IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Harnessing Nature's Pharmacy: The Role Of Phytoconstituents In Combating Inflammation

Mukul Nishad*[1], Mansi Chauhan[1]

*[1]Assistant Professor, School of Pharmaceutical Sciences, Department of Pharmaceutics, MUIT, Noida, Uttar Pradesh 201304, India
Orcid ID: 0009-0005-3956-6647

[1]Assistant Professor, School of Pharmaceutical Sciences, Department of Pharmaceutics, MUIT, Noida, Uttar Pradesh 201304, India
Orcid ID: 0009-0002-7711-3057

Abstract: Inflammation is a complex biological response to harmful stimuli, playing a crucial role in various diseases, including autoimmune disorders, cardiovascular conditions, and neurodegenerative diseases. Medicinal plants have long been a source of bioactive compounds with anti-inflammatory properties, offering promising alternatives to synthetic drugs. This review explores the molecular mechanisms through which plant-derived compounds, such as flavonoids, alkaloids, phenolic acids, and terpenoids, modulate inflammatory pathways. Special emphasis is placed on their interaction with key inflammatory mediators, including cytokines, transcription factors, and eicosanoids. Additionally, the classification and mechanisms of non-steroidal anti-inflammatory drugs (NSAIDs) are discussed to highlight the potential of phytochemicals in developing novel anti-inflammatory therapies. By integrating traditional knowledge with modern pharmacological advancements, plant-based compounds present an innovative approach to inflammation management, warranting further research and clinical validation.

Keywords: Anti-inflammatory, Phytoconstituents, Medicinal Plants, Inflammation Mediators, Drug Development, AI Applications

I. INTRODUCTION

It is estimated that there are more than five hundred thousand species of plants in the world. The diversity and intricacy of plant metabolites pose a barrier to the research of the chemical repertoire available (Corlett, 2016; Laurance et al., 2012).

The utilization of medicinal plants remains a fascinating avenue for obtaining natural remedies for a range of ailments. There are thought to have been studies on over 150,000 different plant species, many of which have been shown to have useful medicinal agents. The medicinal uses of new plant compounds have gradually increased in the last few years (Abima Shazhni et al., 2018; Cao & Deng, 2017).

From ancient times, plants have been used extensively in human health treatment. Plants produce a wide range of biologically active compounds to protect themselves from environmental stressors and diseases. These minuscule chemical entities are generated through secondary metabolism and serve a

variety of biological purposes. The most notable of the several roles are the anti-inflammatory ones (Manju et al., 2012; Nardi et al., 2016).

It is well-recognized that inflammation is a vital survival mechanism and a protective process that has been conserved throughout evolution (Liu et al., 2017). It consists of highly coordinated tissue alterations intended to eliminate the agent causing the cell damage, which may have been an infectious agent, a physical agent (such as radiation, burns, or trauma), a chemical (such as caustic substances), or a product of their metabolism (such as bacteria and toxins) (Fialho et al., 2018; Jang et al., 2016). Inflammation symptoms involved localized redness, pain, swelling, heat, and function loss (Manju et al., 2012).

Anti-inflammatory drugs can change how inflammation is produced, minimizing tissue damage and enhancing patient comfort. Anti-inflammatory agents can be broadly classified into two groups: NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)and glucocorticoids. These are essentially different in how they work. In summary, corticosteroids, which are used to treat autoimmune inflammatory response and asthma among other conditions, and prostaglandins and proteins implicated in inflammatory processes are inhibited by glucocorticoids. On the other hand, non-steroidal drugs are advised for the management of moderate to mild pain and the control of body temperature since they function by blocking the cyclooxygenase enzyme. Among the non-steroidal drugs is acetylsalicylic acid. When it comes to managing inflammation-related pain, both acute and chronic, NSAIDs are the most often prescribed drugs worldwide. NSAIDs encompass a broad range of compounds, all of which function by suppressing COX activity, which is necessary for the manufacture of prostaglandins and thromboxanes (Pereira-leite et al., 2016; Sostres & Lanas, 2016).

There are two different kinds of enzymes, COX-1 and COX-2, that function in different ways and are connected to the effects of NSAIDs. Most cells, including those found in amniotic and embryonic fluid, contain COX-1, which aids in physiological processes like defense and control. On the other hand, inflammation and proinflammatory cytokines activate COX-2 (Golden et al., 2024; Inotai et al., 2010).

II. ANTI-INFLAMMATORY DRUG CLASSIFICATION

2.1.Based on the Categories of NSAIDs

There are four categories into which NSAIDs can be divided: (Pope & Deer, 2017; Süleyman et al., 2007)

a) Selective COX-1 inhibitors
b) Non-selective inhibitor of COX
c) Relatively selective inhibitor of COX-2
d) Highly selective inhibitor of COX-2

2.2.Based on the Chemical Structure of NSAIDs

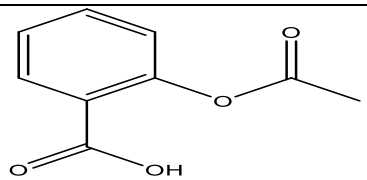
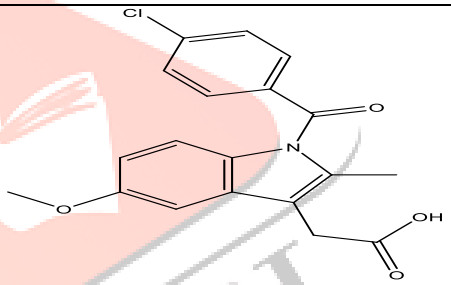
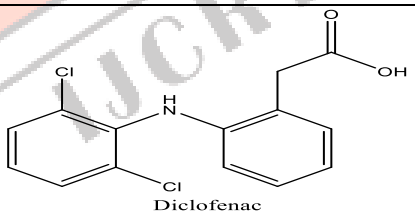
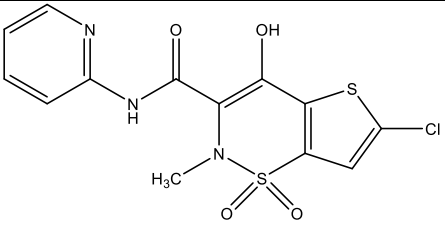
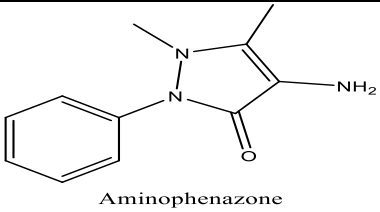
As per their molecular structure, NSAIDs are divided into many families, including anthranilates, oxicams (enol acids), aryl as well as heteroaryl acetic acid derivatives, salicylates, and indole/indene acetic acid derivatives (Kowalski & Makowska, 2015).

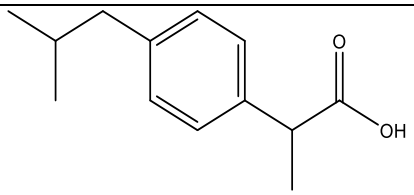
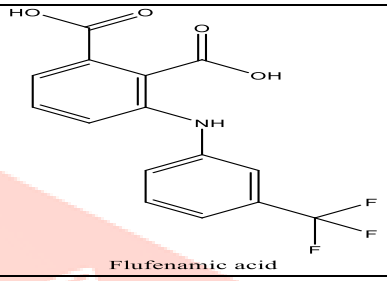
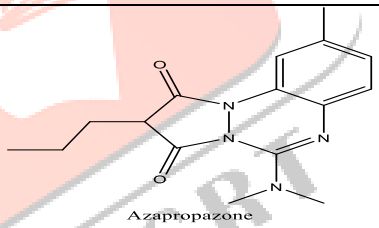
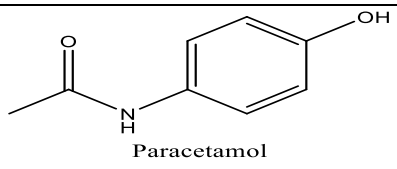
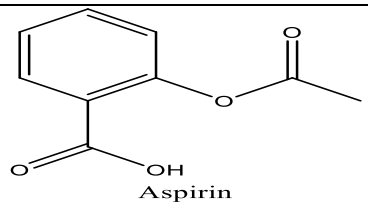
The main structural component of an NSAID is an acidic moiety, such as an enol or carboxylic acid, attached to a planar aromatic functional group. NSAIDs have been first found as salicylates after the salicylic acid had been extracted through the bark of willow. Salicylic acid, or 2-hydroxybenzoic acid, is the source of these compounds. Medical practitioners first employed salicylic acid as sodium salt; however, aspirin, an acetylated derivative, eventually took the role of this molecule in therapeutic applications. Aspirin's “esterification of the phenolic hydroxyl group or diflunisal's insertion of a hydrophobic/lipophilic group at C-5 increased the drug's therapeutic value. Aryl or heteroaryl acetic acid derivatives are a noteworthy class of nonsteroidal anti-inflammatory drugs (NSAIDs) following salicylates. Some of the most popular NSAIDs are fenoprofen, ibuprofen, oxaprozin, and naproxen; these

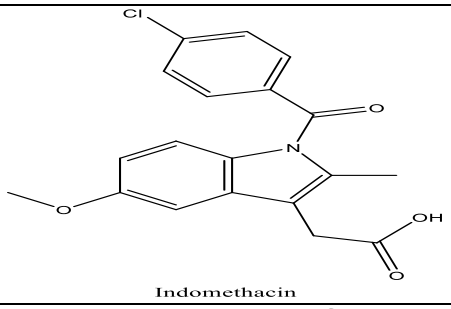
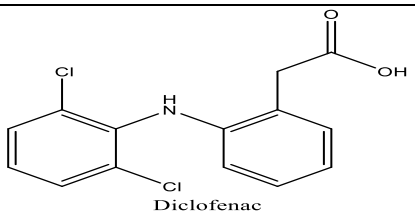
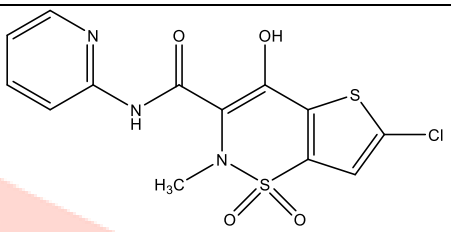
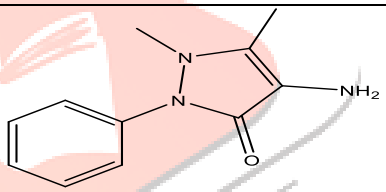
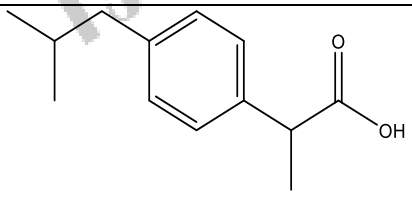
are structural derivatives of aryl as well as heteroaryl acetic acid. Next up in the list of NSAIDs is indole, also known as indene acetic acid", that comprises well-known analgesics like sulindac and indomethacin. Further, anthranilates represent another type of NSAID and are anthranilic acid's N-aryl substituted derivatives.

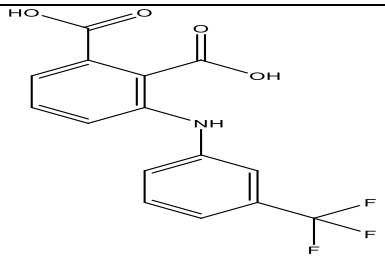
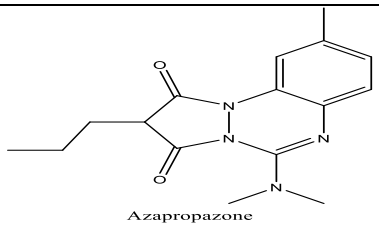
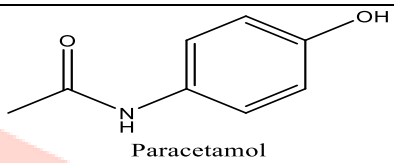
The most popular anthranilate NSAID is diclofenac, a derivative of 2-aryl acetic acid that comes in a variety of forms such as fast-acting sprays, topical ointments, injections, and painkiller pills. Anthranilic acid is also the source of mefenamic and meclofenamic acids. The final structural class of NSAIDs is called oxicams, and it is mostly made up of meloxicam and piroxicam. It is distinguished by the presence of the 4-hydroxy-benzothiazine heterocycle (Montinari et al., 2019). The chemical structure is another way to categorize NSAIDs: (Bindu et al., 2020; Blanca-Lopez et al., 2019; Kowalski et al., 2013) Table 2.2.1.

Table 2.2.1: Classification of NSAIDs Based on Chemical Structure

Chemical Groups	Drugs	Structures
Salicylic acid derivates	Aspirin (Acetylsalicylic acid)	 Aspirin
	Benorilate	
	Diflunisal	
	Etersalate	
	Lysine clonixinate	
	Salicylamide	
	Salsalate	
Indoleacetic acid derivatives	Acemethacin	 Indomethacin
	Difenpiramide	
	Glucamethacin	
	Indomethacin	
	Proglumethacin	
	Oxamethacin	
	Sulindac	
	Tolmetin	
Aryl acetic derivatives	Aceclofenac	 Diclofenac
	Alclofenac	
	Bufexamac	
	Diclofenac	
	Etodolac	
	Fentiazac	
	Ketorolac	
	Lonazolac	
	Zomepirac	
Enolic acids		
Oxicans	Droxicam	 Lornoxicam
	Lornoxicam	
	Meloxicam	
	Oxaprozin	
	Piroxicam	
	Tenoxicam	
Pyrazolones	Aminophenazone	 Aminophenazone
	Feprazone	
	Kebuzone	
	Metamizole (Dipyrone)	
	Mofebutazone	
	Nifenazone	
	Oxyphenbutazone	

	Phenylbutazone	
	Suxinuzone	
Arylpropinoc derivatives	Alminoprofen	 Ibuprofen
	Benoxaprofen	
	Butibufen	
	Dexetoprofen	
	Flunoxaprofen	
	Flurbiprofen	
	Ibuprofen	
	Ibuproxam	
	Indoprofen	
	Ketoprofen	
	Oxaprozin	
	Phenoprofen	
	Phenobufen	
	Pyprophene	
	Suprofen	
	Tiaprofen	
Phenemates	Etofenamate	 Flufenamic acid
	Flufenamic acid	
	Meclofenamic acid	
	Mefenamic acid	
	Niflumic acid	
	Tolipanic acid	
Others		
	Azapropazone	 Azapropazone
	Benzidamine	
	Diacerhein	
	Feprazone	
	Glucosamine	
	Glucosaminoglycan	
	Morniflumato	
	Nimesulide	
	Ordotein	
	Proquazone	
	Tenidap	
Coxibs	4-Aminophenol	 Paracetamol
	Celecoxib	
	Etoricoxib	
	Parecoxib	
	Paracetamol (Acetaminophen)	
	Rofecoxib	
	Valdecoxib	
Chemical Groups	**Drugs**	 Aspirin
Salicylic acid derivates	Aspirin (Acetylsalicylic acid)	
	Benorilate	
	Diflunisal	
	Etersalate	
	Lysine clonixinate	
	Salicylamide	
	Salsalate	
Indoleacetic acid derivatives	Acemethacin	
	Difenpiramide	
	Glucamethacin	

	Indomethacin Proglumethacin Oxamethacin Sulindac Tolmetin	 Indomethacin
Aryl acetic derivatives	Aceclofenac Alclofenac Bufexamac Diclofenac Etodolac Fentiazac Ketorolac Lonazolac Zomepirac	 Diclofenac
Enolic acids		
Oxicans	Droxicam Lornoxicam Meloxicam Oxaprozin Piroxicam Tenoxicam	 Lornoxicam
Pyrazolones	Aminophenazone Feprazone Kebuzone Metamizole (Dipyrone) Mofebutazone Nifenazone Oxyphenbutazone Phenylbutazone Suxinuzone	 Aminophenazone
Arylpropinoc derivatives	Alminoprofen Benoxaprofen Butibufen Dexetoprofen Flunoxaprofen Flurbiprofen Ibuprofen Ibuproxam Indoprofen Ketoprofen Oxaprozin Phenoprofen Phenobufen Pyprophene Suprofen Tiaprofen	 Ibuprofen
Phenemates	Etofenamate Flufenamic acid Meclofenamic acid Mefenamic acid Niflumic acid	

	Tolipanic acid	 Flufenamic acid
Others		
	Azapropazone	 Azapropazone
	Benzidamine	
	Diacerhein	
	Feprazone	
	Glucosamine	
	Glucosaminoglycan	
	Morniflumato	
	Nimesulide	
	Ordotein	
	Proquazone	
	Tenidap	
Coxibs	4-Aminophenol	 Paracetamol
	Celecoxib	
	Etoricoxib	
	Parecoxib	
	Paracetamol (Acetaminophen)	
	Rofecoxib	
	Valdecoxib	

III. MECHANISM OF ACTION

Cell membrane disruption is a prerequisite for inflammation. Consequently, phospholipase A2 facilitates the release of phospholipids from leucocytes and platelets by pro-inflammatory cytokines like interleukin (IL)-1 and TNF-alpha (tumor necrosis factor-alpha). The breakdown of phospholipids by phospholipase A2 results in arachidonic acid, which when broken down, forms prostaglandins, prostacyclins, and thromboxanes by the enzyme cyclooxygenase (COX), and leukotrienes by the enzyme lipoxygenase. During the inflammatory process, COX also referred to as synthetase prostaglandins, initiates the production of prostaglandins from arachidonic acid. Through the process of oxygenation, it changes arachidonic acid into two unstable substances, prostaglandin G2 and prostaglandin H2. These are then converted by isomerases into prostacyclin, thromboxane A2, and prostaglandins D2, E2, and F2 alpha. Because it increases pain sensitivity and has pyrogenic properties, prostaglandin E2 is significant. COX1 and COX2 are the two isoforms of Cox. These enzymes have distinct gene codes even though their protein structures are extremely similar. COX1 is found in nearly every tissue, including kidneys, gut, stomach, blood vessels, and platelets (constitutive). IL-1, IL-2, TNF, and other cytokines, together with growth factors and endotoxins, are present in close proximity to the site of inflammation and serve as mediators that encourage the production of COX2 (also known as inducible COX2). Monocytes, synoviocytes, and macrophages-cells implicated in inflammation are the main ones that express it. Some organs and tissues that have been found to contain COX2 are the kidneys, brain, ovaries, uterus, bones, cartilage, and vascular endothelium. Arachidonic acid also helps to produce leukotrienes by acting as an enzyme that catalyzes the liver. The modes of action of some anti-inflammatory medicines are shown in Fig. 3.1. (Yatoo et al., 2018).

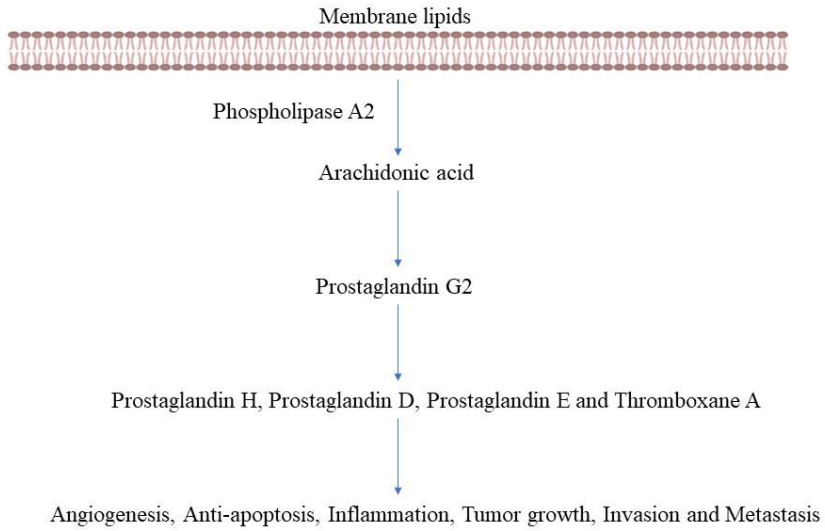


Fig. 3.1: Mechanism of action of anti-inflammatory agent

Alkaloids, resins, essential oils, flavonoids, polysaccharides, cannabinoids, phenolic compounds, steroids, plant glycoproteins, fatty acids, lignans, and other phytoconstituents with scientifically demonstrated anti-inflammatory activity all work against inflammation in different ways. By suppressing one or more enzymes, proteins, factors, or hormones involved in the inflammatory process, they may influence inflammatory pathways or promote anti-inflammatory mechanisms. It is necessary to investigate the precise mechanisms, though. Some plants that reduce inflammation may act through multiple channels or influence multiple organisms.

By blocking the "phospholipase A2 enzyme and preventing the production of AA (Arachidonic Acid) by the membrane phospholipids", phospholipase A2 inhibitors stop the first stage of an inflammatory response. There is potential for phospholipase A2 inhibition in several herbal plants. (Barbosa et al., 2004). Arachidonic acid is not converted to prostaglandins or thromboxane by COX inhibitors. Research has been done on COX inhibitor medicinal plants and their phytoconstituents. (Jachak, 2006). By blocking the synthesis of leukotrienes from arachidonic acid, LOX inhibitors assist (Schneider & Bucar, 2005a). Certain therapeutic plants function as dual inhibitors by inhibiting both COX and LOX (H. P. Kim et al., 1998). Plants that suppress prostaglandin/leukotriene also have anti-inflammatory properties (Boudreau et al., 2017).

One of the few substances that share characteristics with hormones, prostaglandin is involved in several physiological functions, including blood pressure regulation, inflammatory regulation, blood vessel dilation and constriction, and smooth muscle contraction and relaxation. The enzyme arachidonate 5-lipoxygenase in leukocytes oxidizes the essential fatty acids AA and EPA (Eicosapentaenoic Acid), generating leukotrienes, a class of eicosanoid inflammatory mediators. mastocytoma cells, Leukocytes, macrophages, and any other tissues along with cells come together to create these physiologically active molecules in response to both nonimmunological as well as immunological stimuli. Among other biological actions, these compounds have the ability to attract and activate leukocytes, increase vascular permeability, and trigger bronchial smooth muscle contraction. Thus, medicinal herbs have demonstrated anti-prostaglandin and anti-leukotriene properties, and prostaglandin and leukotriene inhibitors decrease inflammation through distinct pathways (Anilkumar et al., 2017).

IV. PHYTOCONSTITUENTS

Phytoconstituents such as alkaloids (Placak, 1953), resins (Seo & Suk, 2007), essential oils (Dordević et al., 2007), polysaccharides (Xie et al., 2008), flavonoids (Kwon et al., 2005), phenolic compounds (Wu et al., 2006), cannabinoids (Formukong et al., 1988), steroids (Ko et al., 2008), fatty acids (Singh et al., 2008), plant glycoproteins, and lignans (L. C. Lin et al., 2006) Are commonly found to exhibit anti-

inflammatory effects. However, many phytoconstituents are believed to have an anti-inflammatory activity like Azadiradione. (Ilango et al., 2013), phenolic compounds, flavonoids, polyphenols (Ojewole, 2005), curcumin (Shoskes et al., 2005), rosmarinic acid (Amaral et al., 2013), gamma linoleic acid (GLA) (Kast, 2001), linear aliphatic alcohols (e.g., octacosanol), phenolic compound (ferulic acid), and GLA, sterols like campesterol as well as beta-sitosterol (Rezapour-Firouzi et al., 2013), harpagoside (Setty & Sigal, 2005), galactolipid (Kharazmi, 2008), carnosic & carnosol acid are phenolic diterpenes (Poeckel et al., 2008), anthocyanins, n-6 polyunsaturated fatty acid (PUFA), gamma-linoleic acid, as well as alpha-linolenic acid.

V. INFLAMMATORY MEDIATORS

5.1.Cytokines

Cytokines are important signalling proteins that play a major part "in the host response against inflammation as well as the system of immune. They belong to the following categories: factors of growth, (IL) interleukins, interferons, chemokines, TNF (tumor necrosis factors), and colony-stimulating factors. They are further divided into pro- and anti-inflammatory cytokines (TNFα), TGFβ, IL-4, IL-10, IL-13, and interferon γ (IFNγ), and pro-inflammatory cytokines (IL-1, IL-6, IL-15, IL-17, IL-23, and TNFα) (Berczi & Szentivanyi, 2003). Each of them, which had several purposes, was created by immune cells as well as stromal cells in response to inflammatory or damaging stimuli. The cytokine class involves the following main inflammatory mediators":

5.1.1. Tumor Necrosis Factor α

TNFα is one of the main cytokines that mediate inflammation. It affects many kinds of cells, like endothelial cells, inflammatory cells, and fibroblasts. (Berczi & Szentivanyi, 2003). T cells and macrophages are activated by various inflammatory stimuli, which results in their subsequent secretion of TNFα. Through a positive feedback loop, the released TNFα stimulates the release of further TNFα and other cytokines, including IL-8. (Balkwill, 2006). Conversely, an uncontrolled or persistent synthesis of TNFα may facilitate several pathologies, such as cancer, autoimmune diseases, and chronic inflammatory diseases, by the extra-inflammatory mediators as well as protease secretion which (Aggarwal et al., 2006), depending on the downstream signalling promoters, can also directly damage DNA and have either an apoptotic or anti-apoptotic function (Balkwill & Mantovani, 2010). Increased blood and intestinal mucosal levels of TNFα have been found in patients who have been suffering from Crohn's disease, ulcerative colitis, and inflammatory bowel disease (IBD) (Danese, 2011).

Two receptors play an essential part in the mediated effects of TNF: TNFRI, which exists in most body cells, and "TNFRII, primarily expressed in the hematopoietic cells. Upon activation, TNF receptors bind their intracellular adaptor proteins and initiate many signalling cascades. The TNFRI activation increases the FAS-associated signal through death domain (FAS-associated death domain FADD)/caspase3/caspase8, mitogen-activated kinase (MAPK), receptor-interacting protein (RIP) 3, Jun Kinase (JNK)/activation protein-1 (AP-1), and IκB kinase (IKK)-NF-κB pathways. Through the JNK/AP-1, MAPK, and NF-κB pathways, the gene expression of IL-1, IL-6, COX-2, chemokines, MMP, and adhesion molecules is stimulated. Since FADD/caspase3/caspase8 can trigger apoptosis and the activation of receptor-interacting protein (RIP), it can lead to necrosis. On the other hand, TNFRII activation triggers the transcription factors NF-κB or AP-1", which subsequently trigger a range of growth factors and mediators of inflammation. This cascade results in the activation of negative apoptosis regulators, including superoxide dismutase, c-FLIP ("c-FLICE-like inhibitory protein"), and Bcl-2 ("B-cell lymphoma 2") (Kuraishy et al., 2011).

5.1.2. Interleukins

Interleukins are a significant subclass of cytokines that are critical for immunological control. Among them, IL-1 plays a part in the production of ROS as well as reactive oxygen molecules (RNS) by phagocyte infiltrates at the time of the inflammatory states or cancers, and also the inflammatory molecules synthesis such integrins, MMPs, and chemokines. (Apte et al., 2006). There are two agonist versions and IL-1β, IL-

1α, and one antagonist form known as IL-1 receptor antagonist (IL-1Ra) (Arena et al., 1998). IL-1α is found in the cytosol or cell membrane and is involved in the intracellular environment. The enzyme known as interleukin-1β-converting enzyme (ICE) transforms IL-1β into its active form before its extracellular secretion. IKKβ kinase is triggered upon IL-1 & IL-6 binding to their respective receptors, resulting in the IkBα degradation. Following this, proteins are released into the nucleus, where they aid in the gene's transcription by acting either alone or in concert with proteins of STAT. Phosphorylated STAT binds to p65 to stimulate histone acetyltransferase p300, which functions secondary and maintains p65 active in the nucleus. IL-1 contributes to the formation of RNS & ROS as well as inflammatory mediators such integrins, MMPs, and chemokines when phagocyte infiltrates are transformed under inflammatory or malignant situations (Apte et al., 2006).

Another important molecule during acute inflammation is IL-6, and many inflammatory disorders are caused by unchecked synthesis of this molecule. (Balkwill & Mantovani, 2010). At the location of inflammation, T cells, macrophages, and monocytes are the main producers of substances linked to inflammation. NF-κB and AP-1 are two transcription factors that are necessary for the synthesis and release of IL-6 in the interim. gp130 chains dimerize and associated Janus kinases (JAKs) are activated when IL-6 interacts with its receptor, IL-6R. Further phosphorylation of gp130 by JAKs results in the recruitment and activation of several other molecules (SHP2, phosphoinositide-3-kinase PI3K, and Ras-MAPK) as well as the transcription factors STAT3 and STAT1 (Heinrich et al., 2003).

5.2.Chemokines

Chemokines and chemoattractant cytokines control the actions of several biological molecules, mediating tasks like invasion of cells, survival, motility, and interactions by the extracellular matrix at the time of the inflammatory & immunological reactions. More than fifty chemokines and at least 18 human chemokine receptors have been found thus far (Locati & Murphy, 1999). G-proteins have 7 transmembrane domains that are connected to receptors of chemokine. TNFα, hypoxia, IL-1β, and steroidal hormones (androgens, estrogens) control the production of IL8, a key chemokine that promotes inflammation. IL-8 exhibits a strong affinity for its widely distributed receptors. Through the PI3K pathway as well as the downstream signaling with the AKT, IL-8 regulates cell death along with proliferation while promoting chemotaxis. AKT phosphorylates the pro-apoptotic protein BAD and stops it from associating with the anti-apoptotic protein Bcl-xl (A. Li et al., 2003). AKT also results in the IκB degradation, the NF-κB inhibitor, and IKK activation (X. Li et al., 2015). Furthermore, IL-8 activates the Raf-1/MAP/ERK kinase 1/ERK cascade (Profita et al., 2008).

5.2.1. Transforming growth factor β

TGFβ is a regulatory cytokine included in the control of inflammation. (Yang et al., 2010). Different activators cleave TGFβ from its precursor to activate the dimer. Paired with its receptors, type I & II, which are serine/threonine kinases, activate TGFβ dimer signals. When type II receptors are paired with type I receptors, the type II receptors phosphorylated the type I receptors, and the Smad transcription factors were phosphorylated downstream to transmit the signal further. Transcriptional coactivators along with the suppressors which could simultaneously activate or inhibit 100s of target genes are drawn in by the activation of Smad complexes. (Wotton & Massague, 2000). Moreover, TGFβ functions as a cytostatic regulator through the inhibition of kinase inhibitors p15 & p21 and the suppression of c-Myc, a crucial transcriptional inducer of cell division & growth (Seoane et al., 2001).

5.3.Transcription Factors

One essential role of transcription factors is to control the pro-inflammatory mediator's expression at the time of the inflammation. Examples of these transcription factors are STAT1/STAT3, NF-κB, Nrf2, HIFs, and AP-1 (Gilmore, 2006).

5.3.1. NF- κB

NF-κB is among the well-known heterodimeric transcription factors. The two main subunits of this protein are p50 and p65; together, they are termed the NF-κB/Rel complex. Inhibitory-κB, also known as IκB, is an inactive compound form that does not change cytoplasmically. (Gilmore, 2006). NF-κB could be activated by pro-inflammatory stimuli including viruses, cytokines, or lipopolysaccharides (LPS) through the phosphorylation and degradation of IkBα. As a result, NF-κB translocates as well as binds to the nucleus genes promoter regions that encode pro-inflammatory mediators like cytokines, iNOS, and COX-2. (Wu et al., 2014). It has been discovered that NF-κB is actively involved in chronic inflammatory disorders such as Crohn's disease, inflammatory lung diseases, IBD (Inflammatory Bowel Disease), and diseases of the kidney. Additionally, it contributes to the transcriptional regulation of over 150 genes. (Pahl, 1999). The genes targeted include those that are involved in the regulation of inflammation (TNF-α, IL-6, IL-8, COX-2), cell proliferation inducers (cyclin D1, c-MYC), invasion as well as metastasis effectors (adhesion molecules, MMPs [Matrix Metalloproteinases]), DNA damage promoters (ROS, RNS), anti-apoptotic proteins (BCL-2), and angiogenic factors (angiopoietin, VEGF) (Brivanlou & Darnell, 2002).

Pro-inflammatory substances (TNF-α, IL-1), viruses, growth factors, oncogenes in the cells of the tumour, the toll-like receptor (TLR)-MyD88 complex, stress of genotoxic, and hypoxia all activate the NF-κB signal transduction pathway. (Brivanlou & Darnell, 2002).

5.3.2. STATs

Tyrosine residue phosphorylation in response to specific stimuli activates redox-sensitive transcription factors or STATs. [66] STATs participate in downstream signalling that is triggered by cytokines like the “IL-6 family, IL-23, IL-21, PDGF, VEGF, and EGF. Of these, STAT activation is mostly caused by cytokine receptors. JAK family tyrosine kinases phosphorylate STAT to start signalling downstream. Phosphotyrosine-SH2 interactions result in the phosphorylation of STAT tyrosine residues, which stabilizes the Src-homology 2 (SH2) domain. The next step is the creation of STAT dimers, which translocate and attach to the nucleus' promoter regions of genes encoding” regulatory proteins for proliferation of cell and inflammatory modulators. Both maintaining NF-κB activation and ensuring that it remains in the nucleus require STAT3. Additionally, the p300 histone acetylase is brought into the nucleus by STAT3 and engages in interaction with the NF-κB RelA/p65 subunit. These interactions have been required for the acetylation of RelA as well as the transcription of genes that are dependent on STAT3. By enhancing NF-κB's nuclear retention along with activity in the nucleus, these actions extend the protein transcriptional activity (Yu et al., 2009).

5.3.3. Hypoxia-inducible factor (HIF)

The regulation of alterations in metabolism, function, and vascular function in response to the hypoxia is largely dependent on hypoxia-inducible factors, or HIFs (Semenza, 2011). In the interim, they play an essential part in regulating the metabolism & operation of diverse immune cells. (Palazon et al., 2014). It possesses HIF-α isoforms, HIF1α or HIF-2α and HIF-1β, and is composed of a heterodimeric complex. All types of immune cells, including neutrophils, dendritic cells, lymphocytes, and macrophages, are known to express HIF-1α, which is broadly expressed. Prolyl hydroxylases (PHDs), iron-dependent enzymes that hydroxylate HIF-α and increase its stability, are responsible for controlling HIF-α in the presence of plentiful oxygen. PHDs become dormant during hypoxic conditions, which causes HIF-α to build up and exacerbate inflammation. In addition to hypoxia, any stimulus that increases NF-κB activity can also stimulate HIF-1α expression, which in turn triggers the transcription of HIF-1α mRNA (Rius et al., 2008).

5.4.Complement Activation Pathways

Immune cells recognize a variety of chemicals found in foreign bodies and pathogens “called pathogen-associated molecular patterns, or PAMPs. The complement system is triggered when PAMPs are recognized by PRRs (Pattern Recognition Receptors), which include Toll-like receptors (TLRs),

mannose receptors, and nucleotide-binding oligomerization domain-like receptors expressed on innate immunity cells (Wills-Karp, 2007). Through three distinct pathways—the lectin, alternative, and classical pathways—C3 convertase activates central component C3 as a result of the complement system. The first stage in the traditional method is the immune complexes creation, which have been produced by antibodies known as IgG or IgM, which adhere to infections or other foreign substances. The steps involved in the development of the C3 convertase enzyme activate C3, which in turn causes the manufacture of C3b (opsonization molecule), C5b, C6b, C7, C8, and C9, and C3a, C4a, and C5a. The second mechanism that binds to foreign compounds and recognition by the PRRs triggers the lectin pathway by H-, M-, L-ficolin, or MBL. MBL-associated serine protease 1 (MASP1), MAP19, MASP3, MASP2, and these PRRs work together to perform their functions. As with the conventional process, pathogen contact with the MBL-MASP complex triggers the hydrolysis of C2 and C4 along with the activation of C3 convertase. Conversely, pathogenic proteins, lipids, and carbohydrates activate the alternative pathway by binding to and being detected by receptors. This interaction causes C3 to be cleaved and interacts with the complement factors B & D, which in turn activates C3 convertase (Wagner & Frank, 2010).

Robust inflammatory proteins, C3a, C4a, and C5a exhibit diverse actions on a range of cells, including chemoattractant, oxidative burst-inducing, generating pro-inflammatory cytokines, histamine release, and other activities. The way that G protein-coupled receptors (GPCRs), namely C3aR (the C3a receptor), C5aR (the C5a receptor), and C5L2 (the C5a receptor-like 2), are bound by C3a and C5a allows them to operate. Among the most numerous receptor families are GPCRs, which control extracellular signals related to a wide range of physiological processes. GPCR conformationally changes when it binds to complement, resulting in the displacement of GDP by GTP and the dissociation of the Gα subunit from the Gβγ. As a result, the signalling pathway proceeds downstream by facilitating interactions between numerous effector molecules and free subunits. (Pundir & Kulka, 2010). Numerous reactions, such as the migration of inflammatory cells and the inflammatory mediators production, are brought on by the binding of C5a and C3a to C5aR and C3aR, correspondingly. Phospholipase C (PLC)β as well as PLCγ are triggered when phosphoinositol-3-kinase (PI3K) is activated by C3a binding to the C3aR. This promotes the synthesis of diacylglycerol (DAG) as well as inositol triphosphate (IP3), which in turn triggers the activation of phosphokinase C (PKC) and cascade of calcium ions. Moreover, PI3K drives the MEK/ERK cascade, which increases the synthesis of many chemokines and inflammatory cytokines. MAPK stands for mitogen-activated protein kinase. PLCβ, phospholipase D (PLD), PI3K-γ, and downstream signaling are involved in C5aR-associated Gαi subunit signaling (Rabiet et al., 2007). Additionally, by postponing neutrophil death, C5aR lengthens the inflammatory response. This activity activates the transcription factor cAMP response element-binding protein, or CREB. (Perianayagam et al., 2004). Furthermore, C5a activates PAK, which is essential for the growth of many MAPK signalling pathways and the NF-κB consequent activation. Otherwise, C5a stimulates neutrophils, which sets off the ERK cascade and phosphorylates STAT3 (Kuroki & O'Flaherty, 1999).

5.5.Eicosanoids

When arachidonic acid or other PUFAs are oxidised, eicosanoids—bioactive signalling molecules having a localised effect—are also formed. This process results in thromboxane, prostaglandins, endocannabinoids, iso-eicosanoids, and leukotrienes (Khanapure et al., 2007). Because they are strong inhibitors of cyclooxygenase enzymes, eicosanoids play an essential part in regulating various physiological processes, particularly during the immune response. The fact that NSAIDs, or non-steroidal anti-inflammatory medicines, are frequently used to treat inflammatory illnesses serves as evidence of this. Phospholipase A2 (PLA2) is the first enzyme that is activated to initiate the formation of eicosanoid. Following its release from membrane phospholipids, LOX, COX, and cytochrome p450 enzymes break down arachidonic acid (AA) (D'Cruz, 2001). The two isoforms of cyclooxygenases that are most common are COX-1 & COX-2. There is proof that COX-2 contributes to inflammation. The products of COX's metabolism of arachidonic acid are thromboxane, prostacyclin, and prostaglandins. LOX exists in multiple forms, including 5-LOX, 12-LOX, and 15-LOX, and in 2 isoforms, 15-LOX 1 and 15-LOX 2. The huge collection of physiologically active moieties is produced at the time of the biosynthesis of AA and related compounds, and it serves as the starting point for numerous signalling domains within cells via their

corresponding receptors. The huge collection of physiologically active moieties is produced during the biosynthesis of AA and related compounds, and it serves as the starting point for numerous signalling domains within cells via their corresponding receptors (Khanapure et al., 2007).

The manifestation of pain, heat, swelling, redness, inflammation, and function loss is caused by the combination of COX-induced signalling pathways. The breakdown of COX results in the production of prostaglandin H2 (PGH2). Following this PGH2's downstream conversion by several isomerases, prostanoids—also known as thromboxane A2 (TXA2)—are detected in the vascular system, central nervous system, smooth muscle, vascular endothelium, gastric mucosa, and platelets. (Dennis & Norris, 2015). Pain associated with inflammation is brought on by prostaglandin E2 (PGE2) binding to GPCR receptors and activating EP receptors in neurons. When EP receptors link to leukocytes, it could raise the creation of IL-10 & decrease TNF, resulting in a net decrease in inflammatory signals. (Shinomiya et al., 2001). PGE2 and thromboxane A2 predominate during inflammatory reactions. COX/PGE2 functions by way of the RasMAPK/ERK pathway. Furthermore, PGE2 has been demonstrated to stimulate the signalling pathways for EGFR, PI3/AKT, ERK, and cAMP/protein kinase A (Dennis & Norris, 2015).

5.6.ROS AND RNS

The molecules known as reactive oxygen species (ROS), which have been formed when partial reduction of oxygen takes place, are commonly seen in biological systems. Hypochlorous acid (HOCl), superoxide (O2 •-), diatomic oxygen (O2), peroxide ion (O2 2-), hydroxyl radical (•OH), and H_2O_2 are a few examples of ROS (Halliwell, 1991). Under typical circumstances, the formation of ROS is balanced out by antioxidant defence mechanisms such as glutathione peroxidase, superoxide dismutase, catalase, peroxiredoxins, and thioredoxin (Halliwell, 1996). However, when ROS formation exceeds the cell's capacity to function as an antioxidant, shear oxidative stress occurs, damaging lipids, proteins, and DNA. To modulate adaptive immune responses to inflammatory stimuli, oxidative stress is essential. One of the main roles of the enzyme family NADPH oxidase (NOX), which has seven isoforms, is to produce ROS in both phagocytic and non-phagocytic cells. The process of producing reactive oxygen species (ROS) involves several steps. Firstly, oxygen is reduced to superoxide in the presence of NADPH. Ultimately, superoxide is converted to hydrogen peroxide. According to some research, ROS formation during acute and chronic inflammation may primarily originate from members of the NOX family (Block & Gorin, 2012). NOX is involved in both the production of ROS and the host's defence against various harmful stimuli (Knight et al., 2010). The NOX family member Duox2 has been shown to have significantly elevated expression in IBD patients. (Lipinski et al., 2009) Growth factors and cytokines are two examples of the many inflammatory mediators that control the production of NOX isoforms. INF-γ, STAT1, GATA, IRF1, and NF-κB are transcription factors that contribute to the upregulation of NOX family member expression. The NOX1-Rac1 pathway is activated at regions of DNA damage and inflammation when NOX expression is upregulated (Woolley et al., 2013). NOX-generated ROS also causes various additional kinases, as well as inactivate protein tyrosine phosphatases, increase “growth factor-mediated tyrosine autophosphorylation, and induce receptor tyrosine kinases. An additional clue to NOX-mediated DNA damage as well as senescence is the genomic instability of the Ras oncogene, which is triggered by ROS. The signalling processes and the types of impacts that ROS create, like activation & inhibition of gene expression, remain” largely unexplored despite a wealth of studies on the topic. As active players in the innate and immune systems, ROS and RNS can influence various stages of these reactions (Kodama et al., 2013).

RNS, such as peroxynitrite, nitrogen dioxide, and other forms, are created when NO interacts with other ROS. NO• is a cellular or intracellular signalling chemical that is produced by activating NO synthases. Two NOS isoforms found in neuronal cell types are nNOS and eNOS3, which are found in endothelial cell types, respectively. The activation of these enzymes is mostly dependent on intracellular Ca2+ rises. (Gaston et al., 1994). The inflammatory immune system's cells contain the third isoform, iNOS, which is mostly generated under inflammatory circumstances. (Alderton et al., 2001). By nitrating or oxidizing different cellular moieties, RNS can change the physiology of cells. One important mechanism of RNS-mediated protein regulation is tyrosine residue nitration, which may be harmful in inflammatory disorders. (Radi, 2004).

VI. NATURAL PRODUCTS MOLECULAR TARGETS IN INFLAMMATION

6.1.Transcription Activators

Proteins referred to as transcription activators, or factors, bind to certain DNA sequences to control the genetic information transcription from the "DNA to mRNA. Transcription factors are proteins that can work alone or in combination with other proteins to either promote or hinder the RNA polymerase recruitment to certain genes. The aberrant expression of these molecules could cause a variety of characteristics of cancer, involving raised proliferation, decreased apoptosis, inflammation, conversion of malignant, metastasis, invasion" of tissue, and angiogenesis. Over the last few decades, a great deal of transcription factors have been discovered, and many of them are connected to inflammatory and cancerous processes. (Aggarwal & Shishodia, 2006; Grivennikov et al., 2010).

6.2.Nuclear Factor-Kappa B

Nearly every type of mammalian cell contains a protein complex known as NF-κB. It is a crucial regulator of the way cells react to several stimuli since it belongs to the family of "rapid-acting" primary factors of transcription, which are factors of transcription present in dormant cells that could be activated without the need for new protein synthesis. It is known that several factors can activate NF-κB, including reactive oxygen species, inflammatory agents like TNFα and "IL-1β, bacterial endotoxins, chemical toxins and carcinogens, X-rays, and UV light. NF-κB complex activation happens when signal-induced degradation of IκB proteins takes place. This is primarily due to the activation of an IKK kinase. Following the IκB degradation, the NF-κB complex relocates from the cytoplasm to the nucleus, where it ultimately stimulates the transcription of the rising number of the target genes. Some of these genes are Bcl-XL & Bcl-2, which decrease apoptosis; COX-2, 5-LOX, iNOS, TNF-α, NADPH oxidase [NOX], and others"; c-myc, cyclin D1, and others; and VEGF, vascular endothelial growth factor, which promotes inflammation and angiogenesis (Singh & Aggarwal, 1995).

6.3.Activator Protein-1

Members of the DNA-binding protein families Fos and Jun make up the transcriptional regulator known as activator protein-1 (AP-1). Different stimuli, like as growth factors, cytokines, UV radiation, and bacterial and viral infections, can all affect how AP-1 controls the expression of certain genes. Increased innate immune response, cell transformation, proliferation, and inflammation are all associated with AP-1 activation. AP-1 appears to stimulate the proliferation of cells by inhibiting suppressor genes like p16, p53, and p21cip1/waf1 and increasing cyclin D1 (Eferl & Wagner, 2003).

The following proinflammatory cytokines are regulated by AP-1/NFAT: TNFβ, TNFα, IFNγ, Fas ligand (FasL), granulocyte-macrophage colony-stimulating factor (GM-CSF), and CD40 ligand (CD40L). Consequently, the inflammatory process is greatly aided by AP-1 overexpression. (Zenz et al., 2008).

6.4.Tumor Necrosis Factor

TNF, which was first identified by Kolb & Granger in 1968, is a crucial inflammatory cytokine that is mostly formed by monocytes and activated macrophages (Kolb & Granger, 1968). TNF's main function is to control the many types of immune cells. Heat, edema, redness, discomfort, and function loss are the hallmarks of inflammation that arise from a localized increase in TNF in tissues. Many human disorders, like as cancer and inflammatory bowel disease, have been linked to TNF dysregulation. The primary mechanism by which TNF induces the expression of proinflammatory genes is through its capacity to activate NF-κB in many cell types. (Brynskov et al., 2002; Locksley et al., 2001).

6.5.Cyclooxygenase-2

Arachidonic acid (AA) is converted by the enzyme cyclooxygenase (COX), also known as prostaglandin H synthase, producing the prostanoids prostaglandins, prostacyclin, and thromboxane. (Marnett & Kalgutkar, 1999). Increased cell division, inflammation, angiogenesis, and decreased apoptosis can all be consequences of excessive prostanoid synthesis. There are 2 primary isoforms of the COX: COX-1 & COX-2. The majority of normal tissues do not have COX-2, although the majority of mammalian cells do contain COX-1, an enzyme that is constitutively present. Activated macrophages and other cells in inflammatory areas are rich in COX-2, which is also triggered in tissues by proinflammatory cytokines like TNF, growth hormones, and a variety of toxins and carcinogens. Several transcription factors, involving NF-κB, AP-1, and STAT-3, can activate COX-2 transcription, depending on the inducer and type of cell. Furthermore, several studies have shown that combinations of naturally occurring substances can inhibit the expression of COX-2. (E. J. Kim et al., 2008; Subbaramaiah & Dannenberg, 2003).

6.6.Lipoxygenase

The essential enzymes for converting AA into physiologically active leukotrienes are lipoxygenases (LOX). LOX comes in three different varieties: 5-LOX, 12-LOX, and 15-LOX. Numerous research points to a connection between 5-LOX and the emergence of cancer in both humans and animals. Since COX-2 and 5-LOX, two of the AA-metabolizing enzymes, are frequently overexpressed in tumours, inhibiting both enzymes at the same time is thought to be a viable treatment strategy for inflammatory illnesses, including cancer. Dual 5-LOX/COX inhibitors and 5-LOX inhibitors are abundant in the plant kingdom. It's noteworthy that naturally occurring inhibitors of 5-LOX frequently work well to lower COX expression levels. A number of the more well-known inhibitors were identified, including β-sitosterol, silibinin, rosmarinic acid, luteolin, EGCG, ferulic acid, gingerol, and linoleic, oleic, and palmitic acids (Schneider & Bucar, 2005b).

6.7.Inducible Nitric Oxide Synthase

Lithium arginine is converted to nitric oxide (NO) by three enzymes belonging to the nitric oxide synthases family. Not only does NO play a crucial role in cellular signalling, but it is also a cytotoxic or innate immune response molecule. (Kröncke et al., 1998). The temporary (seconds to minutes) periods of NO production occur once “constitutively expressed endothelial NO synthase (eNOS) or neuronal NO synthase (nNOS) is activated. On the other hand, NO is produced for much longer periods (hours to days) by inducible NO synthase, or iNOS, which is only expressed during cell activity. The main inducers of interferon-α (iNOS) in various kinds of cells are lipopolysaccharides (LPS) and proinflammatory cytokines such as TNF-α, IL-1β, and IFN-γ. (Bogdan, 2001). Furthermore, iNOS expression is partially determined by activation of the NF-κB signalling pathway and the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway. (Kleinert et al., 1998)”.

By downregulating NF-κB, resveratrol was reported to suppress the production of iNOS in C6 glioma cells treated with beta-amyloid (Tsai et al., 1999). It has also been demonstrated that a variety of combinations of naturally occurring substances, typically in conjunction with COX-2, are efficient at downregulating the expression of iNOS. (O. K. Kim et al., 1998).

6.8.Proinflammatory Cytokines

Apart from the stroma that envelops cancer cells, the tumour microenvironment comprises both the adaptive and innate immune cells, involving T & B lymphocytes, as well as myeloid-derived suppressor cells, mast cells, neutrophils, macrophages, dendritic cells, and natural killer cells. These cells can communicate indirectly & directly through the formation of cytokines & chemokines that both autocrine and paracrine control the growth of tumours. The two immune cells that are most common in the tumour microenvironment are T lymphocytes and tumour-associated macrophages (TAMs). TAMs are crucial for

angiogenesis, invasion, and metastasis, and they promote tumour growth, making them one of the most important components of inflammation and cancer. (Condeelis & Pollard, 2006).

TAMs can also be classified as M1 or M2 types, just like Th1 and Th2 T cells. TNF-α, IL-1β, IL-6, IL-12, and IL-23 are examples of proinflammatory cytokines that are significantly expressed by M1 macrophages when they are activated by several stimuli, like LPS and IFNγ. IL-4, IL-10, and IL-13, on the other hand, stimulate M2 macrophages, resulting in an upregulation of IL-12 production and an upregulation of IL-10, an anti-inflammatory cytokine. M1 cytokines (TNF-α, IL-1β, IL-6, IL-12, or IL-23) encourage the growth of tumors, whereas the M2 cytokine IL-10 suppresses tumor growth (W.-W. Lin & Karin, 2007).

VII. TREATMENT OF INFLAMMATION BY NATURAL PRODUCTS

7.1.Joint inflammation

Joint inflammation manifests as joint pain, stiffness, swollen joints, and loss of joint functions. Rheumatoid arthritis (R.A.) is a complex immune system and system condition that causes chronic inflammation of the synovial joints, which can cause severe disability. According to reports, the primary healing symptom of R.A. is a painful inflammation of the cartilage and joints (Nemudzivhadi & Masoko, 2014; Vaou et al., 2021). The effectiveness of medicinal plants in treating joint inflammation is determined by extraction techniques and phytochemical mechanisms of action (Murugananthan & Mohan, 2013). Studies conducted in vitro revealed that phytochemicals prevent the synthesis of leukotrienes by inhibiting LOX-5, NF-κB activation, and the production of pro-inflammatory cytokines that lead to joint damage and swelling (Dragos et al., 2017; Singh et al., 2020). It was shown that oxyacanthine and berberine, which were separated from the root extract of B. vulgaris, reduced chronic joint inflammation. Angiogenesis regulation was demonstrated by Sinomenine, the stem portion of S. acutum isolate. Flavone aglycones, alkaloids, gallic tannins, and saponins from the bark portion of F. sycomorus showed a decrease in skeletal muscular contraction. Several medicinal plants and their isolates have been studied in vitro to alleviate inflammation in the joints (Wambugu et al., 2011; Xia et al., 2020).

7.2.Cardiovascular inflammation

There have been reports of several medicinal plants having some verified anti-inflammatory properties linked to heart conditions. The phytochemicals flavonoids, terpenoids, saponins, and polysaccharides are the most effective and have been shown to have possible protective effects on the heart and blood vessels. Factors that enhance endothelial function, activate enzymes that play a major role in the development of atherosclerosis and boost transcriptional messengers are linked to cardiovascular inflammations (Maione et al., 2016; Shaito et al., 2020). It has been claimed that the phytochemical components found in the aqueous extract of G. biloba leaves, including quercetin, ferulic acid, allicin, ginsenosides, myricetin, and kaempferol, inhibit the angiotensin-converting enzyme and reduce the inflammatory effects on the cardiovascular system (Liperoti et al., 2017). The diterpene chinone found in S. miltiorrhiza's rhizome demonstrated the ability to regulate cardiovascular inflammation by preventing the activation of the NF-κB and MAPK pathways (Z. Li et al., 2018). It has been observed that the essential oil components linalool, eugenol, and α-berga matone from O. basilium leaves may decrease the release of pro-inflammatory cytokines (Arranz et al., 2015).

7.3.Gastrointestinal inflammation

Cellular fatigue may lead to inflammatory consequences in the gastrointestinal tract. It has been demonstrated that phytochemicals extracted from medicinal plants have anti-inflammatory properties, either directly or indirectly. For example, quercetin glycoside and polyphenols are the cause of the documented antibacterial activity, which indirectly lowers inflammation in the gastrointestinal tract (Bunte et al., 2019; Xu et al., 2020). It was observed that coumarins, polyphenols, and quercetin glycoside, which were separated from the root and leaf extracts of A. sylvestris and V. vinifera, respectively, inhibited the generation of inflammatory mediators called IL-8 (Sangiovanni et al., 2015; Vogl et al., 2013). Through lowering myeloperoxidase activity, 1,8-cineole's anti-inflammatory properties were shown to be effective in treating gastrointestinal inflammation (Sá et al., 2014).

7.4.Lung inflammation

Lung inflammation symptoms and signals are linked to the release of many inflammatory mediators, including histamine, TNF, leukotrienes, nitric oxides, and interleukins (Santana et al., 2016). Some of the ways that phytochemicals work to treat lung inflammation include inhibiting heme-oxygenase, lowering pro-inflammatory cytokines, and reducing cyclooxygenase production(Perera et al., 2016). One possible source of medications to treat lung inflammation is natural compounds made from medicinal plants (Ram et al., 2011). Lung inflammation is inhibited by flavonoids and their derivatives (H. P. Kim et al., 2017). It has been observed that certain phytochemicals, including flavonoids, lactiflorin, iri doids, paeoniflorin, and albiflorin, may decrease the production of pro-inflammatory cytokines (Santana et al., 2016).

7.5.Skin inflammation

Numerous studies have demonstrated the ability of pure components and crude extracts of medicinal plants to cure various skin irritation problems. It has also been noted that essential oils extracted from therapeutic herbs are a significant source of anti-inflammatory compounds (Dawid-Pać, 2013). Prostaglandin and leukotriene synthesis were reported to be inhibited by α-Bisabolol, matricin, luteolin apigenin, and apigenin-7-glucoside, the primary chemical constituent of the aqueous extract of the flower section of M. recutita. Skin inflammation is caused by vascular endothelial growth factor (VGEF) and the chemokine interleukin-8 (IL-8), which are induced by TNF alpha-activating epidermal cells. One possible chemical component found in C. viticella and C. longa extracts is curcumin, which has been utilized to modulate human skin disruption and has been shown to reduce the release of NO and TNF α (Kırmızıbekmez et al., 2019; Wedler et al., 2014).

7.6.Liver inflammation

One of the most frequent causes of liver damage or dysfunction is inflammation illness. As studies on medicinal plants progress, it is evident that using extracts and pure chemicals to treat liver illnesses is very successful in blocking, inhibiting, or reducing the signal pathways that cause the liver's inflammatory factors (X. Li et al., 2019). Liver stress was significantly reduced by some flavonoids that were extracted from the aerial section of B. vulgaris using methanol (Asadi-Samani et al., 2015). It has been reported that a geniposide molecule that was extracted from G. jasminoides fruit inhibits liver fibrosis and suppresses CYP2E1 expression (Zhang et al., 2021).

VIII. AI APPLICATIONS IN NATURAL PRODUCTS

Advances in computational omics technology offer a wide range of uses in medication research, including the development of hidden natural product variants. Simultaneously, exciting developments in AI methods such as machine learning have been made in computational drug design, which makes it simpler to forecast biological action and develop novel medications for target molecular targets (Romano & Tatonetti, 2019).

AI has affected computer-aided drug development. The growing use of machine learning, particularly deep learning models, in a variety of scientific fields as well as improvements in computer hardware and software further aid in this evolution. Early worries that pharmaceutical discoveries will supplant AI have improved medicinal chemistry (Jiménez-Luna et al., 2021).

Naturally occurring chemicals made by bacteria, plants, animals, fungus, and other creatures are a rich resource for modern medicine development. Because of their structural diversity and biological significance, natural products are desirable beginning points for the creation of novel medications. In the process of developing drugs based on natural products, computational methods can be a useful supplement or prelude to in vitro testing (Chen et al., 2017).

The pharmaceutical industry has made significant strides in machine learning algorithms, and various supervised and unsupervised learning techniques are applied at various phases of the drug discovery process. Clustering techniques have been utilized in de novo molecular design, protein target drug-ability prediction, and cell-type picture segmentation. Potential Huntington's disease targets were found using supervised learning approaches such as regressions and classifications. They postulated biological

activities and the properties of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) for the purpose of drug creation and numerous other applications (Vamathevan et al., 2019).

Natural product research, a reliable source of modern small molecule drug discovery, has progressively included machine learning and artificial intelligence (AI) computational approaches. For example, the NP chemical space was mapped and organic molecules were digitized primarily in the early 2000s using dimensionality reduction techniques (principal component analysis, self-organizing maps). The next decade saw the development of machine learning binary classifiers to predict their biological roles. The use of neural network topologies for genome mining and molecular design has recently increased (Ernst et al., 2015).

Modeling and predicting the characteristics and bioactivities of nanoparticles (NPs) or any chemical structure requires converting them into computer-readable format or formats, or so-called molecular representations. Chemical information is often encoded with a specific purpose in most formats. Chemical compounds with similar names can be obtained by utilizing both their original IUPAC and generic names. Matching chemical structures with their bi-dimensional molecular graph descriptions was the computational effort. In order to facilitate effective structural searches or to lightweight maintain chemical information, early molecular representations were created. Three tools were developed: the SMILES arbitrary target specification (SMARTS, Daylight CIS, and OpenEye Scientific Software); the simplified input line entry system (SMILES); and the international chemical identifier (InChI) to store and retrieve molecular information and identify common molecular features or substructures from databases (Okibe & Samuel, 2024).

Apart from fingerprints, which are commonly used by chemo informaticians, computational chemists would compute hundreds of features or variables, called molecular descriptors, using well-defined procedures employing molecular representations. Certain easily understood molecular characteristics (such atomic properties, size, shape, flexibility, polarity, lipophilicity, and pharmacophore) are captured by these descriptors. A crucial element in the development of predictive QSA/PR modeling has been molecular descriptors. Their ability to characterize the distributions of synthesized compounds and nanoparticles has proven invaluable in low-dimensional depictions of chemical space. One area in which machine learning is applied in drug discovery is the bioactivity of natural substances. Machine-learning algorithms can be trained using datasets that comprise chemical structures and the biological activities that correspond to them. Because these models can predict the potential bioactivity of new compounds, drug research can thus move more swiftly forward. Support Vector Machines (SVM) and Random Forest are two examples of supervised learning algorithms that have been used to predict the bioactivity of compounds made from natural materials (Dhudum et al., 2024).

The bioactivity of natural substances has been predicted using deep language models. These models are very useful for complicated tasks like bioactivity prediction because they can automatically learn feature representations from raw data. Deep language has proven its ability to improve drug development processes by outperforming conventional machine learning techniques in a number of studies (Chen & Kirchmair, 2020).

Moreover, natural language processing methods can be used to mine literature for data regarding the bioactivity of natural substances. NLP algorithms can find chemicals with documented bioactivity by processing and analysing published research articles. They can then compile this data into structured databases. Researchers might find intriguing natural chemicals for additional study with the help of this automated knowledge extraction (Shultz, 2018).

ML can also help identify potential protein targets for chemical compounds. This is accomplished by analyzing the interactions between proteins and microscopic molecules using algorithms. It is feasible to predict which proteins a particular medicine will most likely interact with when machine learning is combined with methods such as docking simulations. DL has also been used to address the problem of identifying protein targets. Advanced techniques like graph neural networks (GNNs) can represent the interactions between chemicals and proteins more accurately than traditional methods. Finding protein targets can be aided by NLP's ability to extract relevant information from scientific publications. Named entity recognition (NER) technologies can identify references to proteins, genes, and chemicals in the

literature, whereas relation extraction approaches can show the connections between these things (Zhao et al., 2022).

IX. CONCLUSION

The exploration of plant-derived anti-inflammatory agents has unveiled a diverse range of bioactive molecules capable of modulating key inflammatory pathways. Phytoconstituents such as flavonoids, alkaloids, phenolic compounds, and cannabinoids demonstrate significant potential in targeting transcription factors, cytokines, and eicosanoids, reinforcing their therapeutic value. Understanding the classification and mechanisms of NSAIDs further aids in developing plant-based alternatives with improved safety and efficacy. Future research should focus on identifying novel phytochemicals, elucidating their precise molecular mechanisms, and optimizing drug formulations through computational approaches and artificial intelligence. Additionally, clinical trials are essential to validate their therapeutic effectiveness in chronic inflammatory diseases. By fostering interdisciplinary collaboration and integrating traditional botanical knowledge with cutting-edge scientific advancements, the potential of nature's pharmacy can be fully realized in addressing inflammation and its associated disorders.

X. DECLARATIONS

Ethics Approval: Not applicable

Competing Interests: Not applicable

Funding: Not applicable

Availability of Data and Material: Not applicable

Author's Contributions: The manuscript is written by Mukul Nishad and Mansi Chauhan while the manuscript study conception and design is contributed by Sushma Verma. The data collection and data interpretation/analysis are done by Navneet Khurana and Arvind Kumar respectively.

REFERENCES

[1] Abima Shazhni, J. R., Renu, A., & Vijayaraghavan, P. (2018). Insights of antidiabetic, anti-inflammatory and hepatoprotective properties of antimicrobial secondary metabolites of corm extract from Caladium x hortulanum. Saudi Journal of Biological Sciences, 25(8), 1755–1761. https://doi.org/10.1016/j.sjbs.2018.03.013

[2] Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. Biochemical Pharmacology, 71(10), 1397–1421. https://doi.org/10.1016/j.bcp.2006.02.009

[3] Aggarwal, B. B., Shishodia, S., Sandur, S. K., Pandey, M. K., & Sethi, G. (2006). Inflammation and cancer: How hot is the link? Biochemical Pharmacology, 72(11), 1605–1621. https://doi.org/10.1016/j.bcp.2006.06.029

[4] Alderton, W. K., Cooper, C. E., & Knowles, R. G. (2001). Nitric oxide synthases: Structure, function and inhibition. Biochemical Journal, 357(3), 593–615. https://doi.org/10.1042/0264-6021:3570593

[5] Amaral, G. P., de Carvalho, N. R., Barcelos, R. P., Dobrachinski, F., Portella, R. de L., da Silva, M. H., Lugokenski, T. H., Dias, G. R. M., da Luz, S. C. A., Boligon, A. A., Athayde, M. L., Villetti, M. A., Antunes Soares, F. A., & Fachinetto, R. (2013). Protective action of ethanolic extract of Rosmarinus officinalis L. in gastric ulcer prevention induced by ethanol in rats. Food and Chemical Toxicology, 55, 48–55. https://doi.org/10.1016/j.fct.2012.12.038

[6] Anilkumar, K., Reddy, G. V., Azad, R., Yarla, N. S., Dharmapuri, G., Srivastava, A., Kamal, M. A., & Pallu, R. (2017). Evaluation of Anti-Inflammatory Properties of Isoorientin Isolated from Tubers of Pueraria tuberosa. Oxidative Medicine and Cellular Longevity, 2017. https://doi.org/10.1155/2017/5498054

[7] Apte, R. N., Krelin, Y., Song, X., Dotan, S., Recih, E., Elkabets, M., Carmi, Y., Dvorkin, T., White, R. M., Gayvoronsky, L., Segal, S., & Voronov, E. (2006). Effects of micro-environment- and malignant cell-derived interleukin-1 in carcinogenesis, tumour invasiveness and tumour-host

interactions. European Journal of Cancer, 42(6), 751–759. https://doi.org/10.1016/j.ejca.2006.01.010

[8] Arena, W. P., Malyak, M., Guthridge, C. J., & Gabay, C. (1998). Interleukin-1 receptor antagonist: Role in biology. Annual Review of Immunology, 16, 27–55. https://doi.org/10.1146/annurev.immunol.16.1.27

[9] Arranz, E., Jaime, L., de las Hazas, M. C. L., Reglero, G., & Santoyo, S. (2015). Supercritical fluid extraction as an alternative process to obtain essential oils with anti-inflammatory properties from marjoram and sweet basil. Industrial Crops and Products, 67, 121–129.

[10] Asadi-Samani, M., Kafash-Farkhad, N., Azimi, N., Fasihi, A., Alinia-Ahandani, E., & Rafieian-Kopaei, M. (2015). Medicinal plants with hepatoprotective activity in Iranian folk medicine. Asian Pacific Journal of Tropical Biomedicine, 5(2), 146–157.

[11] Balkwill, F. (2006). TNF-α in promotion and progression of cancer. In Cancer and Metastasis Reviews (Vol. 25, Issue 3, pp. 409–416). https://doi.org/10.1007/s10555-006-9005-3

[12] Balkwill, F., & Mantovani, A. (2010). Cancer and inflammation: Implications for pharmacology and therapeutics. Clinical Pharmacology and Therapeutics, 87(4), 401–406. https://doi.org/10.1038/clpt.2009.312

[13] Barbosa, N. R., Fischmann, L., Talib, L. L., & Gattaz, W. F. (2004). Inhibition of platelet phospholipase A2 activity by catuaba extract suggests antiinflammatory properties. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 18(11), 942–944.

[14] Berczi, I., & Szentivanyi, A. (2003). Cytokines and chemokines. In Neuroimmune biology (Vol. 3, pp. 191–220). Elsevier.

[15] Bindu, S., Mazumder, S., & Bandyopadhyay, U. (2020). Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology, 180(April). https://doi.org/10.1016/j.bcp.2020.114147

[16] Blanca-Lopez, N., Soriano, V., Garcia-Martin, E., Canto, G., & Blanca, M. (2019). Nsaid-induced reactions: Classification, prevalence, impact, and management strategies. Journal of Asthma and Allergy, 12, 217–233. https://doi.org/10.2147/JAA.S164806

[17] Block, K., & Gorin, Y. (2012). Aiding and abetting roles of NOX oxidases in cellular transformation. Nature Reviews Cancer, 12(9), 627–637. https://doi.org/10.1038/nrc3339

[18] Bogdan, C. (2001). Nitric oxide and the regulation of gene expression. Trends in Cell Biology, 11(2), 66–75. https://doi.org/10.1016/S0962-8924(00)01900-0

[19] Boudreau, L. H., Lassalle-Claux, G., Cormier, M., Blanchard, S., Doucet, M. S., Surette, M. E., & Touaibia, M. (2017). New Hydroxycinnamic Acid Esters as Novel 5-Lipoxygenase Inhibitors That Affect Leukotriene Biosynthesis. Mediators of Inflammation, 2017. https://doi.org/10.1155/2017/6904634

[20] Brivanlou, A. H., & Darnell, J. E. (2002). Transcription: Signal transduction and the control of gene expression. Science, 295(5556), 813–818. https://doi.org/10.1126/science.1066355

[21] Brynskov, J., Foegh, P., Pedersen, G., Ellervik, C., Kirkegaard, T., Bingham, A., & Saermark, T. (2002). Tumour necrosis factor α converting enzyme (TACE) activity in the colonic mucosa of patients with inflammatory bowel disease. Gut, 51(1), 37–43.

[22] Bunte, K., Hensel, A., & Beikler, T. (2019). Polyphenols in the prevention and treatment of periodontal disease: A systematic review of in vivo, ex vivo and in vitro studies. Fitoterapia, 132, 30–39.

[23] Cao, Z., & Deng, Z. (2017). De novo assembly, annotation, and characterization of root transcriptomes of three caladium cultivars with a focus on necrotrophic pathogen resistance/defense-related genes. International Journal of Molecular Sciences, 18(4). https://doi.org/10.3390/ijms18040712

[24] Chen, Y., de Bruyn Kops, C., & Kirchmair, J. (2017). Data resources for the computer-guided discovery of bioactive natural products. Journal of Chemical Information and Modeling, 57(9), 2099–2111.

[25] Chen, Y., & Kirchmair, J. (2020). Cheminformatics in natural product-based drug discovery. Molecular Informatics, 39(12), 2000171.

[26] Condeelis, J., & Pollard, J. W. (2006). Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. Cell, 124(2), 263–266. https://doi.org/10.1016/j.cell.2006.01.007

[27] Corlett, R. T. (2016). Plant diversity in a changing world: Status, trends, and conservation needs. Plant Diversity, 38(1), 10–16. https://doi.org/10.1016/j.pld.2016.01.001

[28] D'Cruz, I. A. (2001). Book and Multimedia Reviews. Echocardiography, 18(6), 543–544. https://doi.org/10.1046/j.1540-8175.2001.00543.x

[29] Danese, S. (2011). What's hot in inflammatory bowel disease in 2011? World Journal of Gastroenterology, 17(5), 545–546. https://doi.org/10.3748/wjg.v17.i5.545

[30] Dawid-Pać, R. (2013). Medicinal plants used in treatment of inflammatory skin diseases. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 30(3), 170–177.

[31] Dennis, E. A., & Norris, P. C. (2015). Eicosanoid storm in infection and inflammation. Nature Reviews Immunology, 15(8), 511–523. https://doi.org/10.1038/nri3859

[32] Dhudum, R., Ganeshpurkar, A., & Pawar, A. (2024). Revolutionizing Drug Discovery: A Comprehensive Review of AI Applications. Drugs and Drug Candidates, 3(1), 148–171.

[33] Dordević, S., Petrović, S., Dobrić, S., Milenković, M., Vučićević, D., Žižić, S., & Kukić, J. (2007). Antimicrobial, anti-inflammatory, anti-ulcer and antioxidant activities of Carlina acanthifolia root essential oil. Journal of Ethnopharmacology, 109(3), 458–463. https://doi.org/10.1016/j.jep.2006.08.021

[34] Dragos, D., Gilca, M., Gaman, L., Vlad, A., Iosif, L., Stoian, I., & Lupescu, O. (2017). Phytomedicine in joint disorders. Nutrients, 9(1), 70.

[35] Eferl, R., & Wagner, E. F. (2003). AP-1: A double-edged sword in tumorigenesis. Nature Reviews Cancer, 3(11), 859–868. https://doi.org/10.1038/nrc1209

[36] Ernst, P., Siu, A., & Weikum, G. (2015). Knowlife: a versatile approach for constructing a large knowledge graph for biomedical sciences. BMC Bioinformatics, 16, 1–13.

[37] Fialho, L., SANTA-MARIA, A. F., MADUREIRA, F. A., & IGLESIAS, A. C. (2018). Comparative study of systemic early postoperative inflammatory response among elderly and non-elderly patients undergoing laparoscopic cholecystectomy. Revista Do Colégio Brasileiro de Cirurgiões, 45, e1586.

[38] Formukong, E. A., Evans, A. T., & Evans, F. J. (1988). Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. Inflammation, 12(4), 361–371. https://doi.org/10.1007/BF00915771

[39] Gaston, B., Drazen, J. M., Loscalzo, J., & Stamler, J. S. (1994). The biology of nitrogen oxides in the airways. American Journal of Respiratory and Critical Care Medicine, 149(2 I), 538–551. https://doi.org/10.1164/ajrccm.149.2.7508323

[40] Gilmore, T. D. (2006). Introduction to NF-κB: Players, pathways, perspectives. In Oncogene (Vol. 25, Issue 51, pp. 6680–6684). https://doi.org/10.1038/sj.onc.1209954

[41] Golden, J. M., Escobar, O. H., Nguyen, M. V. L., Mallicote, M. U., Kavarian, P., Frey, M. R., & Gayer, X. C. P. (2024). Ursodeoxycholic acid protects against intestinal barrier breakdown by promoting enterocyte migration via EGFR- and COX-2-dependent mechanisms. 46, 259–271. https://doi.org/10.1152/ajpgi.00354.2017

[42] Grivennikov, S. I., Greten, F. R., & Karin, M. (2010). Immunity, Inflammation, and Cancer. Cell, 140(6), 883–899. https://doi.org/10.1016/j.cell.2010.01.025

[43] Halliwell, B. (1991). Reactive oxygen species in living systems: Source, biochemistry, and role in human disease. The American Journal of Medicine, 91(3 SUPPL. 3). https://doi.org/10.1016/0002-9343(91)90279-7

[44] Halliwell, B. (1996). Antioxidants in human health and disease. Annual Review of Nutrition, 16(1), 33–50.

[45] Heinrich, P. C., Behrmann, I., Haan, S., Hermanns, H. M., Müller-Newen, G., & Schaper, F. (2003). Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochemical Journal, 374(1), 1–20. https://doi.org/10.1042/BJ20030407

[46] Ilango, K., Maharajan, G., & Narasimhan, S. (2013). Anti-nociceptive and anti-inflammatory activities of Azadirachta indica fruit skin extract and its isolated constituent azadiradione. Natural Product Research, 27(16), 1463–1467. https://doi.org/10.1080/14786419.2012.717288

[47] Inotai, A., Hankó, B., & Mészáros, Á. (2010). Trends in the non-steroidal anti-inflammatory drug market in six Central–Eastern European countries based on retail information. Pharmacoepidemiology and Drug Safety, 19(2), 183–190.

[48] Jachak, S. (2006). Cyclooxygenase Inhibitory Natural Products: Current Status. Current Medicinal Chemistry, 13(6), 659–678. https://doi.org/10.2174/092986706776055698

[49] Jang, C. H., Kim, Y. Y., Sung, J. Y., Kang, S. H., Jung, E. K., Sung, C. M., Kim, S. B., & Cho, Y. B. (2016). Clinical characteristics of pediatric external auditory canal cholesteatoma. International Journal of Pediatric Otorhinolaryngology. https://doi.org/10.1016/j.ijporl.2016.05.029

[50] Jiménez-Luna, J., Grisoni, F., Weskamp, N., & Schneider, G. (2021). Artificial intelligence in drug discovery: recent advances and future perspectives. Expert Opinion on Drug Discovery, 16(9), 949–959.

[51] Kast, R. E. (2001). Borage oil reduction of rheumatoid arthritis activity may be mediated by increased cAMP that suppresses tumor necrosis factor-alpha. International Immunopharmacology, 1(12), 2197–2199. https://doi.org/10.1016/S1567-5769(01)00146-1

[52] Khanapure, S., Garvey, D., Janero, D., & Gordon Letts, L. (2007). Eicosanoids in Inflammation: Biosynthesis, Pharmacology, and Therapeutic Frontiers. Current Topics in Medicinal Chemistry, 7(3), 311–340. https://doi.org/10.2174/156802607779941314

[53] Kharazmi, A. (2008). Laboratory and preclinical studies on the anti-inflammatory and anti-oxidant properties of rosehip powder - Identification and characterization of the active component GOPO®. Osteoarthritis and Cartilage, 16(SUPPL. 1), 5–7. https://doi.org/10.1016/S1063-4584(08)60003-5

[54] Kim, E. J., Raval, A. P., & Perez-Pinzon, M. A. (2008). Preconditioning mediated by sublethal oxygen-glucose deprivation-induced cyclooxygenase-2 expression via the signal transducers and activators of transcription 3 phosphorylation. Journal of Cerebral Blood Flow and Metabolism, 28(7), 1329–1340. https://doi.org/10.1038/jcbfm.2008.26

[55] Kim, H. P., Lim, H., & Kwon, Y. S. (2017). Therapeutic potential of medicinal plants and their constituents on lung inflammatory disorders. Biomolecules & Therapeutics, 25(2), 91.

[56] Kim, H. P., Mani, I., Iversen, L., & Ziboh, V. A. (1998). Effects of naturally-occurring flavonoids and biflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea-pigs. Prostaglandins Leukotrienes and Essential Fatty Acids, 58(1), 17–24. https://doi.org/10.1016/S0952-3278(98)90125-9

[57] Kim, O. K., Murakami, A., Nakamura, Y., & Ohigashi, H. (1998). Screening of edible Japanese plants for nitric oxide generation inhibitory activities in RAW 264.7 cells. Cancer Letters, 125(1–2), 199–207. https://doi.org/10.1016/S0304-3835(97)00513-2

[58] Kırmızıbekmez, H., İnan, Y., Reis, R., Sipahi, H., Gören, A. C., & Yeşilada, E. (2019). Phenolic compounds from the aerial parts of Clematis viticella L. and their in vitro anti-inflammatory activities. Natural Product Research, 33(17), 2541–2544.

[59] Kleinert, H., Wallerath, T., Fritz, G., Ihrig-Biedert, I., Rodriguez-Pascual, F., Geller, D. A., & Förstermann, U. (1998). Cytokine induction of NO synthase II in human DLD-1 cells: Roles of the JAK-STAT, AP-1 and NF-κB-signaling pathways. In British Journal of Pharmacology (Vol. 125, Issue 1, pp. 193–201). https://doi.org/10.1038/sj.bjp.0702039

[60] Knight, J., Caseldine, C., & Boykoff, M. T. (2010). Forum review: Forum review. Geographical Journal, 176(3), 267–269.

[61] Ko, H. H., Hung, C. F., Wang, J. P., & Lin, C. N. (2008). Antiinflammatory triterpenoids and steroids from Ganoderma lucidum and G. tsugae. Phytochemistry, 69(1), 234–239. https://doi.org/10.1016/j.phytochem.2007.06.008

[62] Kodama, R., Kato, M., Furuta, S., Ueno, S., Zhang, Y., Matsuno, K., Yabe-Nishimura, C., Tanaka, E., & Kamata, T. (2013). ROS-generating oxidases Nox1 and Nox4 contribute to oncogenic Ras-induced premature senescence. Genes to Cells, 18(1), 32–41. https://doi.org/10.1111/gtc.12015

[63] Kolb, W. P., & Granger, G. A. (1968). Lymphocyte in vitro cytotoxicity: characterization of human lymphotoxin. Proceedings of the National Academy of Sciences, 61(4), 1250–1255.

[64] Kowalski, M. L., Asero, R., Bavbek, S., Blanca, M., Blanca-Lopez, N., Bochenek, G., Brockow, K., Campo, P., Celik, G., Cernadas, J., Cortellini, G., Gomes, E., Nizankowska-Mogilnicka, E., Romano, A., Szczeklik, A., Testi, S., Torres, M. J., Wöhrl, S., & Makowska, J. (2013). Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy: European Journal of Allergy and Clinical Immunology, 68(10), 1219–1232. https://doi.org/10.1111/all.12260

[65] Kowalski, M. L., & Makowska, J. S. (2015). Seven steps to the diagnosis of NSAIDs hypersensitivity: How to apply a new classification in real practice? Allergy, Asthma and Immunology Research, 7(4), 312–320. https://doi.org/10.4168/aair.2015.7.4.312

[66] Kröncke, K. D., Fehsel, K., & Kolb-Bachofen, V. (1998). Inducible nitric oxide synthase in human diseases. Clinical and Experimental Immunology, 113(2), 147–156. https://doi.org/10.1046/j.1365-2249.1998.00648.x

[67] Kuraishy, A., Karin, M., & Grivennikov, S. I. (2011). Tumor Promotion via Injury- and Death-Induced Inflammation. Immunity, 35(4), 467–477. https://doi.org/10.1016/j.immuni.2011.09.006

[68] Kuroki, M., & O'Flaherty, J. T. (1999). Neutrophils Stimulated By Chemotactic Factors and Cytokines. Biochemical Journal, 696, 691–695.

[69] Kwon, H. M., Choi, Y. J., Jeong, Y. J., Kang, S. W., Kang, I. J., Soon, S. L., & Kang, Y. H. (2005). Anti-inflammatory inhibition of endothelial cell adhesion molecule expression by flavone derivatives.

Journal of Agricultural and Food Chemistry, 53(13), 5150–5157. https://doi.org/10.1021/jf047854d

[70] Laurance, W. F., Carolina Useche, D., Rendeiro, J., Kalka, M., Bradshaw, C. J. A., Sloan, S. P., Laurance, S. G., Campbell, M., Abernethy, K., Alvarez, P., Arroyo-Rodriguez, V., Ashton, P., Benítez-Malvido, J., Blom, A., Bobo, K. S., Cannon, C. H., Cao, M., Carroll, R., Chapman, C., … Zamzani, F. (2012). Averting biodiversity collapse in tropical forest protected areas. Nature, 489(7415), 290–293. https://doi.org/10.1038/nature11318

[71] Li, A., Dubey, S., Varney, M. L., Dave, B. J., & Singh, R. K. (2003). IL-8 Directly Enhanced Endothelial Cell Survival, Proliferation, and Matrix Metalloproteinases Production and Regulated Angiogenesis. The Journal of Immunology, 170(6), 3369–3376. https://doi.org/10.4049/jimmunol.170.6.3369

[72] Li, X., Liu, Y., Wang, L., Li, Z., & Ma, X. (2015). Unfractionated heparin attenuates LPS-induced IL-8 secretion via PI3K/Akt/NF-κB signaling pathway in human endothelial cells. In Immunobiology (Vol. 220, Issue 3, pp. 399–405). https://doi.org/10.1016/j.imbio.2014.10.008

[73] Li, X., Sun, R., & Liu, R. (2019). Natural products in licorice for the therapy of liver diseases: Progress and future opportunities. Pharmacological Research, 144, 210–226.

[74] Li, Z., Xu, S., & Liu, P. (2018). Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. Acta Pharmacologica Sinica, 39(5), 802–824.

[75] Lin, L. C., Shen, C. C., Shen, Y. C., & Tsai, T. H. (2006). Anti-inflammatory neolignans from Piper kadsura. Journal of Natural Products, 69(5), 842–844. https://doi.org/10.1021/np0505521

[76] Lin, W.-W., & Karin, M. (2007). A cytokine-mediated link between innate immunity, ... [J Clin Invest. 2007] - PubMed result. The Journal of Clinical Investigation, 117(5), 1175–1183. https://doi.org/10.1172/JCI31537.data

[77] Liperoti, R., Vetrano, D. L., Bernabei, R., & Onder, G. (2017). Herbal medications in cardiovascular medicine. Journal of the American College of Cardiology, 69(9), 1188–1199.

[78] Lipinski, S., Till, A., Sina, C., Arlt, A., Grasberger, H., Schreiber, S., & Rosenstiel, P. (2009). DUOX2-derived reactive oxygen species are effectors of NOD2-mediated antibacterial responses. Journal of Cell Science, 122(19), 3522–3530. https://doi.org/10.1242/jcs.050690

[79] Liu, C. H., Abrams, N. D., Carrick, D. M., Chander, P., Dwyer, J., Hamlet, M. R. J., Macchiarini, F., Prabhudas, M., Shen, G. L., Tandon, P., & Vedamony, M. M. (2017). Biomarkers of chronic inflammation in disease development and prevention : challenges and opportunities. Nature Publishing Group, 18(11), 1175–1180. https://doi.org/10.1038/ni.3828

[80] Locati, M., & Murphy, P. M. (1999). Chemokines and chemokine receptors: Biology and clinical relevance in inflammation and AIDS. Annual Review of Medicine, 50, 425–440. https://doi.org/10.1146/annurev.med.50.1.425

[81] Locksley, R. M., Killeen, N., & Lenardo, M. J. (2001). The TNF and TNF receptor superfamilies: Integrating mammalian biology. Cell, 104(4), 487–501. https://doi.org/10.1016/S0092-8674(01)00237-9

[82] Maione, F., Russo, R., Khan, H., & Mascolo, N. (2016). Medicinal plants with anti-inflammatory activities. Natural Product Research, 30(12), 1343–1352.

[83] Manju, K., Jat, R. K., & Anju, G. (2012). a Review on Medicinal Plants Used As a Source of Anticancer Agents. Int. J. Drug Res. Tech., 2(1), 177–183.

[84] Marnett, L. J., & Kalgutkar, A. S. (1999). Cyclooxygenase 2 inhibitors: Discovery, selectivity and the future. Trends in Pharmacological Sciences, 20(11), 465–469. https://doi.org/10.1016/S0165-6147(99)01385-1

[85] Montinari, M. R., Minelli, S., & De Caterina, R. (2019). The first 3500 years of aspirin history from its roots–A concise summary. Vascular Pharmacology, 113, 1–8.

[86] Murugananthan, G., & Mohan, S. (2013). Anti-arthritic and anti-inflammatory constituents from medicinal plants. Journal of Applied Pharmaceutical Science, 3(4), 161–164.

[87] Nardi, G. M., De Farias Januário, A. G., Freire, C. G., Megiolaro, F., Schneider, K., Perazzoli, M. R. A., Do Nascimento, S. R., Gon, A. C., Mariano, L. N. B., Wagner, G., Niero, R., & Locatelli, C. (2016). Anti-inflammatory activity of berry fruits in mice model of inflammation is based on oxidative stress modulation. Pharmacognosy Research, 8, S42–S49. https://doi.org/10.4103/0974-8490.178642

[88] Nemudzivhadi, V., & Masoko, P. (2014). In vitro assessment of cytotoxicity, antioxidant, and anti-inflammatory activities of Ricinus communis (euphorbiaceae) leaf extracts. Evidence-Based Complementary and Alternative Medicine, 2014(1), 625961.

[89] Ojewole, J. A. O. (2005). Antinociceptive, anti-inflammatory and antidiabetic effects of Bryophyllum pinnatum (Crassulaceae) leaf aqueous extract. Journal of Ethnopharmacology, 99(1), 13–19.

https://doi.org/10.1016/j.jep.2005.01.025

[90] Okibe, G., & Samuel, H. S. (2024). Harnessing Artificial Intelligence for the Discovery and Development of Natural Product-Based Therapeutics. Faculty of Natural and Applied Sciences Journal of Scientific Innovations, 6(1), 45–57.

[91] Pahl, H. L. (1999). Activators and target genes of Rel/NF-κB transcription factors. In Oncogene (Vol. 18, Issue 49, pp. 6853–6866). https://doi.org/10.1038/sj.onc.1203239

[92] Palazon, A., Goldrath, A. W., Nizet, V., & Johnson, R. S. (2014). HIF Transcription Factors, Inflammation, and Immunity. Immunity, 41(4), 518–528. https://doi.org/10.1016/j.immuni.2014.09.008

[93] Pereira-leite, C., Jamal, S. K., Cuccovia, I. M., & Reis, S. (2016). Therapy : A Journey Toward Safety. 0, 1–58. https://doi.org/10.1002/med

[94] Perera, H. D. S. M., Samarasekera, J. K. R. R., Handunnetti, S. M., & Weerasena, O. V. D. S. J. (2016). In vitro anti-inflammatory and anti-oxidant activities of Sri Lankan medicinal plants. Industrial Crops and Products, 94, 610–620.

[95] Perianayagam, M. C., Balakrishnan, V. S., Pereira, B. J. G., & Jaber, B. L. (2004). C5a delays apoptosis of human neutrophils via an extracellular signal-regulated kinase and Bad-mediated signalling pathway. European Journal of Clinical Investigation, 34(1), 50–56. https://doi.org/10.1111/j.1365-2362.2004.01273.x

[96] Placak, J. C. (1953). Treatment of tuberculosis fifty years ago: Chairman's address. Journal of the American Medical Association, 153(9), 795–799. https://doi.org/10.1001/jama.1953.02940260019007

[97] Poeckel, D., Greiner, C., Verhoff, M., Rau, O., Tausch, L., Hörnig, C., Steinhilber, D., Schubert-Zsilavecz, M., & Werz, O. (2008). Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes. Biochemical Pharmacology, 76(1), 91–97. https://doi.org/10.1016/j.bcp.2008.04.013

[98] Pope, J. E., & Deer, T. R. (2017). Treatment of Chronic Pain Conditions: A Comprehensive Handbook. Treatment of Chronic Pain Conditions: A Comprehensive Handbook, 1–358. https://doi.org/10.1007/978-1-4939-6976-0

[99] Profita, M., Bonanno, A., Siena, L., Ferraro, M., Montalbano, A. M., Pompeo, F., Riccobono, L., Pieper, M. P., & Gjomarkaj, M. (2008). Acetylcholine mediates the release of IL-8 in human bronchial epithelial cells by a NFkB/ERK-dependent mechanism. European Journal of Pharmacology, 582(1–3), 145–153. https://doi.org/10.1016/j.ejphar.2007.12.029

[100] Pundir, P., & Kulka, M. (2010). The role of G protein-coupled receptors in mast cell activation by antimicrobial peptides: Is there a connection. Immunology and Cell Biology, 88(6), 632–640. https://doi.org/10.1038/icb.2010.27

[101] Rabiet, M. J., Huet, E., & Boulay, F. (2007). The N-formyl peptide receptors and the anaphylatoxin C5a receptors: An overview. Biochimie, 89(9), 1089–1106. https://doi.org/10.1016/j.biochi.2007.02.015

[102] Radi, R. (2004). Nitric oxide, oxidants, and protein tyrosine nitration. Proceedings of the National Academy of Sciences of the United States of America, 101(12), 4003–4008. https://doi.org/10.1073/pnas.0307446101

[103] Ram, A., Balachandar, S., Vijayananth, P., & Singh, V. P. (2011). Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): current status and future perspectives. Fitoterapia, 82(2), 141–151.

[104] Rezapour-Firouzi, S., Arefhosseini, S. R., Mehdi, F., Mehrangiz, E. M., Baradaran, B., Sadeghihokmabad, E., Mostafaei, S., Fazljou, S. M. B., Torbati, M. ali, Sanaie, S., & Zamani, F. (2013). Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. Complementary Therapies in Medicine, 21(5), 473–480. https://doi.org/10.1016/j.ctim.2013.06.006

[105] Rius, J., Guma, M., Schachtrup, C., Akassoglou, K., Zinkernagel, A. S., Nizet, V., Johnson, R. S., Haddad, G. G., & Karin, M. (2008). NF-κB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1α. In Nature (Vol. 453, Issue 7196, pp. 807–811). https://doi.org/10.1038/nature06905

[106] Romano, J. D., & Tatonetti, N. P. (2019). Informatics and computational methods in natural product drug discovery: a review and perspectives. Frontiers in Genetics, 10, 368.

[107] Sá, R. de C. da S. e, Nalone Andrade, L., dos Reis Barreto de Oliveira, R., & de Sousa, D. P. (2014). A review on anti-inflammatory activity of phenylpropanoids found in essential oils. Molecules, 19(2),

1459–1480.

[108] Sangiovanni, E., Di Lorenzo, C., Colombo, E., Colombo, F., Fumagalli, M., Frigerio, G., Restani, P., & Dell'Agli, M. (2015). The effect of in vitro gastrointestinal digestion on the anti-inflammatory activity of Vitis vinifera L. leaves. Food & Function, 6(8), 2453–2463.

[109] Santana, F. P. R., Pinheiro, N. M., Mernak, M. I. B., Righetti, R. F., Martins, M. A., Lago, J. H. G., Lopes, F. D. T. Q. dos S., Tibério, I. F. L. C., & Prado, C. M. (2016). Evidences of herbal medicine-derived natural products effects in inflammatory lung diseases. Mediators of Inflammation, 2016(1), 2348968.

[110] Schneider, I., & Bucar, F. (2005a). Lipoxygenase inhibitors from natural plant sources. Part 1: Medicinal plants with inhibitory activity on arachidonate 5-lipoxygenase and 5-lipoxygenase/cyclooxygenase. Phytotherapy Research, 19(2), 81–102. https://doi.org/10.1002/ptr.1603

[111] Schneider, I., & Bucar, F. (2005b). Lipoxygenase inhibitors from natural plant sources. Part 2: Medicinal plants with inhibitory activity on arachidonate 12-lipoxygenase, 15-lipoxygenase and leukotriene receptor antagonists. Phytotherapy Research, 19(4), 263–272. https://doi.org/10.1002/ptr.1604

[112] Semenza, G. L. (2011). Oxygen Sensing, Homeostasis, and Disease. 537–547.

[113] Seo, Y. A., & Suk, K. D. (2007). Analgesic and anti-inflammatory activity of Resina Pini. Natural Product Sciences, 13(4), 347–354.

[114] Seoane, J., Pouponnot, C., Staller, P., Schader, M., Eilers, M., & Massagué, J. (2001). TGFβ influences myc, miz-1 and smad to control the CDK inhibitor p15INK4b. In Nature Cell Biology (Vol. 3, Issue 4, pp. 400–408). https://doi.org/10.1038/35070086

[115] Setty, A. R., & Sigal, L. H. (2005). Herbal medications commonly used in the practice of rheumatology: Mechanisms of action, efficacy, and side effects. Seminars in Arthritis and Rheumatism, 34(6), 773–784. https://doi.org/10.1016/j.semarthrit.2005.01.011

[116] Shaito, A., Thuan, D. T. B., Phu, H. T., Nguyen, T. H. D., Hasan, H., Halabi, S., Abdelhady, S., Nasrallah, G. K., Eid, A. H., & Pintus, G. (2020). Herbal medicine for cardiovascular diseases: efficacy, mechanisms, and safety. Frontiers in Pharmacology, 11, 422.

[117] Shinomiya, S., Naraba, H., Ueno, A., Utsunomiya, I., Maruyama, T., Ohuchida, S., Ushikubi, F., Yuki, K., Narumiya, S., Sugimoto, Y., Ichikawa, A., & Oh-ishi, S. (2001). Regulation of TNFα and interleukin-10 production by prostaglandins I2 and E2: Studies with prostaglandin receptor-deficient mice and prostaglandin E-receptor subtype-selective synthetic agonists. In Biochemical Pharmacology (Vol. 61, Issue 9, pp. 1153–1160). https://doi.org/10.1016/S0006-2952(01)00586-X

[118] Shoskes, D., Lapierre, C., Cruz-Corerra, M., Muruve, N., Rosario, R., Fromkin, B., Braun, M., & Copley, J. (2005). Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: A randomized placebo controlled trial. Transplantation, 80(11), 1556–1559. https://doi.org/10.1097/01.tp.0000183290.64309.21

[119] Shultz, M. D. (2018). Two decades under the influence of the rule of five and the changing properties of approved oral drugs: miniperspective. Journal of Medicinal Chemistry, 62(4), 1701–1714.

[120] Singh, S., & Aggarwal, B. B. (1995). Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane)(∗). Journal of Biological Chemistry, 270(42), 24995–25000.

[121] Singh, S., Nair, V., Jain, S., & Gupta, Y. K. (2008). Evaluation of anti-inflammatory activity of plant lipids containing α-linolenic acid. Indian Journal of Experimental Biology, 46(6), 453–456.

[122] Singh, S., Singh, T. G., Mahajan, K., & Dhiman, S. (2020). Medicinal plants used against various inflammatory biomarkers for the management of rheumatoid arthritis. Journal of Pharmacy and Pharmacology, 72(10), 1306–1327.

[123] Sostres, C., & Lanas, Á. (2016). Appropriate prescription, adherence and safety of non-steroidal anti-inflammatory drugs. Medicina Clínica (English Edition), xx. https://doi.org/10.1016/j.medcle.2016.05.006

[124] Subbaramaiah, K., & Dannenberg, A. J. (2003). Cyclooxygenase 2: A molecular target for cancer prevention and treatment. Trends in Pharmacological Sciences, 24(2), 96–102. https://doi.org/10.1016/S0165-6147(02)00043-3

[125] Süleyman, H., Demircan, B., & Karagöz, Y. (2007). Anti-inflammatory and side effects of cyclooxygenase inhibitors. Pharmacological Reports, 59(3), 247–258.

[126] Tsai, S. H., Lin-Shiau, S. Y., & Lin, J. K. (1999). Suppression of nitric oxide synthase and the down-regulation of the activation of NFκB in macrophages by resveratrol. In British Journal of Pharmacology (Vol. 126, Issue 3, pp. 673–680). https://doi.org/10.1038/sj.bjp.0702357

[127] Vamathevan, J., Clark, D., Czodrowski, P., Dunham, I., Ferran, E., Lee, G., Li, B., Madabhushi, A., Shah, P., & Spitzer, M. (2019). Applications of machine learning in drug discovery and development. Nature Reviews Drug Discovery, 18(6), 463–477.

[128] Vaou, N., Stavropoulou, E., Voidarou, C., Tsigalou, C., & Bezirtzoglou, E. (2021). Towards advances in medicinal plant antimicrobial activity: A review study on challenges and future perspectives. Microorganisms, 9(10), 2041.

[129] Vogl, S., Picker, P., Mihaly-Bison, J., Fakhrudin, N., Atanasov, A. G., Heiss, E. H., Wawrosch, C., Reznicek, G., Dirsch, V. M., & Saukel, J. (2013). Ethnopharmacological in vitro studies on Austria's folk medicine—An unexplored lore in vitro anti-inflammatory activities of 71 Austrian traditional herbal drugs. Journal of Ethnopharmacology, 149(3), 750–771.

[130] Wagner, E., & Frank, M. M. (2010). Therapeutic potential of complement modulation. Nature Reviews Drug Discovery, 9(1), 43–56. https://doi.org/10.1038/nrd3011

[131] Wambugu, S. N., Mathiu, P. M., Gakuya, D. W., Kanui, T. I., Kabasa, J. D., & Kiama, S. G. (2011). Medicinal plants used in the management of chronic joint pains in Machakos and Makueni counties, Kenya. Journal of Ethnopharmacology, 137(2), 945–955.

[132] Wedler, J., Daubitz, T., Schlotterbeck, G., & Butterweck, V. (2014). In vitro anti-inflammatory and wound-healing potential of a Phyllostachys edulis leaf extract–identification of isoorientin as an active compound. Planta Medica, 80(18), 1678–1684.

[133] Wills-Karp, M. (2007). Complement activation pathways: A bridge between innate and adaptive immune responses in asthma. Proceedings of the American Thoracic Society, 4(3), 247–251. https://doi.org/10.1513/pats.200704-046AW

[134] Woolley, J. F., Corcoran, A., Groeger, G., Landry, W. D., & Cotter, T. G. (2013). Redox-regulated growth factor survival signaling. Antioxidants and Redox Signaling, 19(15), 1815–1827. https://doi.org/10.1089/ars.2012.5028

[135] Wotton, D., & Massague, J. (2000). Transcriptional control by the TGF-b / Smad signaling system. In EMBO Journal (Vol. 19, Issue 8, pp. 1745–1754).

[136] Wu, Y., Antony, S., Meitzler, J. L., & Doroshow, J. H. (2014). Molecular mechanisms underlying chronic inflammation-associated cancers. Cancer Letters, 345(2), 164–173. https://doi.org/10.1016/j.canlet.2013.08.014

[137] Wu, Y., Zhou, C., Song, L., Li, X., Shi, S., Mo, J., Chen, H., Bai, H., Wu, X., Zhao, J., Zhang, R., Hao, X., Sun, H., & Zhao, Y. (2006). Effect of total phenolics from Laggera alata on acute and chronic inflammation models. Journal of Ethnopharmacology, 108(2), 243–250. https://doi.org/10.1016/j.jep.2006.05.017

[138] Xia, X., May, B. H., Zhang, A. L., Guo, X., Lu, C., Xue, C. C., & Huang, Q. (2020). Chinese Herbal Medicines for Rheumatoid Arthritis: Text-Mining the Classical Literature for Potentially Effective Natural Products. Evidence-Based Complementary and Alternative Medicine, 2020(1), 7531967.

[139] Xie, G., Schepetkin, I. A., Siemsen, D. W., Kirpotina, L. N., Wiley, J. A., & Quinn, M. T. (2008). Fractionation and characterization of biologically-active polysaccharides from Artemisia tripartita. Phytochemistry, 69(6), 1359–1371. https://doi.org/10.1016/j.phytochem.2008.01.009

[140] Xu, L., Wang, Y.-Y., Huang, J., Chen, C.-Y., Wang, Z.-X., & Xie, H. (2020). Silver nanoparticles: Synthesis, medical applications and biosafety. Theranostics, 10(20), 8996.

[141] Yang, L., Pang, Y., & Moses, H. L. (2010). TGF-β and immune cells: an important regulatory axis in the tumor microenvironment and progression. In Trends in Immunology (Vol. 31, Issue 6, pp. 220–227). https://doi.org/10.1016/j.it.2010.04.002

[142] Yatoo, M. I., Gopalakrishnan, A., Saxena, A., Parray, O. R., Tufani, N. A., Chakraborty, S., Tiwari, R., Dhama, K., & Iqbal, H. M. N. (2018). Anti-Inflammatory Drugs and Herbs with Special Emphasis on Herbal Medicines for Countering Inflammatory Diseases and Disorders - A Review. Recent Patents on Inflammation & Allergy Drug Discovery, 12(1), 39–58. https://doi.org/10.2174/1872213x12666180115153635

[143] Yu, H., Pardoll, D., & Jove, R. (2009). STATs in cancer inflammation and immunity: A leading role for STAT3. Nature Reviews Cancer, 9(11), 798–809. https://doi.org/10.1038/nrc2734

[144] Zenz, R., Eferl, R., Scheinecker, C., Redlich, K., Smolen, J., Schonthaler, H. B., Kenner, L., Tschachler, E., & Wagner, E. F. (2008). Activator protein 1 (Fos/Jun) functions in inflammatory bone and skin disease. Arthritis Research and Therapy, 10(1), 1–10. https://doi.org/10.1186/ar2338

[145] Zhang, H., Chen, S., Jia, X., Huang, Y., Ji, R., & Zhao, L. (2021). Comparation of the phytotoxicity between chemically and green synthesized silver nanoparticles. Science of The Total Environment, 752, 142264.

[146] Zhao, L., Zhu, Y., Wang, J., Wen, N., Wang, C., & Cheng, L. (2022). A brief review of protein–ligand interaction prediction. Computational and Structural Biotechnology Journal, 20, 2831–2838.