesoid X receptor and modulates the expression of proteins with anti-apoptotic (IAP1, XIAP, Bfl-1/A1, Bcl-2, cFLIP, and survivin), cell survival, cell proliferation (cyclin D1 and c-Myc), angiogenic, and metastatic (matrix metalloproteinase-9, COX 2, and vascular endothelial growth factor) activities in tumor cells. Modulation of gene expression by guggulsterone leads to inhibition of cell proliferation, induction of apoptosis, suppression of invasion, and abrogation of angiogenesis. Guggulsterone mediates gene expression through the regulation of various transcription factors, including NF-kappaB, STAT-3, and CCAAT enhancer binding protein alpha, and various steroid receptors such as androgen receptors and glucocorticoid receptors. Guggulsterone can be used to suppress tumor

Table 2: Plant gums and their bioactive components and mechanisms of anti-inflammatory action

Gum	Source plant	Components and mechanism of action	
C-glycosylated and sulfated derivative		Chemo preventive effects.	Hirayama I[49]
	Polysaccharides Leucaena leucocephala	Polysaccharides from seeds used to prepare C-glycosidic 2-propanol derivative (PE), and its sulfated derivative (SPE). PE acts as a potent anti-inflammatory agent while SPE may act as an inducer of macrophage functions against pathogens.	Gamal-Eldeen AM[50]
Gum guggul	Commiphora Muku	Used for treatment of inflammation, nervous disorders, hyperlipidemia, and associated cardiac disorders such as hypertension and ischemia, skin disorders, cancer, and urinary disorders.	Shah R[52]
Oleo gum resin	Terpenes, sterols, ferrulates, flavanones, and sterones.	Gum guggul, contains active constituents Z- and E-guggulsterones, these bind to nuclear receptors and modulate the expression of proteins involved in carcinogenic activities.	Shah R[52]
Guggul	Guggulsterone	Mediates gene expression through regulation of various transcription factors, including NF-kappaB, STAT-3, and CCAAT enhancer.	Used to suppress tumor initiation, promotion, and metastasis. Shishodia S.[53]

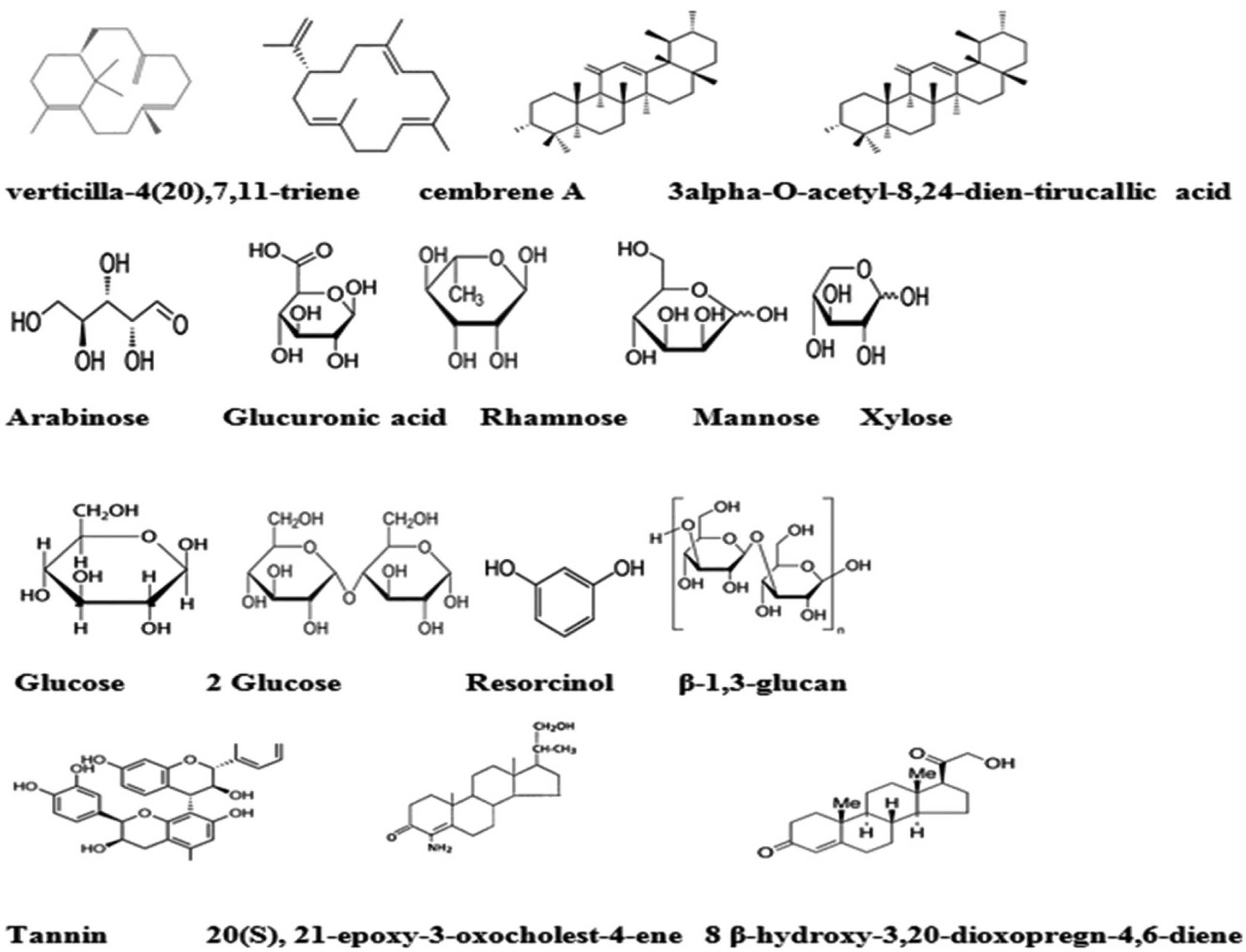

Figure 3: Important bio-organic constituents found in different plant gums

initiation, promotion, and metastasis[53] [Table 2 and Figure 3].

The gum, minerals, EOs, terpenes, sterols, ferrulates, flavanones, and sterones that makeup oleo gum resin, which is extracted by cutting through the bark, are complicated. Shah *et al*.[50] C secretes it. Gum guggul, another name for mukul, is a common Ayurvedic medication. Its primary ingredients are Z- and E-guggulsterone, which could bind to nuclear receptors and alter the expression of proteins implicated in carcinogenesis. One of this gum resin's main active ingredients has been found to be guggulsterone.[53] It has also been documented that guggulsterone controls the expression of genes by influencing other molecular targets, such as steroid receptors, STAT, and transcription factors such as NF-κB. In addition, this steroid binds to the farnesoid X receptor and alters the expression of proteins that exhibit antiapoptotic (IAP1, XIAP, Bfl-1/A1, Bcl-2, cFLIP, and survivin) as well as angiogenic, cell survival, proliferation (cyclin D1 and c-Myc), and metastatic (matrix metalloproteinase-9, COX 2, and vascular endothelial growth factor) properties in tumor cells. Guggulsterone modulates gene expression, which results in apoptosis induction, invasion suppression, angiogenesis abrogation, and cell proliferation inhibition. NF-kappaB, STAT-3, and CCAAT enhancer binding protein alpha are among the transcription factors that are regulated by gobulsterone, which mediates gene expression.[53] [Table 2 and Figure 3].

PLANT LATEX

Highly specialized cells called laticifers secrete the natural plant polymer latex. It is a sticky substance that resembles an emulsion and is released from different plant parts following minor tissue damage. It offers protection from infections and plant herbivory. The majority of plant species release latex from their bark in the form of white glue. Proteins, alkaloids, starch, sugars, oils, tannins, resins, and gums are all part of this complex mixture. Furthermore, a wide range of bioactive compounds found in plant latex have demonstrated various biological activities, including anti-inflammatory, anti-carcinogenic, anti-proliferative, vasodilatory, antioxidant, antimicrobial, antiparasitic, and insecticidal properties.[54] The majority of laticifer species contain general terpenes, phenolics, alkaloids, and cardenolides. Terpenes are isoprene-derived compounds that are secondary metabolites in plant latex [Table 3 and Figure 4].

Hancornia speciosa latex exhibits strong anti-inflammatory properties by preventing the synthesis of cytokines, PGE2, and NO[55]. The latex of *H. speciosa* is widely used to treat inflammation, bursitis, warts, and acne. In addition, the latex reduced inflammation brought on by subcutaneous carrageenan injection, cell migration, exudate volume, protein extravasation, elevated levels of inflammatory mediators (NF-α, PGE2, NO, and IL-6) generated in the pouch, and elevated expression of the enzymes COX2 and NO synthase[55] In addition, non-steroidal anti-inflammatory compounds found in plants are very helpful in the treatment of infections.[56] Calotropis procera possesses strong analgesic and anti-inflammatory qualities[57] [Table 3 and Figure 4]. It exhibits similar properties when used in animal model characteristics.[58] Similar to this, Himatanthus drasticus (*Apocynaceae*) latex contains lupeon, a pentacyclic triterpene with anti-inflammatory qualities. It also stimulates the synthesis of a few bioactive constituents, including the pentacyclic triterpene lupeol, and lupeol acetate (LA), which exhibits pro-inflammatory cytokines.[59] NFκB, cFLIP, Fas, Kras, phosphatidylinositol-3-kinase (PI3K)/Akt, and Wnt/β-catenin are crucial molecular pathways that are targeted by lupeol, a multi-target agent with enormous anti-inflammatory potential.[60] It also treats inflammation and cancer by acting as a chemopreventive and therapeutic agent.[61] In addition, only a small number of synthetic substances, such as phenylbutazone, have analgesic properties. While lactucin functions as a more potent analgesic and anti-inflammatory, tramadol is used to treat rheumatic pain.[60] It is a medication that relieves pain from muscle spasms, painful menstruation, and abdominal colic.[62] Similarly, it is said that latex from *Ficus carica* and *Euphorbia lactea* can be used to treat inflammation[63] [Table 3 and Figure 4].

PLANT PIGMENTS

Plant pigments are nutritious, edible, and useful in medicine. These are present in fruits, vegetables, flowers, sprouted seeds, and colored cereals. A wide range of pigments from different plant families may have anti-cancer properties. Plant pigments used in food have therapeutic benefits that

Table 3: Plant latex and their bioactive components and mechanisms of anti-inflammatory action

Plant Latex			
Plant Latex	Secondary metabolites isoprene-derived terpenes, phenolics, alkaloids, and cardenolides	Anti-carcinogenic, anti-proliferative, anti-inflammatory, vasodilatory, antioxidant, antimicrobial, antiparasitic and insecticidal. activities	Mesquita ML *et al*., 2005[54]
Hancornia speciosa	Secondary metabolites	Display significant anti-inflammatory activity through the inhibition of nitric oxide, PGE2 and cytokine production.	Marinho DG[55]
Hancornia speciosa	Latex components	Inhibited inflammation induced by subcutaneous carrageenan injection, increase the levels of inflammatory mediators (nitric oxide, prostaglandin E2, TNF-α, and IL-6) produced in the pouch,	Marinho DG[55]
Alchornea cordifolia	Latex components	Possess non-steroidal anti-inflammatory agents which are highly useful for treatment of infections.	Osadebe PO[56]
Calotropis procera	Latex components	Potent anti-inflammatory and analgesic properties.	Dhar ML[57]
Himatanthus drasticus	lupeon a pentacyclic triperpene	Similarly, (Apocynaceae) latex contain that show anti-inflammatory properties	Lucetti DL[59]
Himatanthus drasticus	Lupeol	Anti-inflammatory potential and target key molecular pathways which involve nuclear factor kappa B (NFκB), cFLIP, Fas, Kras, phosphatidylinositol-3- kinase (PI3K)/Akt and Wnt/β-catenin	Pasero G[60]
		Chemopreventive agent for treatment of inflammation and cancer.	Saleem M[61]
Lactuca virosa and Cichorium intybus	Tramadol	Sesquiterpene lactones, Used for the treatment of rheumatic painwhile lactucin work as a stronger analgesic and anti-inflammatory agent.	Pasero G[60] Wesołowska A[62]
	Ficus carica and Euphorbia latea	Can be used to treat inflammation phenolic compounds, volatile compounds, pectin or ficin.	Ali *et al*., 2011[63]

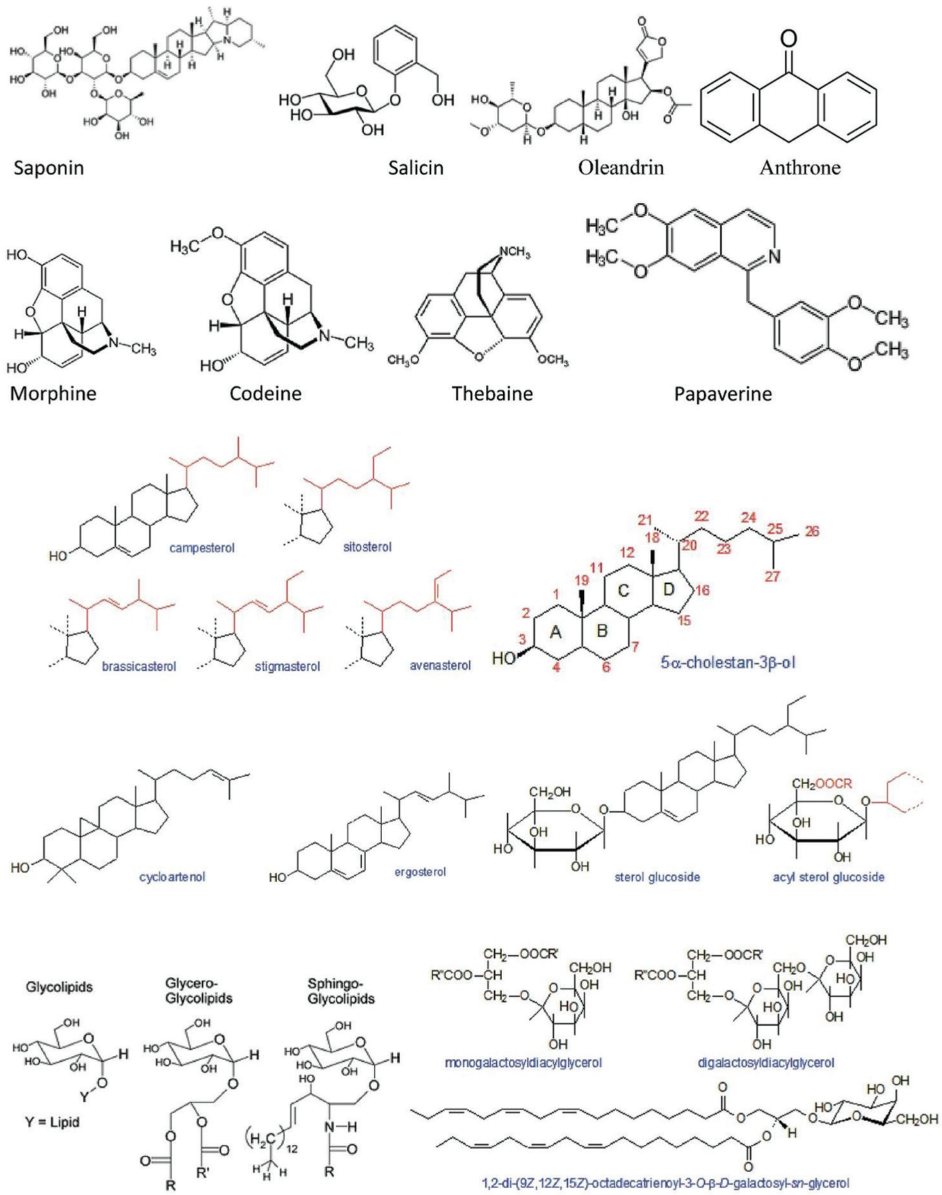

Figure 4: Major components isolated from latex of different plant species

improve health. People are becoming more interested in eating processed, low-energy, antioxidant-rich foods. Utilizing recombinant gene technology, these could be harvested to be added as a coloring agent to processed foods, expanding their use. Pigments found in plants, i.e. betalains, carotenoids, lycopene, anthocyanins, and chlorophyll, are examples of secondary metabolites. These inhibit the growth and division of cancer cells, thereby preventing their proliferation. These cause cancer cells to undergo apoptosis, autophagy, cell cycle, and signaling pathway inhibition. In addition to their anticancer properties, these help stabilize cardiovascular issues and manage high blood pressure, obesity, hyperglycemia, and hypercholesterolemia. Naturally occurring plant pigments or their byproducts are very helpful in the creation of a wide range of functional foods, digestive aids, additives, and cosmetics. These could be organically incorporated into genetically appropriate modified foods through the use of genomic technologies [Table 4 and Figure 5].

Porphyrins, betalains, carotenoids, and anthocyanins are among the various types of biomolecules that make up plant pigments. Six common carotenoids are found in plants: Lutein, zeaxanthin, violaxanthin, antheraxanthin, neoxanthin, and β-carotene. These selectively absorb some light wavelengths while reflecting others.[64,65] The most prevalent carotenoid in plants is lutein, a yellow pigment that can be found in fruits and vegetables. Alpha-carotene (found in carrots), lactucaxanthin (found in lettuce), and lutein epoxide (found in many woody species) are some other less common carotenoids in plants.[66] Important carotenoids found in cyanobacteria include echinenone, synechoxanthin, myxoxanthophyll, and canthaxanthin [Figure 1] [Table 4 and Figure 5].

Table 4: Various plant pigments and mechanisms of anti-inflammatory action

Pigment	Source plant	Components	References
Carotenoids, Lutein	Broccoli, spinach, and lettuce	Plants contain six ubiquitous carotenoids: Neoxanthin, violaxanthin, antheraxanthin, zeaxanthin, lutein, and β-carotene. Lutein is a yellow pigment found in fruits and vegetables and is the most abundant carotenoid in plants.	[64]
Porphyrins, carotenoids, anthocyanins	Purple sweet potato, strawberries and red cabbages	Porphyrins, carotenoids, anthocyanins, and betalains. These selectively absorb certain wavelengths of light and reflecting others.[34,35]	[65,67]
β-Carotene	carrots, spinach, lettuce, tomatoes, cantaloupe, and winter squash	Similarly, β-Carotene 9',10' oxygenase modulates the anticancer activity in TRAMP model.[76]	[75]
Lycopene	Tomatoes, pink guavas, apricots, watermelons, and pink grapefruits	Lycopene acts through inhibition of IκB kinase to suppress NF-κB signaling in human prostate and breast cancer cells	[76]
Lycopene	Tomatoes, pink guavas, apricots, watermelons	Lycopene preventive against gastric carcinogenesis.	[77,78]
Lycopene		Lycopene shows anti-proliferative and apoptosis inducing activity against three human breast cancer cell lines	[79]
Lycopene		It affects PI3K/Akt signaling pathway in prostate cancer.	[80]
Lycopene and beta-carotene	Tomatoes, pink guavas, apricots, watermelons, and pink grapefruits	Induce cell-cycle arrest and apoptosis in human breast cancer cell lines	[81,82]
Flavonoids and betalains	B. vulgaris cicla	C-Glycosyl Flavonoids and betalains from B. vulgaris rubra showed strong antioxidant, anticancer, and anti-inflammatory activities.	[91]
Betalains	Beta vulgaris L B. vulgaris rubra, red beetroot	Extract induces apoptosis and autophagic cell death in MCF-7 Cells.	[96]
Flavonoids	Celery, parsley, red peppers, chamomile, mint and ginkgo biloba	Water-soluble and commonly occurring in vacuoles, membrane-enclosed structures within cells that also store water and nutrients.	[91]
Annickia, Coelocline, Rollinia, and	Contain berberine and lycopene pigments.	These are used as nutraceuticals which show strong antioxidant activity. Xylopia), Berberis, Caulophyllum, Jeffersonia, Mahonia, Nandina, and Sinopodophyllum	[98]
lycopene- flavonoids and polyphenol	lycopene-rich tomato, flavonoids and polyphenol	Inhibit melanogenesis. Red and white pitayas are rich in contents, antioxidant and antiproliferative activities	[99]

Anthocyanins belong to the flavonoid class of polyphenols. Within the kingdom of plants, these represent the largest group of water-soluble plant pigments. These can be found in fruits, vegetables, and flowers in a variety of colors, including blue, pink, red, and purple.[67] In general, fruits, flowers, vegetables, and green tea supply anthocyanins which are health-promoting.[68] Anthocyanins-rich plant foods assist in cancer prevention. These also possess anti-inflammatory and anticarcinogenic, antioxidant, and cardiovascular disease prevention activity. These also assist in obesity control and diabetes alleviation.[68] Tomato (*Solanum lycopersicum*) peel, seed, and pulp are rich in anthocyanins and lycopene contents. These showed strong antioxidant properties and were considered to act as cancer-preventing or anticancer agents.[69] Anthocyanins found in Chokeberry *Aronia melanocarpa* show inhibitory effects on the growth of some cancer cells.[70] Chokeberry kills the cancer cells by non-apoptotic pathways. Radish (*Raphanus sativus* L.) contains anthocyanin, glucosinolates, anthocyanidins, and isothiocyanates in mature taproot. Anthocyanidins were found in large amounts in red and pink radish varieties such as pelargonidin and delphinidin, whereas the primary anthocyanidin in the purple radish variety was cyaniding.[71] The anthocyanin found in mature radish taproot reduces the risk of chronic disease through dietary intervention[71] Dietary use of anthocyanins reduces the inflammation and gut bacterial dysbiosis in ulcerative colitis. However, diets rich in anthocyanins decrease inflammation and increase gut permeability as well as improve colon health[72] [Table 4 and Figure 5].

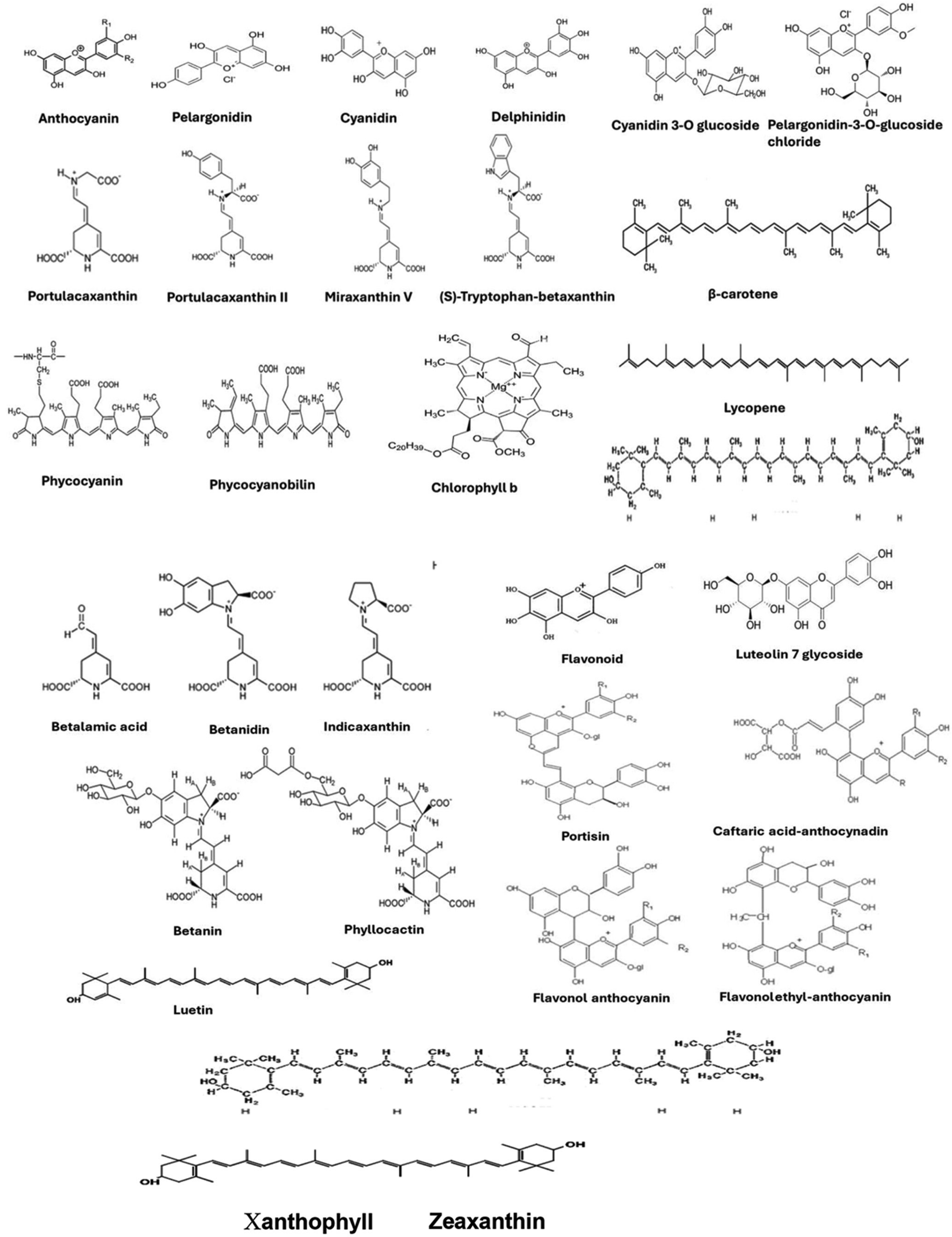

Figure 5: Chemical structures of various plant pigments

LYCOPENE

Natural plant pigments found in fruits, including lycopene, curcumin, β-carotene, and anthocyanins, have potent antitumor properties. Berberine and lycopene pigments are found in red berries (fruits) of the *Tinospora cordifolia* (wild) plant. According to Khan *et al*. 2013,[73] these are utilized as nutraceuticals that exhibit potent antioxidant activity. One type of polyunsaturated hydrocarbon is lycopene. One type of polyunsaturated hydrocarbon is lycopene, either a tetraterpene or an unsubstituted alkene. It is made up of eight isoprene units, each of which is made up of only hydrogen and carbon.[74] It has eleven conjugated double bonds, most of which are transconfigured. Its deep red color and potent antioxidant properties are attributed to these double bonds. Lycopene does not exhibit vitamin-like properties and is insoluble in water[75]). Lycopene is abundant in fruits and vegetables. Lycopene is abundant in a variety of fruits, including sea buckthorn, wolfberry (goji, a tomato berry relative), rosehip, tomatoes, watermelon, pink grapefruit, pink guava, papaya, and autumn olive.[76] Non-red foods such as asparagus, parsley, and green leafy vegetables, as well as certain fruits, also contain lycopene.[75] A potent antioxidant and nutritionally significant substance, lycopene prevents human head and neck squamous cell carcinoma cells from proliferating and invading.[77] Similarly, in the TRAMP model, β-Carotene 9',10' oxygenase regulates the anticancer activity. According to Tan *et al*.),[78] lycopene works by inhibiting IKK to suppress NF-κB signaling in human prostate and breast cancer cells[79] lycopene has also found preventive against gastric carcinogenesis.[76,80] It shows anti-proliferative and apoptosis-inducing activity against three human breast cancer cell lines.[81] It affects PI3K/Akt signaling pathway in prostate cancer.[82] Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines[83] [Table 4 and Figure 5].

High concentrations of lycopene pigments and other bioactive substances that are nourishing and health-promoting can be found in lycopersicum.[84] Free amino acid and phenolic content are abundant in hybrid tomato varieties. Antioxidative and cancer cell-inhibiting properties.[84] Melanogenesis is inhibited by these tomato fruits high in lycopene. An essential component of foods, nutraceuticals, and pharmaceutical products is the peel of white and red pitaya. Flavonoids and polyphenols, which are abundant in its peel, have antiproliferative and antioxidant properties.[85] Stronger antiproliferative activity against AGS and MCF-7 cancer cells was also demonstrated by both peel extracts,[85] [Table 4 and Figure 5].

CAROTENOIDS

Carotenoids are present in various parts of plants, including roots, stems, leaves, flowers, and fruits. These natural fat-soluble pigments are primarily produced during the ripening of fruits and impart vibrant colors such as red, orange, or yellow to the plants. These tetraterpenoids are located within the membranes of plastids, which are organelles characterized by their double membranes. Chloroplasts are responsible for the storage of carotenoids. In higher plants, carotenoids also act as precursors to the plant hormone abscisic acid. Notable carotenoids, including β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin, and astaxanthin, are recognized for their potential in chemoprevention.[86] The consumption of colorful vegetables, flowers, and fruits is associated with a reduced risk of malignant brain tumors, as these foods effectively inhibit the invasion of tumor cells into normal brain tissue.[87] In addition, pinophilins A and B, which are hydrogenated azaphilones, have been identified as inhibitors of human cancer cell proliferation[88] [Table 4 and Figure 5].

FLAVONOIDS

Flavonoids, originating from the Latin term "flavus," meaning yellow, are plant pigments that are extensively found in nature. These compounds contribute vibrant colors to flowers and fruits, thereby attracting pollinators and seed dispersers. Flavonoids are present in citrus fruits such as lemons, oranges, and grapefruits, primarily located in the cytoplasm and plastids of plant cells. They are water-soluble and typically reside in vacuoles, which are membrane-bound structures that store water and nutrients. Numerous processed foods, including dark chocolate, strawberries, blueberries, cinnamon, pecans, walnuts, grapes, and cabbage, are rich in flavonoids. These compounds are known to lower cholesterol levels and possess various antioxidant properties. The dietary intake of flavonoids is associated with numerous health benefits [Figure 1 and Table 1]. Fisetin (3,3',4',7-tetrahydroxyflavone) is a specific flavonoid found in a range of fruits and vegetables, including strawberries, apples, persimmons, grapes, onions, and cucumbers. It serves as a chemopreventive and chemotherapeutic agent against cancer and other diseases[89] [Table 4 and Figure 5].

C-glycosyl flavonoids extracted from Beta vulgaris cicla (BVc) and betalains from Beta vulgaris rubra (BVr) exhibit significant antioxidant, anticancer, and anti-inflammatory properties. According to Ninfali and Angelino[90] dietary intake of betalains can inhibit tumor cell proliferation and their pro-survival pathways. Betanin-rich extracts from red beetroot (*Beta vulgaris* L.) have been shown to induce apoptosis and autophagic cell death in MCF-7 cells.[91] Extracts from BVc and BVr contain apigenin flavonoids, such as vitexin, vitexin-2-O-rhamnoside, and vitexin-2-O-xyloside, which demonstrate antiproliferative effects on cancer cell lines.[92] Betanin has been shown to significantly inhibit cell proliferation and exhibit high cytotoxicity against HepG2 cells [Table 1], as noted by Lee *et al*.[93] [Table 4 and Figure 5].

Betanin and isobetanin have been shown to significantly reduce the proliferation and viability of cancer cells in MCF-7 treated specimens. In addition, these compounds contribute to the restoration of mitochondrial membrane integrity and the intrinsic and extrinsic apoptotic pathways.[91] Furthermore, seed sprouts, which contain betacyanin, exhibit potent anti-inflammatory and anticancer properties.[94] Plant-derived flavonoids demonstrate anti-inflammatory effects both *in vitro* and *in vivo*. The *in vivo* anti-inflammatory mechanisms primarily involve the inhibition of eicosanoid-generating enzymes, such as phospholipase A2, COXs, and lipoxygenases, leading to a reduction in the levels of prostanoids and LT. Flavone derivatives exert their anti-inflammatory effects by modulating the expression of proinflammatory genes, including COX-2, inducible NO synthase, and various key cytokines. Given these distinct mechanisms of action and their significant *in vivo* efficacy, flavonoids serve as natural modulators of proinflammatory gene expression and are recognized as highly effective anti-inflammatory agents, as highlighted by[95] [Table 4 and Figure 5].

BETALAINS

Betalains are pigments that impart color to certain fruits and vegetables, appearing in shades of red-violet (betacyanin) or yellow (betaxanthin). These pigments occur naturally in various fruits and vegetables. Frequently utilized as food coloring agents, betalains are characterized by their water solubility and nitrogen content. At present, betalains are exclusively found in plants belonging to the order Caryophyllales and in certain higher fungi; however, research into metabolic engineering is underway to adapt non-Caryophyllales plants for betalain production. Betacyanin, which is present in tomatoes and potatoes, has demonstrated therapeutic benefits against colitis and inflammation-inducing macrophages in murine studies.[96] The engineering of betalains holds promise for enhancing the commercial production of food, potentially increasing food supply, and providing additional health benefits [Table 4 and Figure 5].

PHYCOBILINS

Phycobilins are photosynthetic pigments that are soluble in water. While they are absent in higher plants, they are present in red algae and cyanobacteria. In addition, phytochrome, which is found in blue-green algae, plays a crucial role in regulating various aspects of plant development, including seed germination, stem elongation, leaf expansion, pigment production, and flowering, as indicated in Table 1. Phytochrome is distributed across most organs of seed plants and free-sporing plants. Cyanidin-3-O-glucoside (C3G) is a type of water-soluble pigment commonly found in numerous plant species. It exhibits significant antioxidant and anti-inflammatory properties. Treatment of THP-1 macrophages with C3G and C3G liposomes has been shown to decrease levels of inflammatory markers such as TNF-alpha, IL-1β, IL-6, and IL-8, which are stimulated by LPS. Furthermore, C3G and its liposomal form can protect macrophages from undergoing apoptosis. LPS exposure leads to an increase in phosphorylated nuclear transcription factor NF-κB and phosphorylated IkBα, whereas C3G and C3G liposomes can inhibit the expression of these phosphorylated proteins[97] [Table 4 and Figure 5].

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their therapeutic effects by inhibiting the COX enzyme, which is responsible for the synthesis of PGs. Selective COX-2 inhibitors are effective anti-inflammatory agents that do not produce adverse effects on the kidneys and stomach. These inhibitors also demonstrate potential as anticancer agents and may slow the progression of Alzheimer's disease.[98] Drugs that exhibit high potency against COX-2 while having minimal impact on COX-1 are associated with strong anti-inflammatory effects and reduced side effects.[99] These COX-2 inhibitors represent a "next-generation" class of NSAIDs that can selectively inhibit the COX-2 isoenzyme without interfering with COX-1 function, highlighting the significant role of the COX-2 enzyme in health and disease prevention[100] [Table 4 and Figure 5].

CONCLUSION

This review emphasizes the anti-inflammatory properties of EOs, gums, latex, and pigments derived from over 200 medicinal plants. These substances hold significant promise for the treatment of various inflammatory diseases and the development of contemporary anti-inflammatory medications. These phytochemicals act by modulating several main inflammatory signaling pathways, including NF-κB, MAPKs, STAT, and Nrf-2 signaling. The modulation of these effects is influenced by factors such as cytokine secretion, histamine release, immunoglobulin production, class switching, cellular co-receptor expression, lymphocyte activity, and phagocytosis. Before using, and having new drug formulations, it is essential to evaluate the anti-inflammatory efficacy of plant-derived natural products through various animal models for *in vivo* studies, cell lines for *in vitro* studies, and *in silico* models. A comprehensive understanding of both phytochemistry and the mechanisms by which phytochemicals combat inflammatory health issues is necessary to identify effective solutions for inflammatory diseases. Undoubtedly, these products could be recommended for regular use as part of a successful and safe strategy to manage chronic inflammatory conditions.

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