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Therapeutic Insights into Anti-Inflammatory Activities Derived from Medicinal Plants

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Many synthetic drugs previously considered for treating inflammatory conditions have lost favor due to their potential side effects and adverse outcomes, along with their proven safety concerns for human use. In recent years, herbal remedies have gained popularity as an alternative treatment for a wide range of human ailments. Herbs possessing anti-inflammatory properties have attracted significant attention because they do not have many of the drawbacks associated with synthetic medications. This review aims to provide a comprehensive overview of recently discovered anti-inflammatory compounds falling into various classes of plant constituents, including alkaloids, glycosides, terpenoids, steroids, polyphenolic compounds, and those derived from marine

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organisms, fungi, and algae. Furthermore, it explores the broader perspective of potential interactions between herbal and synthetic drugs, associated adverse effects, and clinical studies examining the anti-inflammatory properties of herbs.

Keywords: Anti-inflammatory; alkaloids; glycosides; herbal medicine.

1. INTRODUCTION

Inflammation is a natural defense response of the human body to physical injuries, burns, microbial infections, and other potential threats like allergens. Uncontrolled inflammation can lead to a wide range of disorders such as allergies, asthma, rheumatoid arthritis, inflammatory bowel diseases (e.g., Crohn's disease), allergic conjunctivitis, upper respiratory tract infections, chronic sinusitis, rhinitis, cardiovascular issues, metabolic syndrome, cancer, and autoimmune diseases. This imposes a significant economic burden on individuals and society as a whole [1].

Inflammation is characterized by heat, swelling (edema), pain, redness, and altered function in the affected tissue. It results from increased blood flow, enhanced vascular permeability, tissue damage caused by the activation and migration of white blood cells, the generation of reactive oxygen derivatives (oxidative burst), and the production of compounds like platelet-activating factors, leukotrienes, and prostaglandins (PGs) [2]. These molecules are produced locally through the action of enzymes like phospholipase A2, cyclooxygenases (COXs), and lipoxygenases [3].

To manage inflammation, two main categories of medications are used: steroidal and non-steroidal anti-inflammatory agents. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used globally, with an estimated daily usage exceeding 30 million. Steroid anti-inflammatory agents, known as glucocorticoids, are commonly employed to suppress inflammation in chronic inflammatory conditions associated with increased expression of inflammatory genes [4,5].

Most NSAIDs are carboxylic acid-containing drugs, including salicylate derivatives like aspirin, carboxylic and heterocyclic acid derivatives such as indomethacin, propionic acid derivatives like ketoprofen and flurbiprofen, and phenylacetic acid derivatives such as diclofenac. These drugs containing organic acids act at the enzyme's active site, preventing arachidonic acid (AA) access and inhibiting the cyclooxygenase pathway [6,7]. However, despite their potent anti-inflammatory properties, NSAIDs are known for their significant adverse effects, particularly gastrointestinal (GI) issues, such as ulcers, perforations, blockages, and bleeding, which restrict their therapeutic use [8]. GI complications linked to NSAIDs are a common cause of hospitalizations, resulting in over 12,000 hospitalizations and approximately 2,000 deaths [9]. Adverse effects of synthetic drugs account for about 8% of hospital admissions in the United States, with nearly 100,000 deaths annually due to these toxicities [10-12]. Historically, medicinal plants have been used for the treatment of various diseases, with the belief that they are safe and free from significant side effects. Some of these plants exhibit anti-inflammatory properties that can be harnessed to treat inflammatory disorders. These natural compounds have the potential to become the primary class of anti-inflammatory drugs, offering therapeutic benefits without systemic adverse effects. In this review, we explore medicinal plants as potential sources for discovering new anti-inflammatory drugs and discuss their current limitations.

2. INFLAMMATORY PATHWAYS

When a tissue, chemical, or mechanical injury occurs, any cell in the body might release prostaglandins, which are short-lived localized hormones that can cause fever, inflammation, and discomfort once they are present in the intercellular space. Thromboxanes play a crucial role in modulating blood vessel tone, platelet aggregation, and clot formation, thereby amplifying the inflammatory response. Additionally, they function as activators for hormones [13,14]. The inflammatory system generates various other inflammatory mediators through a complex biochemical pathway triggered by damage. This intricate process leads to the initial manifestations of pain and tissue loss before the commencement of healing and recovery [15,16]. The arachidonic acid route is a crucial part of the inflammatory pathway because arachidonic acid is promptly released from damaged cellular membranes. Prostaglandins and thromboxanes are produced from membrane-based arachidonic acid in part due to the enzymatic action of cyclooxygenase (COX)

[17,18]. The COX-1 and COX-2 enzymes are two different forms of COX. These enzymes exhibit similar functions, but targeted inhibition, such as achieved by NSAIDs specifically targeting COX-2, can modify the occurrence of adverse effects. In order to stop the cycle, acetylsalicylic acid irreversibly inhibits the COX enzymes [19]. To lower the formation of inflammatory prostaglandins and thromboxanes and to decrease the inflammatory response, NSAIDs have progressed from blocking both COX-1 and COX-2 to specifically blocking COX-2 [20].

The activation causes the synthesis of prostaglandins, thromboxanes, and leukotrienes to start the local inflammatory response. Their activation requires the enzymes COX and LOX. The COX action can be blocked by NSAIDs, which thus stops the production of COX-derived inflammatory mediators. 5-HPETE = 5-hydroperoxy eicosatetraenoic acid; LTC4 = leukotriene C4; PGE2 = prostaglandin E2; PGF2 = prostaglandin F2; PGI2 = prostacyclin 2; TXA2 = thromboxane 2.

3. ANTI-INFLAMMATORY MEDICINAL PLANT ACTION MECHANISM (AIMP)

Various cellular processes or mechanisms account for the herbal medicines' in vivo anti-inflammatory efficacy. These processes include antioxidative and radical scavenging functions, and modulation of the cellular functions of the cells involved in inflammation, such as mast cells, macrophages, lymphocytes, and neutrophils. (For example, certain substances prevent mast cell production of histamine while others prevent T-cell multiplication), Modulation of the enzymatic activity of the enzymes that produce nitric oxide (NO), such as nitric oxide synthase, as well as those that metabolize arachidonic acid (AA), including phospholipase A2, cyclooxygenase, and lipoxygenase (LOX) (NOS) [21,22]. Anti-inflammatory medicinal plant products (AIMP) block these enzymes, hence reducing the formation of AA, prostaglandins (PG), leukotrienes (LT), and NO, which are essential mediators of inflammation [23]. This means that one of the crucial cellular mechanisms of anti-inflammation is the inhibition of these enzymes by AIMP. Numerous sources of evidence have emerged in recent years to support the hypothesis that certain AIMP regulate gene expression, particularly the expression of pro-inflammatory genes, which dampens the inflammatory reaction [24]. Molecular mechanisms of phytoconstituents are depicted in Fig. 2.

(1) Tyrosine kinase receptors are activated by a variety of illnesses and stimuli. (2) which then triggers IKKs (3) Inactive IκBα-NF-κB complex is further phosphorylated by activated IKKs. (4) IκBα that has been phosphorylated has been ubiquitylated and destroyed. (5) NF-κB -activated B's form enters the nucleus [Phenol/flavonoids blocks its entry] (6) whereby target genes are further activated for (a) Chemokines, cytokines, adhesion molecules, and receptors that promote (b) Cell proliferation, growth and differentiation (7) Arachidonic acid is converted to prostaglandins through the action of Cox2. [Phenol/flavonoids prevent such conversion] (8) Inflammation is brought on by Prostaglandins.

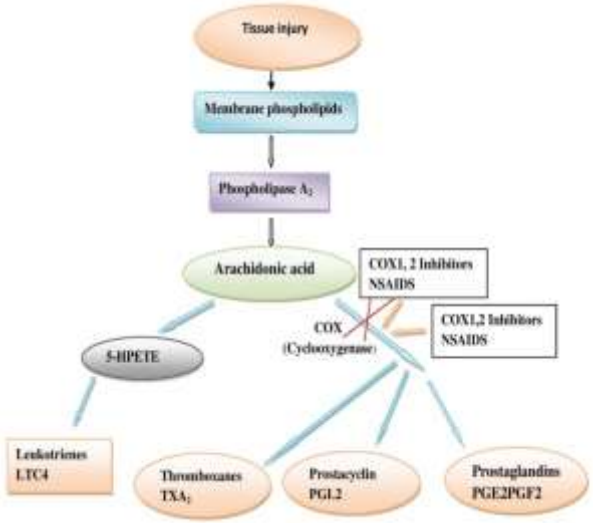

Fig. 1. Activation of the arachidonic acid pathway by damaged cell membrane

Table 1. Plants used as anti-inflammatory agent [25]

Sl. No.	Plant Name	Common name	Familly	Plant parts	Chemical constituents
1	*1. Achillea millefolium Linn.*	Yarrow	2. *Asteraceae*	Whole Plant	Flavonoids
2	*Aconitum heterophyllum*	Atis or Ativisha	*Valeraneaceae*	Roots	Alkaloids, Glycosides, Flavnoids, and Sterols
3	*Adhatoda vasica*	Malabar nut	*Acanthaceae*	Leaves	Alkaloids, tannins, flavonoids, terpenes, sugars, glycosides
4	*Bacopa monnieri Linn.*	Brahmi OR water hyssop,	*Scrophulariaceae*	Whole Plant	Triterpenoids and bacoside
5	*Cassia fistula L.*	Golden Shower	*Caesalpiniaceae*	Whole Plant	Flavonoids
6	*Daphne pontica Linn.*	Twin-flowered or Pontic daphne	*Thymelaeaceae*	Bark, root stem, berries	Flavonoids
7	*Emblica officinalis*	Indian gooseberry	*Euphorbiaceae*	Fruits	Gallic acid, ellagic acid, tannins, minerals, vitamins, amino acids, fixed oils, and flavonoids
8	*Garcinia mangostana Linn.*	Mangosteen	*Guttiferae*	Fruits	Xanthones, α- and γ-mangostins
9	*Lantana camara Linn.*	Lantana or shrub verbena	*Verbenaceae*	Leaves and flowers	Volatile oil
10	*Lycopodium clavatum Linn.*	Common club moss	*Lycopodiaceae*	Whole plant	Alkaloids
11	*Mangifera indica Linn.*	Mango	*Anacardiaceae*	Bark	Flavonoids
12	*Phyllanthus polyphyllus Linn.*	Wild Gooseberry;	*Euphorbiaceae*	Whole plant	Benzenoid and arylnaphalide
13	*Ricinus communis Linn.*	Castor oil plant	*Euphorbiaceae*	Roots	Flavonoids, alkaloids and tannins
14	*Sesbania sesban Linn.*	Egyptian riverhemp	*Leguminosae*	Leaf	Terpenoid and steroidal saponins, tannins and flavnoids
15	*Sida cordifolia Linn.*	Flannel weed, bala, country mallow or heart-leaf sida	*Malvaceae*	Leaf	Asparagine, quinazoline alkaloids, sympathomimetic amines, ephedrine, choline, betaine, rutin, phytosterol, β-sitosterol, hypaphorine, vasicinone, vascicine, vasicinol,etc
16	*Thespesia populnea*	Portia tree	*Malvaceae*	Fruits and leaf	Alkaloids, carbohydrates, Proteins, tannins, phenols, flavonoids, gums & mucilage, saponins and terpenes48

Sl. No.	Plant Name	Common name	Familly	Plant parts	Chemical constituents
17	*Matricaria chamomilla L.*	Chamomile	*Asteraceae*	Flower	Volatile oils including alpha-bisabolol, alpha-bisabolol oxides A & B, and matricin
18	*Arnica montana L.*	Mountain daisy, leopard's bane, and mountain tobacco	*Asteraceae*	Leaf flower rhizome	Essential oils, fatty acids, thymol, pseudoguaianolidesesquiterpene lactones and flavanone glycosides
19	*Glycyrrhiza glabra*	Liquorice	*Liquorice*	Roots	Triterpenes glycyrrhizin (6–13%) and glycyrrhizic acid
20	*Indica L. Indian*	Indian shot	*Aristolochia*	Rhizome	Aristolochic acid
21	*Aristolochia kaempferiWilld*	Dutchman's pipe and pipevine	*Aristolochia*	Fruits	Aristolochic acids and esters
22	*Horsfieldiaamygdalinia*	Myristicaamygdalina	*Myristicaceae*	Fruits, leaf, bark and seed	Alkaloids, tannins, flavonoids, saponins, triterpenoids, steroids, cardiac glycosides, and reducing sugar.
23	*Lonicera japonica Thunb*	Japanese honeysuckle	*Caprifoliaceae*	flowers, stems, and leaves	Organic acids, flavonoids, triterpenoids, and volatile oils,
24	*Sambucus javanicaReinw. E*	Chinese Elder	*Adoxaceae*	Bark and leaves	Glycosides, Carbohydrates
25	*Weigela floribunda*	Crimson weigela	*Caprifoliaceae*	Flower	Flavonoids
26	*Cirsium japonicum DC*	Japanese thistle.	*Asteraceae*	Root	Flavonoids
27	*Crossotephium chinense L. Makino*	Chinese Wormwood	*Asteraceae*	Leaf, root and stem	Flavonoids
28	*Curcuma longa*	Turmeric	*Zingiberaceae*	Rhizome	Essential oils, Terpene, curcumin
29	*Zingiber officinale*	Ginger	*Zingiberaceae*	Rhizome	Phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers
30	*Rosmarinus officinalis*	Rosemary	*Lamiaceae*	Leaves, twigs, and flowering apices	Essential oil, terpenes
31	*Borago officinalis*	Borage	*Boraginaceae*	Flower	Essential oils like borage seed oil
32	*Oenothera biennis*	Evening Primrose	*Onagraceae*	Flower	Fatty acids, phenolic acids, and Flavonoids.
33	*Harpagophytum procumbens*	Devil’s Claw	*Pedaliaceae*	Root and shoots	Mucilage as a major component and tannin.
34	*Boswellia serrata.*	Indian Olibanum	*Burseraceae*	Gum-resin	Resin, amino acids, phenols, terpenes,

Sl. No.	Plant Name	Common name	Familly	Plant parts	Chemical constituents
					polysaccharides, and β-boswellic acid
35	*Rosa canina.*	Dog rose	*Rosaceae*	Flower	Flavonoids, carotenoids, fatty acids, vitamins
36	*Urtica dioica*	Stinging nettle	*Urticaceae*	Leaves and stems, and roots	Essential amino acids, vitamins, tannins, carbohydrates, sterols etc
37	*Uncaria tomentosa*	Cat's claw	*Rubiaceae*	Bark and root	Alkaloids, glycosides, organic acids, proanthocyanidins, sterols, and triterpenes
38	*Salvia officinalis*	Sage	*Lamiaceae*	Leaf	Essential oil,likecamphor, α-thujone, β-thujone, borneol, and viridiflorol.
39	*Ribes nigrum*	Blackcurrant	*Grossulariaceae*	Fruits leaf and seed	Polyphenol
40	*Persea americana*	Avocado	*Lauraceae*	Fruits	Flavonoids like oritentin, isoorientin, vitexin, and isovitexin
41	*Elaeagnus angustifolia.*	Oleaster	*Elaeagnaceae*	Fruit, flower, leaf and bark	Glycosides polysaccharides, alkamides, and flavonoids.
42	*Vaccinium myrtillus*	Bilberry	*Ericaceae*	Fruits and leaf	Flavonoid, tannins, ellagitannins, and phenolic acids
43	*Olea europaea*	Olive	*Oleaceae*	Whole plant	Terpenes like oleuropein

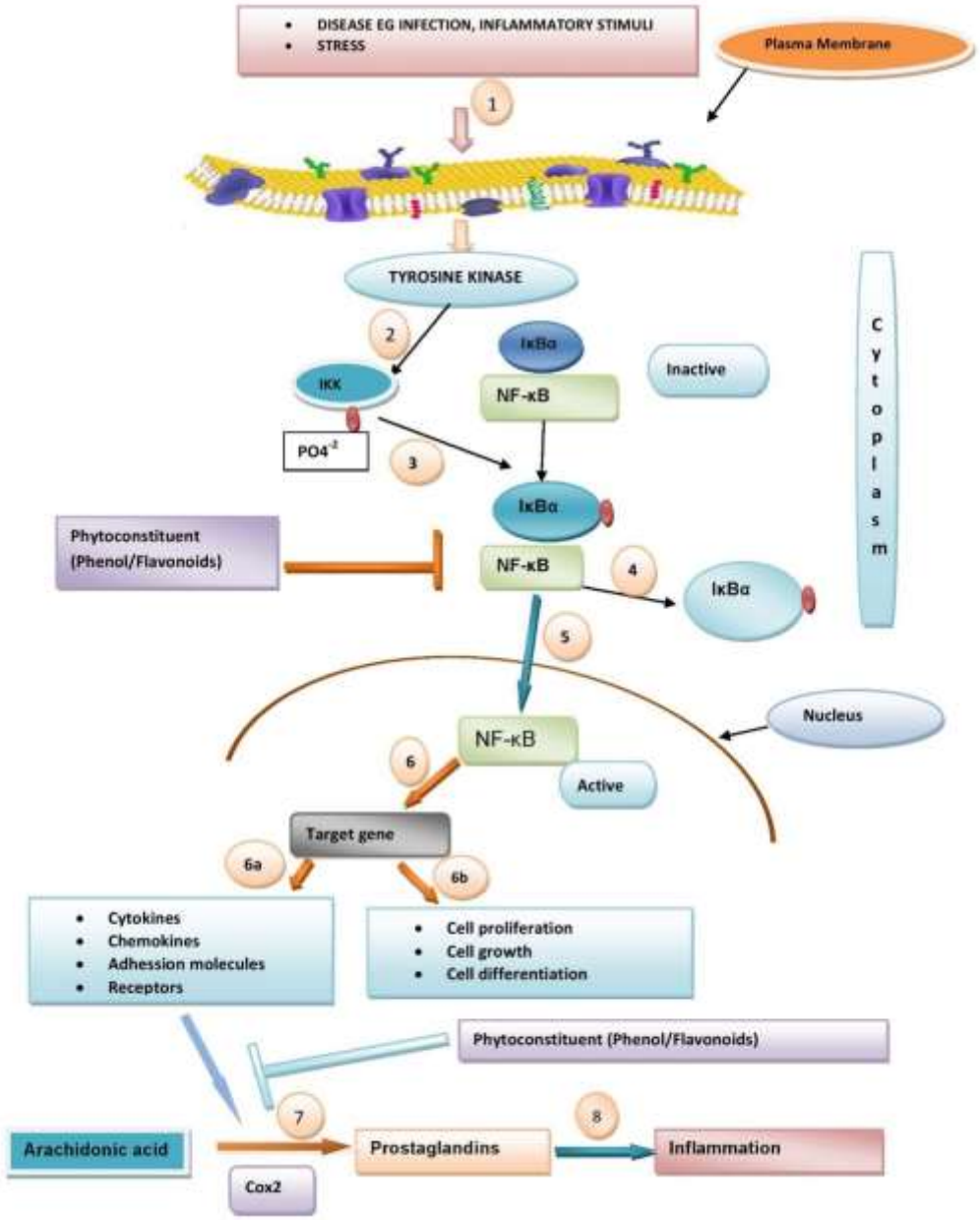

Fig. 2. Molecular mechanism for the anti-inflammatory effects of Pedicularis phytoconstituents [Phenol/flavonoids]

4. ANTI-INFLAMMATORY ACTIVITY OF PHYTOCONSTITUENTS

4.1 Alkaloids

The significant plant groups Solanaceae, Leguminosae, Apocynaceae, Liliaceae, Papaveraceae, Rutaceae, and Ranunculaceae are major plant families that contain alkaloids that have anti-inflammatory properties (AIA). Tetrandrine is one of the most promising substances [26]. Its AIAs are brought on by the suppression of the inflammatory pathways for COX and lipoxygenase production of prostaglandin E2 (PGE2) is found to be significantly more inhibited by berbamine than by tetradine, with larger inhibitory effects on the natural killer cell population. Tetrandrine also inhibits the production of tumour necrosis factor (TNF)-α by monocytes and the release and action of inflammatory cytokines, lipid mediators, and histamine. Tetrandrine is therefore

discovered to be a prototype compound for the development of a new family of anti-inflammatory drugs [27].

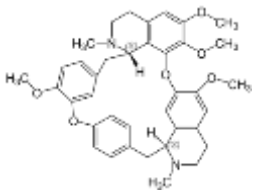

Fig. 3. Structure of Tetrandrine

4.2 Glycosides

Glycosides have the same potential AIA as alkaloids. The Glycosides are discovered naturally in the following families: Leguminosae, Scrophulariaceae, Polygonaceae, Solanaceae, and Myrsinaceae. According to Gomes and colleagues, the leaves of Muesachisia (Myrsinaceae) have a glycosidal fraction that has significant pharmacological benefits for treating inflammation. The aglycone tetrahydroxy triterpene of the oleanene series discovered in the glycosidal fraction was proved to be the primary cause of the activity. In various animal models, including carrageenan-induced pedal oedema in rats, cotton pellet granuloma, formaldehyde-induced arthritis, and Freund's complete adjuvant-induced polyarthritis. M. Chisiu is shown to have AIA similar to that of synthetic substances like aspirin, phenylbutazone, and indomethacin [28].

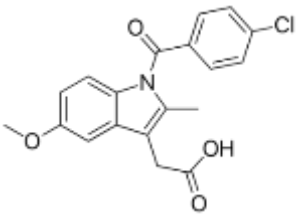

Fig. 4. Structure of Indomethacine

4.3 Terpenoids

There are numerous plant families that contain terpenoids. The main plant families with terpenoids exhibiting AIA are Umbelifereae, Lamiaceae, Taxodiaceae, Capparidaceae, Cucurbitaceae, Burseraceae, and Asteraceae which are they are significant in the field of the study. Diterpenoidalsaponins like artemisin and artemisinin are a key component causing AIA. Sesquiterpene lactones like artemisolide, which are abundant in the herb artemisia asiatica, have been shown to efficiently block the synthesis of nitric oxide (NO), PGE2, and nuclear factor kB (NF-kB) cells when lipopolysaccharide (LPS) causes inflammation in macrophage RAW 264.7 cells [29].

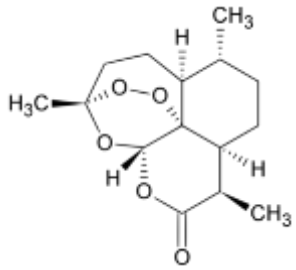

Fig. 5. Structure of Artemisin

4.4 Resins

Boswelliaserrata (salaiguggal), a plant in the Burseraceae family, was discovered to have substantial AIA. Due to the presence of oleogum resin and boswellic acid, Burseraceae plants are reportedly known to contain AIA. The competitive suppression of 5-LOX, leukocyte elastase, and oxygen radicals may be too responsible for the action. Traditional medicines include resin made from dragon's blood (Sanguisdraconis) and Daemonoropsdraco (Palmae), which both had significant results for AIA [30]. The proposed method may entail selective inhibition of intrinsic nitric oxide synthase (iNOS), which controls NO and PGE2, and suppression of NF-kB activation, which controls COX2 gene expression [31].

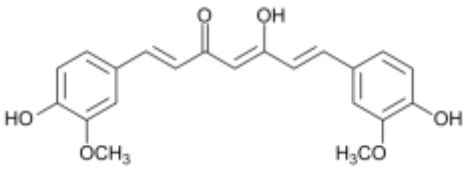

Fig. 6. Structure of Curcumin

4.5 Essential Oils

Essential oils extracted from Carlina acanthifolia's roots demonstrated positive anti-inflammatory and antibacterial effects on gram-positive bacteria. Studies done in vivo revealed pronounced AIA [32]. It was shown that the essential oils of Cordia verbenacea (Boraginaceae) decreased the carrageenan-induced paw edoema in rats that was brought on by substance-P, bradykinin, histamine, and platelet activating factor (PAF) in mice. Sesquiterpene molecules such trans-

caryophyllene and humulene are among the principal components of oil [33].

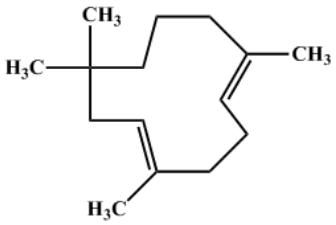

Fig. 7. Structure of Cordia verbanacea

4.6 Polysaccharides

Echinacea purpurea and Echinacea angustifolia (Asteraceae) are plants that have been used for their ability to stimulate the immune system and restore skin since ancient times [34]. Due to the presence of sulfated polysaccharides such xylose, glucose, arabinose, galactose, and galactosamine, Artemisia tripartita (Asteraceae) demonstrated AIA. These polysaccharides change neutrophil count, complement fixation function, and macrophage function [35].

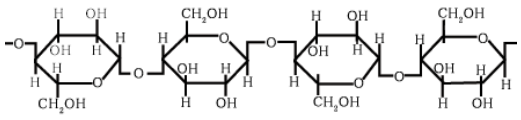

Fig. 8. Structure of Polysaccharides

4.7 Flavonoids

Flavonoids extracted from the leaves and roots of Scutellaria baicalensis (Lamiaceae), Ginkgo biloba (Ginkgoaceae), and Gentiana scabra (Gentianaceae) have demonstrated topical anti-inflammatory activity against chronic skin conditions like atopic dermatitis. This anti-inflammatory effect is likely attributed to their ability to inhibit COX2, PGE2 production, and subsequently reduce the expression of proinflammatory genes [36]. Phenolic flavonoids derived from indigenous plants have been found to express adhesion molecules such as selectins, VECAM-1, and PECAM-1 on endothelial cells. These compounds are known for their significant anti-inflammatory properties and are commonly used in atherosclerosis. Methoxyflavone and hydroxyflavone are two examples of such compounds that have been shown to block monocyte adhesion to TNF-α [37]. In the treatment of anti-inflammatory conditions, the potential mechanisms of action for 5-O-demethylnobiletin may involve the inhibition of 5-LOX and elastase. Additionally, this flavone has been observed to prevent rat neutrophils from producing leukotriene B4 (LTB4) and human neutrophils from releasing elastase [38].

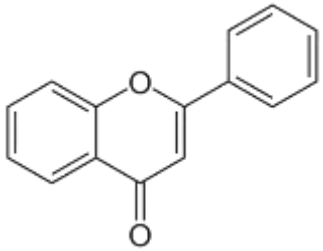

Fig. 9. Structure of Flavonoids

4.8 Phenolic Compounds

The catechol concentration, cepaenes, and unsaturated thiosulfates were the main causes of the AIA and it was discovered that they blocked 5-LOX's effects on swine leukocytes [39]. The physiological inhibition of leukocyte migration, the lowering of serum lysozyme levels, nitric oxide, PGE2, and malondialdehyde levels in a dose-dependent manner may be the most likely mechanisms. The physiological inhibition of leukocyte migration, the lowering of serum lysozyme levels, nitric oxide, PGE2, and malondialdehyde levels in a dose-dependent manner are possible mechanisms [40].

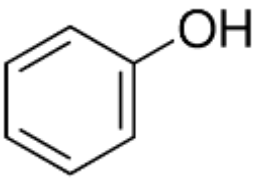

Fig. 10. Structure of naturaly occurring Phenolic compounds

4.9 Cannabinoids

Cannabinoidsare compounds obtain traditionallyin the fruits of Cannabis sativa (Cannabinaceae). The inflammation brought on by Δ-tetrahydro cannabinol (Δ-THC). Cannabinoids and olive oil inhibited the inflammation caused by tetradecanoylphorbolacetate induced erythema in mouse ear and successfully elicited writhing response by phenylbenzoquinone. The inhibition

of prostaglandin production and mobilisation are the mechanism underlying its AIA [41].

4.10 Steroids

Ganoderma lucidum and Ganoderma tsugae are among the plants from which steroidal and triterpenoidal saponins have been extracted. These saponins exhibit anti-inflammatory activity by inhibiting the release of β-glucuronidase from rat neutrophils induced by formyl Met-Leu-Phe (fMLP)/cytochalasin B [42].

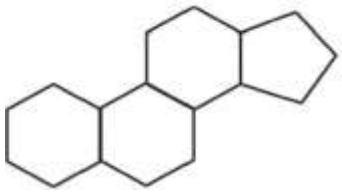

Fig. 11. Structure of main structure of Steroids

4.11 Fatty Acids

Fatty acids have long been known for their medicinal properties, including their anti-inflammatory, antioxidant, free radical scavenging, and antihyperlipidemic effects. A number of immune illnesses may benefit from the therapeutic benefits of fish oils derived from marine organisms. According to research on epidermal enzymes and rat basophilic leukaemia cells, the oil's postulated mechanism of action involves a reduction in lipid levels, which may be caused by 5-LOX, 15-LOX, and 15-HEPE inhibitory activities. The two of the main components which is mainly responsible are Docosahexaenoic acid and Eicosapentaenoic acid [43].

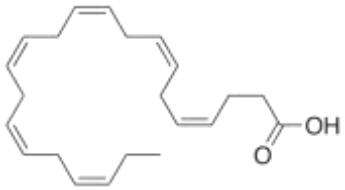

Fig. 12. Structure of Docosahexaenoic

4.12 Plant Glycoproteins

Glycoproteins are naturally present in significant quantities within the bodies of animals. Their potential as anti-inflammatory agents is evident in their ability to inhibit the proteins responsible for inducing inflammation and to reduce NO production during LPS-induced inflammation in RAW264.7 cell lines. Furthermore, the study reveals that plant-derived glycoproteins exhibit strong antioxidant effects against lipid peroxyl radicals in cell-free systems [44].

5. OBSTACLES ASSOCIATED WITH THE UTILIZATION OF HERBAL MEDICINE

5.1 Quality-Related Factors

The process of deriving herbal compounds is intricate, making it challenging to ascertain the precise quantity and concentration of the product. Variations in the extraction method and the specific plant used can influence the actual concentration of the product due to non-standardized preparation procedures. Moreover, there is inconsistency in both inter-manufacturer and intra-manufacturer products. Even though dietary supplements, including herbal ones, do not undergo the same rigorous testing and standards as pharmaceuticals, their production is subject to multiple regulations since they are categorized as food products [45-47].

5.2 Interaction Challenges between Herbal and Allopathic Medicine

Various herbs contain a diverse range of potent phytochemical compounds, each possessing distinct pharmacological, metabolic, and binding properties. These herbal remedies can potentially engage in pharmacokinetic or pharmacodynamic interactions with conventional medications. For instance, the interaction between herbal treatments like Garlic and ginger and allopathic drugs with a narrow therapeutic range can lead to adverse effects. As an example, Garlic and ginger have been observed to reduce platelet count and increase the risk of bleeding, which can be problematic for individuals taking anticoagulant medications like warfarin [48].

5.3 Challenges in Advocating for the Safety of Herbal Remedies

In response to the substantial rise in the consumption of herbal products in recent decades, studies have been carried out to assess both the beneficial and potential adverse effects of herbal medicines. The objective is to provide scientific evidence regarding the safety and effectiveness of these treatments [49].

Various side effects associated with the use of herbal remedies can be attributed to several factors, including the use of the wrong plant species, adulteration, the presence of undisclosed substances, the inclusion of toxic or contaminated materials, excessive dosing, and the misuse of medicinal herbs by both consumers and practitioners. Evaluating the safety of herbal medicines has become a critical concern for consumers, regulatory authorities, and healthcare professionals, as the analysis of adverse effects with herbal medicines is notably more intricate compared to conventional medications [50].

5.4 Challenges in Conducting Clinical Trials Involving Herbal Remedies

Before embarking on the registration of a novel medicinal product for large-scale phase III trials, several challenges pertaining to the investigation of herbal medicines must be addressed. These challenges encompass aspects of research design, quality control, financial considerations, ethical considerations, and regulatory prerequisites. In 2005, the WHO issued operational guidelines outlining the legal prerequisites that facilitate the scientific examination of herbal products [51].

5.5 Challenges Related to Maintaining the Quality of Herbal Medications

Due to the challenges in verifying the presence of all the herbs or raw materials, ensuring the quality of the final herbal product can often be a significant issue, particularly in the case of blended herbal products. Issues related to the harvesting and processing of herbs also contribute to poor quality. These issues encompass a lack of processing technologies, inefficient harvesting practices, haphazard collection, inadequate agricultural methods, and suboptimal propagation processes [52].

Another concern is adulteration, which involves substituting an ineffective pharmacological substance for the original medication. This substitution can involve counterfeit, substandard, defective, damaged, or otherwise inappropriate components from either the same plant or a different source [53]. Adulteration can occur in two ways:

- Deliberate or direct adulteration.
- Unintentional or indirect adulteration.

5.6 The Influence of Regulatory Measures on the Safety and Utilization of Herbal Remedies

The standards for assessing the quality and regulating the manufacturing of herbal medicines are often less stringent and poorly coordinated. In some instances, traditional medicine practitioners may operate without the necessary registration or licensing. Consequently, there has been a growing emphasis on ensuring the safety of both conventional and herbal treatments by national healthcare professionals and the public [54].

Due to the limited resources available for overseeing quality control and production processes, many governments do not conduct safety or toxicological assessments before making herbal treatments and related products available. Consequently, these products frequently reach consumers without a prescription, and individuals may not be fully aware of potential side effects associated with herbal remedies [55].

6. CONCLUSION

Numerous studies have been undertaken to assess the anti-inflammatory attributes of medicinal herbs and to endorse their incorporation into mainstream medicine. Various secondary metabolites synthesized by plants in the form of phytochemical compounds have been identified and continue to hold promise for disease treatment. The intricate process of inflammation remains critical for the body's defense. This review underscores that plant extracts can exhibit anti-inflammatory properties that impact multiple stages of the inflammation process. The investigation of plants with anti-inflammatory properties is an emerging domain in modern biomedicine. It is imperative to expand research on plants possessing these qualities since traditional healers may hold invaluable knowledge about unstudied plants. Simultaneously, numerous ongoing studies in the realm of herbal medicine are exploring novel and safer options for addressing diverse inflammatory reactions. Consequently, to enhance regulatory oversight of herbal product production and marketing, expert insights and commentaries are essential.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bagad AS, Joseph JA, Bhaskaran N and Agarwal A. Comparative evaluation of anti-inflammatory activity of curcuminoids, turmerones, and aqueous extract of Curcuma longa. Adv Pharmacol Sci. 2013;2013:1-7.
2. Onstantopoulos K. Editorial Hot Topic: Molecular biologypathophysiology of inflammation and autoinflammation. Curr Drug Targets Inflamm Allergy 2005;4:1-39.
3. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: New insights on cellular and molecular mechanisms. Trends Immunol. 2007;28:551-8.
4. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: New insights on cellular and molecular mechanisms. Trends Immunol. 2007;28:551-8.
5. Wallace JL, Ferraz JG. New pharmacologic therapies in gastrointestinal disease. Gastroenterol Clin North Am. 2010;39:709-20.
6. Marnett LJ. The COXIB experience: a look in the rearview mirror. Annu Rev PharmacolToxicol 2009;49:265-90.
7. Inotai A, Hanko B, Meszaro A. Trends in the non-steroidal anti-inflammatory drug market in six central-eastern European countries based on retail information. Pharmacoepidemiol Drug Saf 2010;19:183-90.
8. Vonkeman HE, Van de Laar MA. Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. Semin Arthritis Rheum. 2010;39:294-312.
9. Long L, Soeken K and Ernst E. Herbal medicine for the treatment of Osteo Arthritis a Review, Rheumatology. 2001;40:779-93
10. Rosenson RS. Future role for selective phospholipase A2 inhibitors in the prevention of atherosclerotic cardiovascular disease. Cardiovas Drugs Ther. 2009;23:93-101.
11. BrooksPM, March LA. New insight into Osteo Arthritis. Med J Aus. 1995;163:367-9.
12. Philomena G. Concerns regarding the safety and toxicity of medicinal plants - An overview. J Appl Pharmaceut Sci. 2011;1(6):40-4.
13. Nelson AB, Lau BH, Ide N and Rong Y. Pycnogenolinhibits macrophage oxidative burst, lipoprotein oxidation, and hydroxyl radical-induced DNA damage. Drug Dev Ind Pharm. 1998;24:139-44.
14. Rehman Q, Sack KE. When to try COX-2-specific inhibitors: Safer than standard NSAIDS in some situations. Postgrad Med. 1999;106:95-106.
15. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med. 2004;351:1709-11.
16. Harris WS, Von SC. The Omega-3 Index: A new risk factor for death from coronary heart disease, Prev Med .2004;39:212-20.
17. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med. 2004;351:1709-11.
18. Hostanska K, Daum G and Saller R. Cytostatic and apoptosisinducing activity of boswellic acids toward malignant cell lines in vitro. Anticancer Res. 2002;22:2853-62.
19. Mix KS, Mengshol JA, Benbow U, Vincenti MP, Sporn MB, Brinckerhoff CE, et al. A synthetic triterpenoid selectively inhibits the induction of matrix metalloproteinases 1 and 13 by inflammatory cytokines. Arthritis Rheum. 2001;44:1096-104.
20. Schmid B, Lüdtke R, Selbmann HK, Kötter I, Tschirdewahn B, Schaffner W, et al. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: Randomized placebo-controlled double blind clinical trial. Phytother Res. 2001;15:344-50.
21. Vane J, Botting. Inflammation and the mechanism of action of anti-inflammatory drugs, The Faseb J. 1987;1:89-96
22. Chen S. Natural products triggering biological targets - a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. Curr Drug Target. 2011;12(3):288-301.
23. Khanapure SP, Garvey DS, JaneroDR and Letts LG. Eicosanoids in inflammation: biosynthesis, pharmacology, and therapeutic frontiers. Curr Top Med Chem. 2007;7(3): 311-40.
24. Chukwuemeka SN, Peter AA. Anti-inflammatory medicinal plants and the molecular mechanisms underlying their activities. Afr J Tradit Complement Altern Med. 2015;12:52-61.
25. Kumar S, Bajwa BS, Singh K. Kalia AN. Anti-Inflammatory Activity of Herbal Plants: A Review, IJAPBC. 2013;2(2):272-81.
26. Ferrante A, SeowWK, Rowan-Kelly B. Thong YH. Tetrandrine, a plant alkaloid, inhibits the production of tumour necrosis factoralpha (cachectin) by human monocytes. Clin Exp Immunol .1990;80:232-5.
27. Teh BS, SeowWK, Li SY, Thong YH. Inhibition of prostaglandin and leukotriene

generation by the plant alkaloids tetrandrine and berbamine. J Immunopharmacol. 1990;12:321-6.
28. Gomes A, Sharma RM, Ghatak BJ. Pharmacological investigation of a glycosidal fraction isolated from Maesachisia D. *Don var. angustifolia* Hook f and Th. Indian J Exp Biol. 1987;25:826-31
29. Juteaua F, Masotti V, Bessiere JM, Dherbomez M, Vianoa J. Antibacterial and antioxidant activities of Artemisia annua essential oil. Fitoterapia. 2002;73:532-5.
30. Mack T, Ammon HP and Safayhi H. Abstracts of the International Joint Symposium of Biology and Chemistry of Active Natural Substances. Bonn. 1990;177.
31. Choy CS, Hu CM, Chiu WT, Lam CS, Ting Y, Tsai SH, et al. Suppression of lipopolysaccharide-induced of inducible nitric oxide synthase and cyclooxygenase-2 by SanguisDraconis: A dragon's blood resin in raw cells. J Ethnopharmacol. 2008;115:455-62
32. Dordevic S, Petrovic S, Dobric S, Milenkovic M, Vucicevic D, Zizic S, et al. Antimicrobial, anti-inflammatory, anti-ulcer and antioxidant activities of Carlinaacanthifolia root essential oil. J Ethnopharmacol. 2007;109:458-63.
33. Passos GF, Fernandes ES, da Cunha FM, Ferreira J, Pianowski LF, Campos MM, et al. Anti-inflammatory and anti-allergic properties of the essential oil and actie compounds from *Cordia verbenacea*. J Ethnopharmacol. 2007;110: 323-33.
34. Popov SV, Popova GY, OvodovaRG, Ovodov YS. Antiinflammatory activity of the pecticpolysacharide from Comarumpalustre. Fitoterapia 2005;76:281-7.
35. Xie G, Schepetkin IA, SiemsenDW, Kirpotina LN, Wiley JA, Quinn MT. Fractionation and characterization of biologicallyactive polysaccharides from *Artemisia tripartita*. Phytochem 2008; 69:1359-71.
36. Lim H, Son KH, Chang HW, Sang SS, Kim HP, et al. Effects of antiinflammatorybiflavonoid, ginkgetin on chronic skin inflammation. Biol Pharm Bull. 2006;29:1046-9.
37. Kwon HM, Choi YJ, JeongYJ, Kang SW, Kang IJ, Lim SS, et al. Anti-inflammatory inhibition of endothelial cell adhesion molecule expression by flavone derivatives. J Agr Food Chem 2005; 53:5150-7.
38. Bas E, Recio MC, Giner RM, Manez S, Nicholas MC, Rios JL, et al. Anti-inflammatory activity of 5-O-demethylnobiletin, a polymethoxyflavone isolated from Sideretistragoriganum. Planta Med. 2006;72:136-42.
39. Breu T, Ustunes L, Lermioglu F, Ozer A. Antiinflammatory, analgesic, and antipyretic effects of an aqueous extract of Erythraeacentaurium. Planta Med. 1991;57:34-7.
40. Wu Y, Zhou C, Song L, Li X, Shi S, Mo J, et al. Effect of totalphenolics from Laggeraalata on acute and chronic inflammatory models. J Ethnopharmacol. 2006;108:243-50.
41. Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. Inflammation. 1988;12:361-71.
42. Ko HH, Hung CF, Wang JP and Lin CN. Antiinflammatory triterpenoids and steroids from Ganoderma lucidum and G tsugae. Phytochemistry. 2008;69:234-9.
43. Miller C, Yamaguchi RY, Ziboh VA. Guinea pig epidermis generates putative anti-inflammatory metabolites from fish oil polyunsaturated fatty acids. Lipids 1989;24:998-1003.
44. Oh PS, Lee SJ, Lim KT. Glycoprotein isolated from Rhusverniciflua Stokes inhibits inflammation-related protein and nitric oxide production in LPS-stimulated raw cell. Biol Pharm Bull. 2007;30:111-6.
45. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: A systematic review. J Intern Med. 2002;252:107-13.
46. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis on knee-a randomized double blind placebo controlled trial. Phytomedicine. 2003;10:3-7.
47. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. Jama. 2006;296:1633-44.
48. Leite PM. Rev Mech Interact Concomitant Use Herbs Warfarin Ther. Biomed Pharmacother 2016;83:14-21.
49. Rodrigues E, Barnes JJD. Pharmacovigilance of herbal medicines: The potential contributions of

ethnobotanical and ethnopharmacological studies. Drug Saf 2013;36(1):1-12.
50. World health organization. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. World Health Organization; 2004.
51. Kunle OF. Standardization of herbal medicines - A review. Int J Biodvers Conserv 2012;4(3):101-12.
52. Shriwastav A, Gupta SK. Key issues in pilot scale production, harvesting and processing of algal biomass for biofuels. In Algal biofuels. Springer. 2017; 247-58.
53. World health organization. WHO Global Surveillance and Monitoring System for substandard and falsified medical products; 2017.
54. Kasilo O, Trapsida JJAHM. Decade Afr Trad Med. 2011;14:25-31.
55. Bandaranayake WMJMP. Qual Control Screen Toxic Regul Herb Drugs. 2006;10.