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Role of Natural Products in Inflammatory Pharmacology: Harnessing Nature's Potential Through Drug Delivery for Therapeutic Intervention

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ABSTRACT:

Inflammatory disorders encompass a broad spectrum of conditions marked by abnormal immune responses and persistent inflammation, affecting healthcare and patient well-being. Seeking alternative, safe, and efficacious treatments, researchers are turning to natural products within the realm of inflammatory pharmacology. These products, sourced from plants, animals, and microorganisms, hold promise as therapeutic interventions. Natural products exhibit complex interactions with molecular targets and signaling pathways involved in the inflammatory cascade across various diseases. These interactions result in anti-inflammatory (AI) effects and provide potential therapeutic benefits. These advantages may be harnessed via diverse drug delivery methods used for administering these natural products. Plant-derived compounds like CUR (CUR), found in turmeric, exhibit robust AI effects by modulating inflammation-associated pathways. Resveratrol (RES), present in grapes and berries, mitigates inflammation and oxidative stress. Similarly, animal-derived products such as omega-3 fatty acids (OFG) and bee venom components, along with microbial-derived substances like probiotics and fungal metabolites, display notable AI properties. It presents an all-encompassing perspective on the role of natural products in inflammatory pharmacology, scrutinizing their molecular mechanisms, efficacy, and applicability through drug delivery approaches in diverse inflammatory disorders. By synthesizing the latest scientific strides, the article deepens our comprehension of the therapeutic potential of natural products in managing inflammatory conditions through various drug delivery approaches, thereby offering valuable insights for future research and clinical utilization.

Introduction:

Inflammatory disorders encompass a wide range of conditions characterized by an abnormal immune response and chronic inflammation [1]. These disorders pose significant challenges in healthcare and patient quality of life [2]. While conventional therapies exist, the search for alternative, safe, and effective treatments have led researchers to explore the potential of natural products in inflammatory pharmacology. Experts in healthcare express worry over drugs having a somewhat limited therapeutic index in traditional therapy due to the potential for clinically relevant drug interactions [3]. Natural remedies, which originate from a variety of origins including plants, animals, and microbes, possess a rich historical background of traditional usage and are currently gaining recognition for their possible therapeutic effects in regulating inflammatory mechanisms. Additionally, the biofilms undermine the immune system, allowing new bacterial communities to flourish and eventually delaying the healing process [4]. The utilization of herbal remedies in the realm of inflammatory pharmacology presents an intriguing

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option as therapeutics. These bioactive compounds possess a plethora of chemical structures and complex mixtures, providing a rich source of molecules with diverse pharmacological activities. Through their intricate interactions with molecular targets and signaling pathways involved in the inflammatory cascade, natural products exhibit AI effects and offer potential therapeutic benefits. Extensive research has been conducted on natural compounds produced from plants within the field of inflammatory pharmacology [1]. Due to its potent flavor and scent as a spice and flavoring factor in food and beverages as well as its use as a traditional medicine, *Trigonella foenum-graecum* (TFG), often known as fenugreek and belonging to the Leguminosae family, is widely consumed in India. There are numerous findings on the benefits of TFG extract on ulcers, diabetes, wound healing, antioxidants, cancer, inflammation, and fever. Numerous bioactive substances such as trigonelline (TG) and 4-hydroxyisoleucine, are present in the TFG seed extract. A key substance among them is an alkaloid, known as TG. In Alzheimer's disease, TG's antidiabetic and neurodegenerative properties are linked to memory enhancement [5]. For instance, CUR, a bioactive compound found in turmeric, has demonstrated potent AI effects by modulating various inflammatory pathways. RES, a polyphenolic compound present in grapes and berries, has also shown promise in reducing inflammation and oxidative stress. Additionally, animal-derived natural products, such as OFA from fish oil and bee venom components, exhibited amelioration of inflammatory properties in preclinical and clinical studies. Furthermore, microbial-derived natural products, including probiotics and fungal metabolites, have emerged as potential candidates for modulating gut microbiota and attenuating inflammation. A foreign chemical substance that changes the neurotransmitter's circulation will affect some receptors' chemical attachments, which will upset the balance. In essence, the imbalance's effects will reveal the mental disorder. Mental disease can be classified into many different forms, such as delusion, hallucination, depression, schizophrenia, etc., depending on the severity of the alteration [6, 7]. Derivatives of diaryl synthesized by derivatization of cyclic ketones have attracted significant scientific interest due to their notable pharmacological activities [8]. The objective of this article is to present a detailed examination of the function that natural molecules play in the field of inflammatory pharmacology. Specifically, this study will focus on elucidating the molecular pathways via which natural substances exert their effects, evaluating their effectiveness, and identifying new uses for treating different inflammatory disorders. This article will also cover drug delivery approaches of these natural phytomolecules.

Overview of Inflammation:

Acute and chronic inflammation are two distinct types of immune responses that occur in the body. Although both processes entail the stimulation of the immune framework and the subsequent release of diverse inflammation causing agents, they exhibit disparities in terms of their length, underlying mechanisms, and clinical symptoms. Acute inflammation is triggered promptly after tissue injury or infection, allowing the immune system to respond rapidly. This process is inherently self-limiting and often undergoes resolution over a short span of a few days with the removal of the causative stimulus. Blood vessels in the affected area dilate, leading to increased permeability. This allows cells belonging to the immune framework and proteins in the plasma to migrate from the circulation into the tissue, leading to the characteristic swelling, redness, and heat associated with acute inflammation. Neutrophils, are the primary immune cells (IC) involved in acute inflammation. The cells undergo migration towards the location of injury or infection, where they proceed to produce inflammatory mediators in order to combat pathogens and eliminate debris. The heightened vascular permeability induces the effusion of fluid into the adjacent tissues, leading to the manifestation of regional swelling or edema [9]. As the injurious agent is neutralized and tissue healing progresses, acute inflammation resolves, and the affected tissue returns to its normal state. Chronic inflammation is characterized by its long-lasting nature, persisting for an extended period, often due to unresolved triggers or underlying diseases. It involves a cycle of tissue damage and attempted repair. During the course of wound healing, a series of processes take place to assist the restoration of the injured area's integrity. These events include inflammation, cellular proliferation, and its remodeling. Following an injury, the initial onset of inflammation in the affected region is attributed to the release of several inflammatory agents. Following this, there is a manifestation of increased proliferation of fibroblast blood vessel formation (angiogenesis), and remodeling of tissue [4, 10]. The phenomenon of a prolonged immunological response can lead to the destruction of normal tissue and the formation of scar tissue. In contrast to acute inflammation, chronic inflammation is distinguished by the presence of cells from the immune framework, including lymphocytes, macrophages, and cells from plasma, alongside neutrophils. The occurrence of angiogenesis and excessive production of connective tissue (fibrosis) are common features of chronic inflammation [11].

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Cellular players in the inflammatory response: cytokines, chemokines, and IC

Inflammatory mediators: prostaglandins, leukotrienes, and histamine

Prostaglandins: Prostaglandins are arachidonic acid derivatives, which are lipid in nature and functions through the action of cyclooxygenase (COX) enzymes [12]. They have significant involvement in numerous physiological, biochemical and pathological processes, including inflammation. Some plant polyphenolics and synthetic pyrazoline derivatives are reported to have AI property and are also effective antioxidants. This antioxidant activity likely contributes to the inhibitory activities of COX-LOX [12, 13]. Due to the induction of oxidative damage, antioxidant enzyme activities were also noticeably altered, with measurements showing an enhancement in the activities of SOD, APX, and decreased activity of CAT [14]. There are several types of prostaglandins, but the most well-known are prostaglandin E2 (PGE2) and prostaglandin D2 (PGD2). Particularly, prostaglandin E2 (PGE2) induces vasorelaxation and vasodilation, leading to enhanced blood perfusion towards the site of inflammation. [15]. They promote increased permeability of blood vessels, allowing IC and plasma proteins to extravasate into the inflamed tissue and sensitize nerve endings, contributing to the generation of pain and hypersensitivity at the site of inflammation. They contribute significantly in immune cell activation and modulate the functioning of the IC, including neutrophils, macrophages, and lymphocytes, influencing their recruitment and inflammatory functions. Prostaglandins can act on the hypothalamus to raise body temperature, contributing to the development of fever during inflammation.

Leukotrienes: Leukotrienes are arachidonic acid derivatives, which are synthesized through the 5-lipoxygenase (5-LOX) pathway. This acid metabolism may shift to the 5-LOX route as a result of COX enzyme inhibition, which could increase leukotriene synthesis [16]. They are predominantly produced by leukocytes and play crucial roles in allergic and inflammatory reactions. Leukotrienes, particularly leukotriene D4 (LTD4), cause the constriction of smooth muscles in the airways, contributing to bronchoconstriction in conditions such as asthma. They are also responsible for enhancing vascular permeability, promoting the migration of fluid and plasma proteins into the tissues present in the surrounding. Leukotrienes attract and activate cells of immune framework, including eosinophils macrophages and neutrophils leading to their migration to the location of inflammation. They also produce and recruit mucus, contributing to airway obstruction and mucus-related symptoms in inflammatory respiratory conditions.

Histamine: Histamine is a biogenic amine that is released from mast cells, basophils, and other IC during allergic and inflammatory responses [17]. It acts as a potent vasodilator and mediator of immediate hypersensitivity reactions with potentially involvement of H1 receptor [11]. Histamine causes vasorelaxation, increasing the blood flow to the inflamed area and promotes endothelial cell contraction, facilitating the infiltration of plasma proteins and IC into adjacent tissues [18]. They can also cause smooth muscle contraction, contributing to bronchoconstriction, intestinal cramping, and other smooth muscle-related symptoms [19]. Histamine activates sensory nerve endings, leading to sensations of itchiness and pain at the site of inflammation. Histamine modulates immune cell activation and function, influencing processes such as leukocyte recruitment and cytokine release. When patients suffering from pollinosis and allergic model rats with TDI sensitization displayed allergy symptoms, H1R mRNA expression was closely linked with the intensity of those symptoms. Additionally, substances that reduce the expression of the H1R gene are better in reducing allergy symptoms [20]. The production and actions of prostaglandins, leukotrienes, and histamine are tightly regulated to maintain an equilibrium between the inflammatory responses. Enzymes involved in their synthesis, such as COX and 5-LO, can be inhibited by NSAIDs and leukotriene antagonists, respectively. Additionally, AI cytokines and endogenous molecules, such as lipoxins and resolvins, can counteract the effects of these inflammatory mediators and promote the resolution of inflammation [21].

Modulation of NF-κB, AP-1, and STATs

NF-κB modulates multiple genes that play a role in immunological responses, inflammation, cell survival, and proliferation. The NF-κB family consists of five distinct members p50, p52, RelA (p65), RelB, and c-Rel. Typically, NF-κB in cytoplasm, are checked by inhibitory proteins known such as IκBs (inhibitors of NF-κB). The activation of NF-κB commences upon the detection of various extracellular signals, including pro-inflammatory (PRO-I) cytokines like TNF-α and IL-1, as well as microbial products such as lipopolysaccharide. This initiation of NF-κB activation is crucial for initiating and modulating the inflammatory response[22]. These signals are detected by cell surface receptors, which include tumor necrosis factor receptors (TNFRs), interleukin-1 receptors (IL-1Rs), Toll-like receptors (TLRs), and various others. This recognition leads to the oligomerization of receptors and the recruitment of adaptor proteins. In addition to this, several cytokines, such as IL-2, IL-7, IL-15, growth factor (bFGF), and numerous antioxidants, exert control over telomere length, telomerase activity, and the expression of the hTERT (human Telomerase Reverse

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Transcriptase) gene. Elevated levels of cytokines at sites of tissue injury promote immunosuppressive effects [23]. It is well-established that a broad spectrum of bacteria forms biofilms as a protective response when confronted with unfavorable environmental conditions. These biofilms consist of an extracellular matrix that produces polysaccharides and peptides[24]. Acidic and basic functional groups on bacterial surfaces are known to be linked to lipopolysaccharides (LPS), exopolysaccharide (EPS) [25] [26].These polysaccharides facilitates downstream signaling process of TLRs [27]. The recruited adaptor proteins, such as TNF receptor-associated factors (TRAFs) and MyD88, engage in interactions with downstream kinases, notably the IκB kinase (IKK) complex. This IKK complex comprises two catalytic subunits, IKKα and IKKβ, alongside a regulatory subunit known as IKKγ or NEMO. Upon activation, the IKK complex phosphorylates inhibitory proteins known as IκBs (inhibitors of NF-κB). This phosphorylation event triggers their ubiquitination and subsequent degradation by the proteasome. Consequently, NF-κB dimers, typically composed of p65 (RelA) and p50 subunits, are released from the inhibitory IκB complex. With the degradation of IκBs, these freed NF-κB dimers translocate from the cytoplasm to the nucleus, where they bind to specific DNA sequences known as κB sites. It's worth noting that the transcription factor NF-κB, which plays a role in activating numerous genes associated with oxidative stress, can be inhibited by Nrf2 inducers[28]. Inside the nucleus, NF-κB dimers form complexes by binding to κB sites situated within the promoter regions of their target genes. These target genes encompass a wide array of PRO-I genes, including cytokines like interleukin-6 and tumor necrosis factor-alpha (TNF-α), chemokines, adhesion molecules, and enzymes pivotal for the production of inflammatory mediators. The transcriptional activity of NF-κB is intricately regulated by its interactions with various co-activators and co-repressors. These molecular partners exert a significant influence on gene expression, modulating the inflammatory response and fine-tuning cellular processes. NF-κB exhibits the capability to engage in interactions with various other transcription factors, including AP-1 (Activator Protein-1), STATs (Signal Transducers and Activators of Transcription), and CREB (cAMP Response Element-Binding Protein). This collaborative interplay between NF-κB and these transcription factors allows for the coordinated regulation of gene expression and the amplification of the PRO-I response. Indeed, inhibiting the NF-κB signaling pathway holds great promise as a strategic approach to suppress the expression of PRO-I genes and alleviate excessive inflammation. A variety of methods can be applied to address specific stages of this pathway, providing potential therapeutic interventions while preserving the scientific terminology and fundamental concepts. One of these approaches involves the utilization of small molecule inhibitors designed to target the catalytic activity of the IKK complex. Compounds such as BAY 11-7082 and TPCA-1 have demonstrated their capability to effectively impede IκB phosphorylation, subsequently preventing NF-κB activation. This targeted intervention represents a valuable tool in the pursuit of managing inflammatory processes without altering the scientific terminology or underlying meaning. Indeed, inhibiting the NF-κB signaling pathway holds great promise as a strategic approach to suppress the expression of PRO-I genes and alleviate excessive inflammation. A variety of methods can be applied to address specific stages of this pathway, providing potential therapeutic interventions while preserving the scientific terminology and fundamental concepts.

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Molecular Details and Activation of AP-1: The basic architecture of AP-1 consists of homo- or heterodimers including proteins originating from the Jun family (c-Jun, JunB, JunD) and the Fos family (c-Fos, FosB, Fra-1, Fra-2), whereby both Jun and Fos proteins form leucine zipper structures. The protein quality control system consists of two fundamental components, namely molecular chaperones and the degradation machinery. These constituents together govern the cellular maintenance of protein homeostasis. Chaperones play a crucial role in the regulation of protein folding and the management of misfolded proteins by facilitating their recognition and transfer to ubiquitin ligases, which subsequently attach ubiquitin tags to these proteins. This process prepares the misfolded proteins for destruction by either the proteasome or autophagic pathways. Within the mammalian system, it has been shown that there exist around 600 ubiquitin ligases. This substantial number suggests that a collaborative group of ubiquitin ligases functions collectively to safeguard cells against the buildup of misfolded proteins and the subsequent formation of aggregates. Such aggregates have the potential to generate cytotoxic stress.[30]. Upon activation, AP-1 dimers exhibit binding affinity towards certain DNA sequences referred to as AP-1 sites, which are situated inside the promoter regions of target genes.

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The aforementioned binding event exerts regulatory control on the transcriptional activity of the specified genes. Included in the group of genes being targeted are cytokines like IL-2 and IL-8, MMP, and several other proteins that play a significant role in processes such as inflammation and tissue remodeling. The aforementioned processes and mechanisms are explicated without any modifications to the scientific language or fundamental significance.

STATs (Signal Transducers and Activators of Transcription): STATs represent a family of transcription factors that hold a pivotal role in mediating signal transduction and regulating gene expression in response to cytokines and growth factors. This family comprises seven distinct STAT proteins, denoted as STAT1-4, STAT5A, STAT5B, and SAT6. Each of these STAT proteins is associated with specific cellular functions and signaling pathways, contributing to the intricate orchestration of cellular responses to extracellular signals. These characteristics remain consistent with the scientific terminology and core meaning.

Molecular Details and Activation of STATs:
The activation of cytokine receptors, including those for interferons (IFNs) and interleukins (ILs), triggers the phosphorylation of STAT proteins by kinases associated with the receptor, predominantly members of the Janus kinase (JAK) family. Once phosphorylated, STATs can form homo- or heterodimers and subsequently migrate into the cell nucleus, where they bind to specific DNA sequences known as STAT response elements (SREs) situated within the promoters of target genes. Moreover, STATs have the capacity to interact with other transcription factors, leading to the modulation of gene expression. The regulatory role of STATs encompasses the control of gene expression in various cellular processes, including immune responses, cell proliferation, differentiation, and apoptosis. For example, STAT3 is recognized for its involvement in regulating the expression of PRO-I cytokines such as IL-6 and IL-23, while STAT1 plays a crucial role in mediating the antiviral response orchestrated by IFNs. These descriptions remain in alignment with the scientific terminology and core concepts.

The Interplay of NF-κB, AP-1, and STATs in Inflammation:
STATs, NF-κB, and AP-1 often exhibit cross-talk and collaborate to fine-tune the inflammatory response. They can directly interact with each other and regulate expression of overlapping target genes, influencing duration and intensity of inflammation. Additionally, their activation can be influenced by common signaling pathways, such as those involving MAPKs and cytokine receptors.

Signaling pathways: MAPK, PI3K/Akt, and JAK/STAT pathways
Signaling pathways play crucial role in transmitting extracellular signals to the intracellular machinery, regulating various cellular processes, including inflammation. Among the prominent signaling pathways involved in inflammation, the MAPK (Mitogen-Activated Protein Kinase), PI3K/Akt (Phosphatidylinositol 3-Kinase/Protein Kinase B), and JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription) pathways are central in coordinating and modulating the inflammatory response. Understanding the molecular details and interactions within these pathways provides insights into the complex mechanisms underlying inflammation [31].

MAPK (Mitogen-Activated Protein Kinase) Pathway:
The MAPK pathway is a conserved signaling cascade involved in the regulation of numerous cellular processes, including cell proliferation, differentiation, survival, and inflammation. It consists of three main branches: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 and MAPK[32].
Molecular Details of the MAPK Pathway:
The MAPK pathway is triggered by activating cell surface receptors, such as receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs), in response to various extracellular stimuli. Upon activation, the pathway proceeds through a series of phosphorylation events involving three kinases: MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK), and MAP kinase (MAPK). The ERK pathway is primarily involved in cell growth, differentiation, and survival. ERKs are activated by sequential phosphorylation by MEK1/2 (MAPKK) and Raf kinases (MAPKKK). p38 and JNK Pathways: These MAPKs mainly regulate stress, inflammation, and cell death. Both intrinsic and extrinsic pathways can initiate apoptosis, which is followed by the endo-nucleolytic cleavage of chromosomal DNA and the caspase-dependent proteolysis of hundreds of cellular proteins. Other than these two pathways, a third pathway entails perforin and granzyme-dependent cell death as well as cytotoxicity mediated by T cells [32]. However, they are activated by dual phosphorylation by MKK4/7 and MKK3/6, respectively. Activated MAPKs translocate to the nucleus and phosphorylate various transcription factors, including AP-1 (c-Jun and c-Fos) and Elk-1, leading to the modulation of gene expression involved in inflammation.

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PI3K/Akt (Phosphatidylinositol 3-Kinase/Protein Kinase B) Pathway:
The PI3K/Akt pathway is an essential signal transduction mechanism that modulates various cellular functions, such as viability, proliferation, metabolic homeostasis, and inflammatory response. Extracellular stimuli, including growth factors and cytokines, induce its activation.

Molecular Details of the PI3K/Akt Pathway:
The PI3K pathway is initiated by the activation of cell surface receptors, such as receptor tyrosine kinases (RTKs) and GPCRs, leading by stimulating phosphoinositide 3-kinase (PI3K). PI3K converts phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3) by phosphorylation. Akt Activation: PIP3 recruits Akt (also known as protein kinase B) to the plasma membrane, where it is activated through phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) and mammalian target of rapamycin complex 2 (mTORC2). Akt phosphorylates various downstream effectors, including glycogen synthase kinase 3 (GSK3), Forkhead box O (FOXO) transcription factors, and the mammalian target of rapamycin complex 1 (mTORC1), regulating protein synthesis, cell growth, and survival. Akt can also influence inflammation by regulating the activity of transcription factors such as NF-κB and AP-1, as well as modulating the expression of inflammatory mediators and cytokines. JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription) Pathway: The JAK/STAT pathway is primarily involved in cytokine signaling and plays a critical role in inflammation, immune responses, and cellular proliferation.

Molecular Details of the JAK/STAT Pathway:
The process of cytokine binding to cell surface receptors that are particular in nature leads to the activation of Janus kinases (JAKs) that are linked with these receptors. This activation results in the phosphorylation of the receptor, therefore creating docking sites for STAT proteins. Upon recruitment to the receptor, STAT proteins undergo phosphorylation by JAKs and then assemble into homo- or heterodimers. The STAT dimers that have undergone phosphorylation undergo translocation to the nucleus, where they exhibit binding affinity towards particular DNA sequences known as STAT response elements (SREs) located inside the promoters of target genes. The process of binding results in the subsequent activation or suppression of transcription of the target gene. The STAT proteins, including STAT3 and STAT1, are essential in the regulation of PRO-I cytokine production and immunological responses. The MAPK, PI3K/Akt, and JAK/STAT pathways demonstrate interconnectivity and engage in crosstalk, hence impacting the activation and downstream signalling of one another. As an instance, it has been shown that mitogen-activated protein kinases (MAPKs) has the capability to phosphorylate and then activate Akt. In turn, Akt is capable of exerting its influence on the activity of Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway through regulating the suppressor of cytokine signalling (SOCS) proteins. Furthermore, these signalling pathways have the ability to converge on shared transcription factors, such as NF-κB and AP-1, in order to regulate the expression of genes involved in inflammation.

Regulation of cytokines and chemokines synthesis
The regulation of cytokine and chemokine production is a fundamental strategy in the control of inflammatory processes. Cytokines and chemokines are crucial mediators of immune responses, playing roles in inflammation, immune cell activation, and recruitment.

Cytokines: Cytokines are small protein signaling molecules in intercellular communication, playing a crucial function in immunological reactions and inflammation. They have a variety of impacts on target cells and are generated by many cellular components, notably IC.

Molecular Details of Cytokine Production:
Cytokine genes contain specific DNA sequences called cytokine response elements (CyREs) in their promoter regions. Transcription factors like AP-1, NF-κB and STATs, bind to these CyREs and regulate cytokine gene transcription. In reaction to extracellular stimuli like pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), several signaling pathways, including MAPK, PI3K/Akt, and JAK/STAT pathways, can cause cytokine production.
Activation of immune cells (IC): The IC such as macrophages, dendritic cells, and T cells, are essential in the process of cytokine synthesis. Upon initiation, these cells secrete cytokines, which subsequently stimulate and enlist additional IC, so enhancing the immunological response.
Autocrine and Paracrine Signaling: Cytokines have actions in both an autocrine, influencing the cell which produced them, and a paracrine manner, affecting adjacent cellular component. This allows for coordinated immune responses and communication between IC. Cytokine production is tightly regulated to prevent excessive inflammation. Negative feedback mechanisms involve the production of AI cytokines, such as IL-10 and transforming growth factor-beta (TGF-β), which decreases the production of PRO-I cytokines. Various molecules, including inhibitors of

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kinases or transcription factors, can interfere with signaling pathways involved in cytokine production, thereby modulating their expression. Epigenetic modifications, such as methylated DNA can modulate cytokine genetical upregulation. These modifications can be targeted by specific inhibitors, offering potential therapeutic interventions. Regulatory T Cells (Tregs) has a significant potential in maintaining homeostasis by suppressing excessive immune responses with synthesis of PRO-I cytokines.

Chemokines: Chemokines, chemotactic cytokines, modulate the cellular migration and recruitment to sites of inflammation. They are involved in orchestrating immune cell trafficking and directing the movement of specific immune cell subsets.

Molecular Details of Chemokine Production:
Similar to cytokines, chemokine genes contain specific promoter elements that are recognized by transcription factors, such as NF-κB, AP-1, and STATs, leading to their gene transcription.
Various signaling pathways, including MAPK and NF-κB pathways, can activate the production of chemokines in response to inflammatory stimuli or immune cell interactions.
Chemokines are often induced rapidly through specific stimuli which include cytokines, microbial components, or tissue damage signals.

Regulation of Chemokine Production:
Similar to cytokines, chemokine production is regulated through feedback mechanisms. AI cytokines, such as IL-10 and TGF-β inhibit chemokine synthesis. Molecules like SOCS (suppressor of cytokine signaling) proteins can inhibit chemokine production by interfering with signaling pathways involved in their expression. Chemokine gene expression can be influenced by epigenetic modifications, which can be targeted by specific inhibitors to modulate chemokine production. Therapeutic strategies aim to modulate cytokine and chemokine.

Modulating Cytokines and Chemokines in Inflammation:
Production to restore immune balance and mitigate excessive inflammation. Inhibiting key signaling pathways involved in cytokine and chemokine production, including MAPK, PI3K/Akt, or JAK/STAT pathways, can help modulate their expression. Blocking specific PRO-I cytokines, such as TNF-α, interleukin-1 (IL-1), or interleukin-6 (IL-6), using monoclonal antibodies or soluble receptors, can reduce inflammation in diseases where these cytokines play a prominent role. Blocking specific chemokine receptors or their ligands can disrupt the chemotactic gradient and inhibit immune cell recruitment, thereby reducing inflammation and tissue damage. Enhancing the function or number of regulatory T cells (Tregs) can promote immune tolerance, suppress excessive inflammation, offering a potential treatment procedure.

Suppression of nitric oxide (NO) production
Modulating the synthesis of NO, a crucial inflammatory mediator, represents an important strategy in the management of inflammation. NO is produced by different cellular components, such that immune and endothelial cellular components, and plays a vital role in immunization and vascular equilibrium. Understanding the molecular details of NO synthesis and the mechanisms of its suppression provides insights into potential therapeutic strategies for modulating inflammation-related diseases. The inhibitory effects of flavonolignans from *Triticum aestivum* Linn on the formation of NO were seen in RAW 264.7 macrophages activated with LPS. Among the compounds that were studied, it was shown that they effectively decreased the production of NO produced by lipopolysaccharide (LPS) [33, 34].

Molecular Details of NO:
NO is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). There are three isoforms of NOS: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). Each isoform is regulated differently and contributes to NO production under specific conditions. nNOS is constitutively upregulated at brain and skeletal muscles. These modulate in neurotransmission, muscle relaxation, and neuronal signaling. The regulation of nNOS involves calcium-dependent activation and interaction with regulatory proteins. Increased intracellular calcium levels, triggered by neuronal stimulation, activate nNOS. Calcium binds to calmodulin, which associates with nNOS, leading to conformational changes and the catalytic activation of the enzyme. nNOS interacts with various proteins, including PSD-95 and caveolin-3, which can modulate its activity and subcellular localization. nNOS is predominantly localized at the postsynaptic density in neurons, allowing for localized NO production and modulation of synaptic activity. Inducible nitric oxide synthase (iNOS) is an isoform that is not produced constitutively, but rather may be stimulated in response to inflammatory stimuli, including cytokines and microbial metabolites. It is primarily expressed in IC and contributes to the immune response and host defense. iNOS expression is regulated at the transcriptional level. Inflammatory signals including cytokines (e.g., interferon-gamma, TNF-α) and bacterial lipopolysaccharides (LPS), induce the transcription factors upregulation including NF-κB and STATs, which bind to specific sequences in the iNOS

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promoter and enhance its transcription. Unlike nNOS, iNOS is not dependent on calcium for its activation. Instead, it is constitutively active due to its unique structure, allowing for sustained and high levels of NO production. Post-translational modifications modulate iNOS activity, including phosphorylation and S-nitrosylation, which can affect its catalytic function and stability. eNOS is constitutively upregulated in endothelial lining blood vessels. It plays a vital play in regulating vascular tone, blood flow, and platelet aggregation. eNOS is activated in response to increased intracellular calcium levels, which are mediated by various stimuli, including shear stress and receptor-mediated signaling. eNOS interacts with several regulatory proteins, including calmodulin and heat shock protein 90 (Hsp90), which modulate its enzymatic activity and stability. eNOS activity can be regulated by phosphorylation at specific sites, such as serine 1177, which enhances its catalytic function and promotes NO synthesis. In certain inflammatory conditions, excessive NO production can contribute to tissue damage and inflammation-related pathologies. Therefore, strategies to suppress NO synthesis can be employed to mitigate these effects. Inhibition of NOS Enzymes: Non-selective NOS inhibitors, such as L-NMMA (NG-monomethyl-L-arginine) and L-NAME (Nω-nitro-L-arginine methyl ester), can inhibit all isoforms of NOS, reducing overall NO production. Specific inhibitors targeting iNOS, such as aminoguanidine and S-methylisothiourea, can selectively inhibit inducible NO production, sparing constitutive NOS isoforms(35).NF-κB, a transcription factor which induces iNOS upregulation. Inhibiting NF-κB activation through various approaches, such as using specific inhibitors or natural compounds, can suppress iNOS transcription and subsequent NO synthesis. Inflammatory cytokines, such as interferon-gamma and TNF-α, are potent inducers of iNOS expression. Blocking these cytokines or their signaling pathways can attenuate iNOS activation and NO production. Reactive oxygen species (ROS) can activate NOS enzymes and enhance NO production. Antioxidants, can scavenge ROS and reduce their availability, thereby indirectly suppressing NO synthesis. A well-known antioxidant is lycopene. It can shield lipids, proteins, and DNA from oxidation. Lycopene can also interact with ROS[36].

Therapeutic Applications:

Potential of CUR, probiotics, and OFG in IBD

CUR: CUR is a biologically active compound extracted from turmeric, a traditional medicine. It exhibits strong antioxidant, AI as well as immunomodulatory (IMM) properties. CUR exerts its effects by targeting multiple molecular pathways involved in inflammation and immune regulation [37]. CUR has the ability to impede the activation of NF-κB, which is a crucial transcription factor that plays a significant role in the synthesis of pro-inflammatory cytokines. The process involves the inhibition of phosphorylation and degradation of the inhibitory protein IκB, hence impeding the translocation of NF-κB to the nucleus and consequent activation of gene expression related to inflammatory mediators. Cytokine-induced neutrophil chemoattractant has the ability to modulate the MAPK signalling pathway, which encompasses the JNK, ERK, and p38 MAPK. This intricate network of signalling molecules plays a pivotal role in the regulation of inflammatory responses. It inhibits the phosphorylation and activation of MAPKs, thereby attenuation synthesis of PRO-I cytokines. Macrophages as well as neutrophils move at areas of injury as part of the cellular response to inflammation. By phagocytosis and the generation of reactive oxygen species (ROS), these cells fight the invader (1). Additionally, the red blood cells (RBCs) are largely prone to xenobiotics, since they contain significant amounts of PUFAs, they are extremely vulnerable to endogenous oxidative damage (38). The stomach mucosa's inner wall entirely tore apart in experimental animals. Ulceration may result from the formaldehyde-induced injury to the stomach mucosa [39]. CUR exhibits strong antioxidant activity, neutralizing free radicals and alleviating oxidative stress. By neutralizing ROS, CUR helps to mitigate tissue damage and inflammation associated with IBD. CUR can modulate immune responses by affecting immune cell proliferation, differentiation, and cytokine production. The use of AI facilitates the generation of automated responses, while concurrently impeding the activation of IC implicated in the development of IBD.

Probiotics: Probiotics refer to living bacteria that, when ingested in sufficient quantities, have beneficial effects on human health. These entities play a pivotal role in the maintenance of gut homeostasis and the modulation of immunological responses. Several strains of probiotics have shown promise in the treatment of IBD via their ability to target different cellular processes. Dysbiosis, an imbalance in the gut microbiota, is associated with IBD. Probiotics have the ability to reinstate the equilibrium of microorganisms by facilitating the proliferation of advantageous bacteria while impeding the proliferation of detrimental bacteria. These substances aid in enhancing the integrity of the gastrointestinal barrier and modulating immunological responses. Probiotics have the ability to interact with the gut-associated lymphoid tissue (GALT) and regulate the generation of cytokines that possess both PRO-I and AI properties in the context of immune response. One potential mechanism by which they may exert their effects is via the enhancement of regulatory T-cell activity, the suppression of PRO-I immunological responses, and the promotion of immune tolerance. Probiotics enhance the integrity of the gut epithelium by

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facilitating the synthesis of tight junction proteins, such as occludin and claudin, so reinforcing the intestinal barrier. The barrier function serves the purpose of inhibiting the transfer of pathogenic microorganisms and inflammatory chemicals through the intestinal epithelium. Probiotic microorganisms have the ability to undergo fermentation of dietary fibres, resulting in the production of short-chain fatty acids (SCFAs), including butyrate. SCFAs function as a vital energy source for colonocytes and play a significant role in improving gut health. They do this by facilitating AI responses and preserving the integrity of the mucosal lining.

OFG: OFG, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are examples of polyunsaturated fatty acids (PUFA) that are often present in fish liver oil. They exhibit AI properties and have been investigated for their potential in managing IBD. OFG can modulate the production of eicosanoids which are PRO-Iin nature, like prostaglandins, leukotrienes, by competing with omega-6 fatty acids. They act as precursors for the production of less inflammatory eicosanoids, reducing inflammation in the gut.

OFG can affect IC function and cytokine production. They stimulate the synthesis of AI cytokines, like interleukin-10, and suppress the synthesis of PRO-I cytokines, like interleukin-1β and TNF-α. The AI activity of *Pterospermum acerifolium* root extract's ethanolic fraction initially suggests that it might be caused by inhibition of arachidonic acid metabolism. Inhibiting prostaglandin production may also result in gastric hypersecretion and injury to the stomach mucosa in IBD [40, 41]. OFG has a role in maintaining the integrity of the intestinal barrier function via its capacity to upregulate the expression of tight junction proteins and reduce intestinal permeability. The barrier function of the intestine plays a pivotal role in the prevention of luminal antigens and inflammatory chemicals from entering the intestinal tissue.

Rheumatoid Arthritis (RA):

According to chronic inflammatory models of inflammation, it has been shown that the administration of tea extract at the given levels significantly mitigated formaldehyde-induced arthritis in rats. Therefore, suggesting the possibility of possessing similar anti-arthritic capabilities [9]. Chronic NSAID use in arthritic situations may actually make the condition worse [15]. Infections caused by Chlamydia trachomatis, Yersinia, Salmonella, Shigella, and Campylobacter are seen in individuals with a genetic susceptibility, such as HLAB27, leading to the development of persistent inflammation. The precise process by which immune activation occurs and then leads to the migration of IC to distant synovial tissue remains unclear [42]. The bacteria have developed a chemically mediated communication system called quorum sensing to initiate the formation of this matrix [43, 44].

The most prevalent condition that affects cartilaginous joints is osteoarthritis. Rehabilitation and physiotherapy were always recommended to combat joint degradation and prevent muscle atrophy in order to lessen discomfort and increase mobility [45].

Mollugo oppositifolia Linn. (Molluginaceae family) has been traditionally used in the treatment of fever, cough, discomfort, inflammation, jaundice, stomach pain, intestinal and urinary tract infections, appetite disorder, malaria, viral illnesses, helminthiasis, and other disorders [46]. Ethanolic extract of Molluginaceae family has been reported to have AI effect on arthritis in a mouse model [47].

Mechanism of CUR for modulating joint inflammation:

Curcumin (CUR) inhibits the activation of NF-κB, an essential transcriptional regulator that controls the expression of PRO-I genes. The compound inhibits the phosphorylation and degradation process of IκB, hence impeding the translocation of NF-κB to the nucleus and the consequent transcription of genes encoding inflammatory mediators. CUR has the ability to decrease the production of PRO-I cytokines, namely interleukin-1β (IL-1β), interleukin-6 (IL-6), and TNF-α, by inhibiting the activity of NF-κB and other related signaling pathways. The compound CUR has the ability to impede the process of phosphorylation of MAPKs, such as ERK, JNK, and p38 MAPK. These MAPKs are known to have significant involvement in the regulation of inflammatory reactions. By targeting these kinases, CUR reduces the synthesis mediators which are inflammatory in nature. CUR can suppress activity of MMPs, enzymes that degrade cartilage and contribute to joint destruction in arthritis. It inhibits the transcription of MMPs also promotes the synthesis of tissue inhibitors of metalloproteinases (TIMPs). By lowering the production of exopolysaccharide and alginate, CUR from C. longa greatly inhibits the development of biofilm. Instead of microbial cells, hydrated EPS makes up the majority of the biomass in the biofilms [48]. Microcolonies are created from the biofilm cluster by the continuous, dynamic spatial structuring of EPS molecules in the matrix [49]. It is also known that CUR prevents uropathogens from swimming and swarming [50].

Green Tea and Epigallocatechin-3-Gallate (EGCG):

Green tea contains a substantial amount of polyphenols, among which the most prevalent and biologically active ingredient is EGCG (9, 51). The effects of EGCG have been investigated in relation to its impact on AI as well as its potential for mitigating joint inflammation. Epigallocatechin gallate (EGCG) has the capacity to

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impede the activation of NF-κB, hence averting the following synthesis of PRO-I cytokines and chemokines. EGCG has been shown to possess inhibitory properties against the activation and production of matrix metalloproteinases (MMPs), hence exerting a protective effect against cartilage degradation in the context of arthritis. EGCG has the ability to diminish the phosphorylation of mitogen-activated protein kinases (MAPKs), namely extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. This attenuation subsequently results in a decrease in the synthesis of inflammatory mediators. EGCG has antioxidant characteristics and has the ability to eliminate free radicals, hence mitigating oxidative stress and inflammation in joint tissues [14].

Fish Oil and OFG: Fish oil is a dietary source that contains a significant amount of OFG, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These compounds have been extensively studied for their AI properties and possible therapeutic effects on joint inflammation. The OFG have the ability to engage in competition with omega-6 fatty acids in the biosynthesis of eicosanoids, including prostaglandins and leukotrienes. The process of OFG conversion results in the production of eicosanoids with reduced inflammatory properties, hence mitigating joint inflammation. The function of IC and the generation of cytokines may be altered by the administration of OFG. They facilitate the synthesis of AI cytokines, such as interleukin-10 (IL-10), while impeding the synthesis of PRO-I cytokines, such as interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNF-α).

Preservation of Cartilage Integrity: OFG can help maintain cartilage integrity by reducing the production of enzymes, such as MMPs, which contribute to cartilage degradation in arthritis.

Quercetin: Quercetin is a widely studied flavonoid with strong AI properties. It inhibits the activity of COX and 5-LOX enzymes, reducing the production of PRO-Ieicosanoids. Quercetin also modulates NF-κB signaling and downregulates PRO-I cytokines. Branches and leaves of several yew species contain a lot of quercitrin and isoquercitrin [52]. Additionally, Paclitaxal which is obtained from western yew sp, have shown anti-tumor activity [53,54]. To determine whether paclitaxel was soluble in different oils, solubility research was carried out. Triacetin was shown to have a higher level of paclitaxel solubility than other oils. Triacetin was selected as the oil phase for the succeeding stages involved in the development of paclitaxel formulations. This decision was made due to certain factors [55].

Apigenin: Apigenin, found in parsley, chamomile, and celery, possesses AI properties by inhibiting COX-2 and reducing the production of PRO-I cytokines. Apigenin also modulates NF-κB and MAPK signaling pathways. It is also found in *Acanthus ilicifolius*. In various types of inflammation, an extract from the leaves of *Acanthus ilicifolius* showed the existence of considerable AI action. Additionally, the extract was discovered to markedly downgrade production of cytokines as well as to reduce the action of COX and 5-LOX [56].

Resveratrol: Resveratrol (RES), a polyphenolic compound of natural origin. It has been investigated for its potential in managing RA. RES shows AI effects by preventing NF-κB signaling, reducing the generation cytokines of PRO-I nature, as well as suppressing activity of inflammatory enzymes, such as COX-2. Additionally, it modifies the expression of genes that are linked to inflammatory processes and immunological responses. RES has significant antioxidant properties, effectively mitigating the detrimental effects of free radicals and reducing oxidative stress within the joint tissues impacted by rheumatoid arthritis (RA). RES has been demonstrated to affect immunological responses by modulating the generation of cytokines and chemokines, improving immune tolerance, and reducing the activation of IC implicated in RA pathology. RES has demonstrated potential in inhibiting the production of matrix metalloproteinases (MMPs), enzymes responsible for cartilage degradation in RA, thereby protecting against joint damage. trans-RES also has been found in cotton seed. A fluorine-free coating with superhydrophobic and superoleophilic properties, as well as antibacterial and photocatalytic activities, was synthesized in situ on cotton fabric by a simple solution method using zirconium zinc stearate as the main component [57]. Numerous investigations conducted on several types of malignancies, including prostate cancer, have shown the chemopreventive properties of some phytochemicals obtained from dietary sources. Notable examples of these phytochemicals include CUR, ursolic acid (UA), EGCG, and RES. These phytochemicals were synthesized on cotton fabric by a simple solution method using zirconium zinc stearate as the main component [58]. The triterpenoid group's most promising member, UA, is a pentacyclic triterpenoid which has Ursane, lupane, and oleanane form the fundamental structure of UA, resulting in a variety of pharmacological actions. Although it has several physiological benefits, such as AI, anti-cancerous, bone regeneration, anti-fungal, hepatoprotective, and antioxidant qualities, it has one significant drawback: it has lack of solublity in water and has low bio-availability when administered using a drug delivery system.

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Ginger: Ginger is a root spice containing several bioactive compounds which is antioxidant as well as AI. Studies have explored its usefulness in RA. AI Effects: Ginger has been investigated for its potential benefits in RA. It exhibits AI properties by downregulating the expression of PRO-I cytokines, such as TNF-α and IL-1β, and inhibiting the performance of COX and LOX. It also modulates NF-κB signaling and reduces inflammatory genes. Zingerone, main component of ginger, can suppress and eliminate P. aeruginosa biofilms, which also play a vital role in microorganism mediated inflammation [50]. Ginger possesses antioxidant properties, protecting against oxidative stress-induced damage in joint tissues affected by RA. Ginger has shown potential in reducing pain and improving joint function in RA patients. It may exert its effects through the modulation of inflammatory mediators and the improvement of blood circulation to affected joints.

Dermatological Disorders:
Eczema and psoriasis are chronic inflammatory skin conditions characterized by redness, itching, and inflammation. Following are natural resources used in their management.

Aloe Vera: It is plant of succulents having soothing properties. It contains various bioactive compounds, including polysaccharides, anthraquinones, and vitamins, which contribute to its AI effects. Aloe vera can suppress the production of PRO-I cytokines, such as TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6). It inhibits the stimulation of NF-κB, a important factor related to expression of aforementioned cytokines. Aloe vera can regulate immune responses by affecting the proliferation and activation of IC, such as T cells and dendritic cells. It can promote AI responses and inhibit the release of mediators inflammation. Aloe vera enhances wound healing and improve skin barrier function. It promotes the synthesis of collagen and hyaluronic acid, which are essential for tissue repair and barrier integrity.
Chamomile: Chamomile is a herb known for its calming and AI properties. It contains various bioactive compounds, including chamazulene, flavonoids, and terpenoids, which contribute to its AI effects. Chamomile can inhibit cyclooxygenase (COX) and lipoxygenase (LOX), which can release inflammatory mediators like prostaglandins and leukotrienes. Chamomile has been shown to inhibit the synthesis of PRO-I cytokines, namely interleukin-8 (IL-8) and interleukin-17 (IL-17), implicated in the pathogenesis of eczema and psoriasis. Chamomile has antioxidant properties by scavenging free radicals and mitigating skin oxidative stress, perhaps influencing the inflammatory processes seen in eczema and psoriasis.

Liquorice Root: Liquorice root is known for its AI and skin-soothing effects. It contains bioactive compounds, such as glycyrrhizin and flavonoids, which contribute to its AI effects. Liquorice root exerts an inhibitory role on the activity of COX and LOX enzymes, reducing the generation of PRO-I mediators. Liquorice root exhibits IMM effects by suppressing the activation of IC involved in inflammation, such as T cells and dendritic cells. It can also regulate the production of cytokines and chemokines in eczema and psoriasis. Liquorice root enhances the function of skin barrier by promoting the synthesis of ceramides, which are essential for maintaining skin hydration and integrity.

Topical application of natural products for skin inflammation
Aloe Vera Gel: Aloe vera gel which has soothing and AI properties. The following formulations permit its topical usage:

Gel Form: Aloe vera gel is widely available in its natural gel form. It can be directly applied to the affected skin, providing immediate cooling and relief. The gel formulation helps to hydrate the skin, reduce inflammation, and promote wound healing.

Nano-emulgel:
For improvement of therapeutic effect polymeric binding is well known, which can further be beneficial if this drug can be delivered through a nanocarrier system [59] . Nanosized emulsion globules can be created by various processes which includes high or low energy, and then, a gelling agent can be added to convert the substance into nanoemulgel. Nanoemulgel is essentially an topical gel formulation based on an emulsion [60]. Natural, synthetic, and semi-synthetic forms of polymeric polymers, surfactants, and fatty substances are used in the manufacturing of nanoemulgels, with globule sizes having a range of 5 to 500 nm. [61]. It is because of their stability, high solubilization potential, and simplicity of preparation, using nanoemulsions via a number of different routes, has increased for various pharmacological aspects which includes cardiovascular, antimicrobial, anticancer and ophthalmic [62, 63].

Hydrogel:
Hydrogels are effective and often used in the biomedical industry. As part of ongoing efforts to promote wound healing, the AI performance of hydrogel dressings has greatly improved in recent years, addressing a number of clinical issues [64].

Creams and Lotions: Aloe vera gel can be incorporated into creams or lotions, along with other ingredients such

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as moisturizers and emollients, to provide additional hydration and soothe the inflamed skin. Gels with Active Ingredients: Aloe vera gel can be combined with other natural AI compounds, such as chamomile or calendula extracts, to enhance its therapeutic effects. These combinations can be formulated into gels for targeted application and enhanced synergistic benefits.

Chamomile Extract: Chamomile extract has AI and calming effects on the skin. It can be used in the following formulations. Chamomile extract can be incorporated into creams or ointments, along with suitable emollients and skin-nourishing ingredients. These formulations provide a protective barrier, moisturize the skin, and deliver the AI benefits of chamomile.

Herbal Infused Oils: Chamomile flowers can be infused in carrier oils, which includes olive oil or coconut oil, to extract the active compounds. The resulting infused oils can be applied directly to the skin or used as a base for formulating various topical products, including creams, lotions, or balms.
Tea Tree Oil: The antibacterial and AI effects of tea tree oil are well-documented. It can be used in the following formulations.

Diluted Oil: Tea tree oil should always be diluted before application to avoid skin irritation. Dilution can be done in a carrier oil, such as coconut oil or jojoba oil, and applied topically to the affected skin. This formulation helps reduce inflammation, soothe irritation, and address bacterial or fungal infections. Tea tree oil can be incorporated into creams or gels with suitable emollients and skin-friendly ingredients. These formulations provide targeted application and can be used for managing conditions such as acne or eczema.

Calendula Cream: Calendula, derived from marigold flowers, is known for its AI and wound-healing nature. Calendula extracts or infused oils can be incorporated into creams or balms to provide moisturization, reduce inflammation, and promote skin healing. These formulations are commonly used for managing skin irritations, eczema, or minor wounds.
Coconut Oil: Coconut oil is a natural product which is versatile and offers moisturizing and AI effects. Coconut oil can be solidified or combined with other solid ingredients, such as beeswax or shea butter. This formulation is particularly useful for conditions like chapped skin, dry patches, or minor skin irritations. Coconut oil can be applied directly to the skin as a light oil. It helps moisturize, soothe inflammation, and improve the skin barrier function. It is commonly used for conditions like eczema, psoriasis, or dermatitis.

Future Perspectives and Challenges:
Synergy and Combination Therapies:
Synergy and combination therapies involving natural products have gained attention in the field of inflammatory pharmacology. In the context of managing inflammation, combining natural products can potentially offer enhanced efficacy and synergistic effects [65]. Enhanced AI Effects: Combining natural products with complementary mechanisms of action can lead to enhanced AI effects. Different natural products may target distinct molecular pathways involved in inflammation, and their combination can work synergistically to achieve a more comprehensive and potent AI response.

CUR and ginger: Both CUR and ginger exhibit AI properties through NF-κB signaling and suppressing the cytokines, that are PRO-I in nature. Combining them may lead to enhanced inhibition of NF-κB activation and downstream inflammatory pathways.

Resveratrol and quercetin: RES and quercetin both possess AI and antioxidant properties. Their combination may result in synergistic effects by scavenging free radicals, inhibiting inflammatory enzymes, and modulating multiple signaling pathways involved in inflammation.

Modulation of Multiple Molecular Pathways:
Combining natural products with diverse mechanisms of action can provide broader coverage and modulation of these pathways. This approach can lead to a more comprehensive suppression of inflammatory mediators and signaling pathways.

Boswellia serrata extract and green tea extract: Boswellia serrata extract inhibits the 5-LOX pathway, while green tea extract modulates NF-κB and MAPK pathways. The concurrent action of this combination treatment may effectively inhibit the production of PRO-I leukotrienes and modulate the activation of transcription factors implicated in the expression of inflammatory genes.

OFG and vitamin D: OFG have AI effects by inhibiting PRO-Imediators, while vitamin D has IMM properties. Combining them may enhance the AI and IMM effects, potentially benefiting inflammatory conditions like RA or IBD.
Combination therapies can offer an opportunity to reduce the dosage of individual components while maintaining therapeutic efficacy. This approach may help minimize potential side effects or toxicity associated with high doses of a single natural product. By combining substances with complementary mechanisms, lower doses of each component may be

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sufficient to achieve the desired AI actions. Individual variations, including genetic factors and disease characteristics, may influence the response to combination therapies.

Novel Natural Product Sources:
The search for new and effective natural products for drug discovery has led researchers to explore unexplored biodiversity and untapped natural resources. These efforts have revealed the vast potential of diverse ecosystems, including marine environments, as valuable sources of novel natural products with therapeutic properties. The marine-derived natural compounds have the potential as therapeutic leads and promising AI characteristics. As a result, these chemicals have generated a lot of interest from researchers. This section will discuss the investigation of marine biodiversity and the application of naturally occurring compounds originating from marine environments in the search for AI drugs.

Unexplored Marine Biodiversity: Earth's oceans harbor a rich diversity of marine organisms, many of which remain unexplored. These include bacteria, fungi, algae, sponges, corals, and invertebrates. These organisms have evolved unique biochemical and physiological adaptations to survive in challenging marine environments, making them potential sources of novel bioactive compounds. Discovering uncharted marine biodiversity has promising prospects for the identification of naturally occurring substances and phytochemicals with therapeutic potential.

Marine-Derived Natural Products for Anti-inflammatory Drug Discovery: It has been discovered that a range of bioactive substances with AI effects are produced by marine creatures. These compounds have shown the potential for developing novel AI drugs. The largest mollusca phylum in the world, *Telescopium sp*., secretes a blue liquid when agitated. It was discovered that the blue secretion metabolized para-amino benzoic acid (PABA), a N-acetyl transferase (NAT) substrate. The blue secretion of the bioactive fraction was identified, and it was subsequently used as a biomarker to monitor marine pollution (66). These mangrove snails are antioxidant in nature and contain bioactive substances (67)
Marine Sponge-Derived Compounds: Marine sponges are prolific producers of bioactive compounds. Compounds derived from marine sponges, such as alkaloids, terpenes, and peptides, have demonstrated AI effects by modulating various molecular targets involved in inflammation pathways.

Coral-Derived Compounds: Coral reefs are known for their high biodiversity and unique chemical profiles. Coral-derived compounds, including diterpenes, polyketides, and alkaloids, have shown AI activity by targeting pro-inflammatory mediators and signaling pathways involved in inflammation.

Microorganisms from Marine Environments: Marine bacteria and fungi represent a vast and untapped resource for natural product discovery. Secondary metabolites produced by these bacteria have a variety of chemical and biological properties. Several marine-derived microbial compounds have exhibited AI effects by targeting inflammatory mediators, cytokines, and signaling pathways.

Challenges and Future Perspectives: The exploration and utilization of marine biodiversity for AI drug discovery pose several challenges. These include the sustainable collection of marine organisms, the development of effective extraction and purification methods, and the identification of lead compounds with optimal pharmacokinetic properties. One study showed that a developing precursor molecule in medicinal chemistry for the discovery of multifunctional therapeutic drugs is 5-Arylidene-2,4-thiazolidinedione (5-A-TZD). The Knoevenagel Condensation (KC) is one of the best methods in contemporary organic chemistry for synthesis of this precursor molecule. The therapeutic properties of the 5-A-TZD framework include antidiabetic, anticancer, antibacterial, and AI effects [68]. Additionally, the conservation of marine ecosystems and adherence to ethical guidelines are essential for preserving these valuable resources. Future perspectives involve advanced techniques, such as metagenomics and genome mining, to access the untapped genetic potential of marine microorganisms. These approaches enable the identification of biosynthetic gene clusters encoding novel natural products. Furthermore, collaboration between researchers, biotechnological companies, and conservation organizations can facilitate the sustainable development and commercialization of marine-derived natural products.

Standardization and Quality Control:
Standardization of Natural Products: Standardization involves establishing consistent and reproducible quality parameters for natural products. It aims to ensure that each batch of the product contains the same profile and concentration of active compounds, facilitating reliable efficacy and safety evaluations. By combining the concentrations of the analyte and internal standard with the targeted analytical solution and matrix at a consistent concentration, as well as an external substance known as an internal standard, a calibration standard curve is produced [69].

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Botanical Identification: To maintain consistency, it is crucial to accurately identify the plant species and plant components utilised in the product. This is achieved through botanical reference materials, taxonomic expertise, and validated analytical techniques, such as DNA barcoding or chromatography.

Active Compound Quantification: Determining the concentration of active compounds, such as specific phytochemicals or markers, provides a measure of product potency and allows for consistent dosing [70].

Quality Parameters: Defining quality parameters, such as microbial limits, heavy metal content, and pesticide residues, helps ensure the safety and purity of the product [71].

Quality Control in Natural Product Manufacturing: Quality control measures are incorporated into every step of the manufacturing process to monitor and verify the quality of natural products. Strict criteria are established for the selection and sourcing of raw materials. This involves evaluating factors such as geographic origin, cultivation practices, and harvesting methods to ensure consistency and quality. Following Good Manufacturing Practices (GMP) guidelines helps ensure that manufacturing processes are carried out in a controlled and standardized manner. This includes proper documentation, facility cleanliness, equipment calibration, and personnel training. Regular testing of raw elements and finished products is essential to verify their identity, purity, and potency [72]. High-performance liquid chromatography (HPLC) or mass spectrometry (MS), are used to quantify active compounds and detect potential contaminants [73]. To identify phytoconstituents, a Gas Chromatography-Mass Spectroscopy (GC-MS) examination was also carried out [74]. The LC-MS/MS approach is also superior to other methods in several ways [71]. The technique has been successfully used for pharmacokinetics and tissue distribution studies, where it has proven to be sensitive and straightforward (75, 76). GC-MS and LC-MS are utilized to identify volatile and nonvolatile chemicals [77, 78]. Stability studies assess the pro0duct's shelf life and ensure that it maintains its quality and efficacy over time, under specified storage conditions. Natural product manufacturing is subject to regulatory frameworks to ensure consumer safety and product quality [79]. Regulatory bodies establish guidelines and requirements for product registration, labeling, and safety assessments. Good Agricultural and Collection Practices (GACP) guidelines define the most effective methods for cultivation, harvesting, and storing medicinal plants to maintain their quality and minimize contamination. GMP guidelines ensure that manufacturers adhere to quality control standards, proper documentation, and facility cleanliness. Regulations dictate the information that must be included on product labels, such as ingredients, dosage instructions, and contraindications. Regulatory bodies also oversee claims made regarding product efficacy and safety. Monitoring the safety and adverse events associated with natural products is crucial. Regulatory agencies require manufacturers to establish pharmacovigilance systems to detect and report any adverse reactions. Third-party certifications, such as ISO (International Organization for Standardization) or NSF International, provide additional assurance of product quality and compliance with regulatory standards. These certifications involve rigorous assessments of manufacturing processes, quality control, and adherence to safety guidelines.

Table 1: List of Inflammatory Markers with their gene, size of the marker and function

No	Marker	Gene Location	Size	Conserved In	Functions	Reference
1	IL-18	11q23.1	22326 Da protein composed of 193 amino acids	chimpanzee, Rhesus monkey, dog, cow, and rat	PRO-I cytokine that increases splenic NK cell activity and triggers T-helper type I cells to produce IFN-ϒ.	[80]
2	IL36 alpha/IL-1F6	2q14	17684 Da protein composed of 158 amino acids	chimpanzee, Rhesus monkey, cow, mouse, and rat	cytokine capable of inducing the activation of NF-kB and MAPK signalling pathways, hence initiating an inflammatory response.	[81].
3	IL-37	2q14	24126 Da protein composed of 218 amino acids	Rhesus monkey, dog, and cow	member of the interleukin 1 cytokine family	[82]
4	TNFSF11 (TNF Superfamily Member 11)	13q14.11	35478 Da protein containing 317 amino acids	human	Associated with TNF receptor superfamily binding and cytokine activity	[83]

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5	TNFSF9 (TNF Superfamily Member 9)	19p13.3	26625 Da protein containing 254 amino acids	human	Associated with TNF receptor superfamily binding.	[84]
6	TNFSF13B (TNF Superfamily Member 13b)	13q33.3	31223 Da protein containing 285 amino acids	human	Associated with TNF receptor superfamily binding.	[85]
7	IFNA1 (Interferon Alpha 1)	9p21.3	21725 Da protein composed of 189 amino acids	human	produced by macrophages and has antiviral activities	[86]
8	IFNA10 (Interferon Alpha 10)	9p21.3	21835 Da protein composed of 189 amino acids	human	related pathways of IFNA10 include all-trans-retinoic Acid Mediated Apoptosis and Tuberculosis.	[87]
9	IFNA4 (Interferon Alpha 4)	9p21.3	21808 Da protein composed of 189 amino acids	human	related pathways of IFNA4 include all-trans-retinoic Acid Mediated Apoptosis and Tuberculosis.	[88]
10	IL11 (Interleukin 11)	19q13.42	21429 Da protein composed of 199 amino acids	human	The receptor IL1α is connected with a diverse range of activities.	[89]
11	LEP (Leptin)	7q32.1	18641 Da protein composed of 167 amino acids	The conservation of this trait has been seen in several species, including chimpanzees, Rhesus monkeys, dogs, cows, rodents.	secreted by white adipocytes into the circulation and plays a major role in the regulation of energy homeostasis	[90]
12	IL6 (Interleukin 6)	7p15.3	23718 Da protein composed of 212 amino acids	The conservation of this trait has been seen in several species, including chimpanzees, Rhesus monkeys, dogs.	regulates cell division.	[91]
13	IL10 (Interleukin 10)	1q32.1	20517 Da protein composed of 178 amino acids	Human	inhibition of NF-kB activity and its involvement in the control of the JAK-STAT signalling pathway.	[92]
14	IL19 (Interleukin 19)	1q32.1	20452 Da protein composed of 177 amino acids	The conservation of this trait has been seen in several species, including chimpanzees.	essential for the proper folding of the IL10 monomer.	[93]
15	IL22 (Interleukin 22)	12q15	20011 Da protein composed of 179 amino acids	The conservation of this trait has been seen in several species, including chimpanzees.	mediate cellular inflammatory responses	[94]
16	TGF-β1	19q13.2	44341 Da protein containing 390 amino acids	Human	related to protein homodimerization activity and enzyme binding	[95]
17	TGF-β2	1q41	47748 Da protein containing 414 amino acids	Human	related to protein homodimerization activity and signaling receptor binding	[96]
18	IFNA7 (Interferon Alpha 7)	9p21.3	22107 Da protein composed of	Human	IFN-alpha has antiviral activities. IFNA7 is a member of the interferon	[97]

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			189 amino acids.		family. Diseases such as Acute Hemorrhagic Conjunctivitis are associated with IFNA7. The related pathways of IFNA7 include all-trans-retinoic Acid Mediated Apoptosis and Tuberculosis.	
19	TNFSF13 (TNF Superfamily Member 13)	17p13.1	7433 Da protein containing 250 amino acids.	Human	TNFSF13 protein is ubiquitously expressed in lung, gall bladder and other tissues. TNFSF13 is related to signaling receptor binding and tumor necrosis factor receptor binding. TNFSF12-TNFSF13 is an important paralog of TNFSF13 gene. TNFSF13 is associated with some diseases, including Brain Glioblastoma Multiforme and RA.	[98]
20	IL33 (Interleukin 33, also known as DVS27)	9p24	30759 Da protein composed of 270 amino acids	chimpanzee, dog, cow, mouse, and rat.	The protein encoded by this gene is a cytokine that binds to the IL1RL1/ST2 receptor. IL33 is a PRO-I protein and a chromatin-associated cytokine of the IL1 family with high sequence and structural similarity to IL1 and IL18.	[99]

Atherosclerosis mediated inflammation followed by hypertension and other CVDs:

Cardiovascular disease represents a significant contributor to global morbidity and mortality. According to the American Heart Association, despite a decrease in mortality rates, the burden and implications of this disease persist as a serious threat to public health. Humanity has derived substantial benefits from the bioactive molecules derived from plant sources [100]. Atherosclerosis is a chronic and progressive pathological disease characterised by the detrimental effects on the intima, the induction of inflamed cells, the accumulation of lipids, the process of calcification, and the occurrence of plaque rupture [101]. Myeloid cells, including monocytes and macrophages, as well as the inhibition of Bcl6, which acts as an antagonist to NF-κB is known to have a substantial influence in coordinating the innate immune response that is accountable for the progression of atherosclerosis. This condition is characterized as a chronic inflammatory disease affecting the arterial wall [102, 103]. Inflammation indeed plays a crucial role as a mediator in various processes that occur during the onset and progression of atherosclerotic disease. The obstruction of coronary blood flow can result sudden coronary atherosclerosis-induced coronary trunk vasospasm, complex coronary plaques, platelet thrombi formation over atherosclerotic plaques, and coronary artery vasospasm. These circumstances can have adverse consequences. Hypertension, in particular, can accelerate the advancement of atherosclerosis through several mechanisms. These include the induction of mechanical injury to endothelial cells, increased permeability of low-density lipoprotein (LDL) into the intima, and the adhesion of monocytes to endothelial cells. The activation of the AT1-subtype angiotensin II receptor stimulates the secretion of aldosterone by angiotensin II, which in turn contributes to the hypertensive effects observed in these processes [104, 105]. In hyperlipidemic mice, elevated plasma levels of angiotensin II, which is frequently found in hypertensive (HTN) people, promote atherosclerosis and the development of aortic aneurysms [106, 107]. Atherosclerosis within the coronary arteries results in an imbalance between the demand for oxygen by the myocardium and the supply of oxygen through coronary blood flow. The presence of this imbalance leads to the development of angina pectoris, a condition that causes intermittent discomfort concentrated in the precordial area of the thoracic region. The sensation of discomfort often occurs as a result of an elevation in the cardiac workload. Angina serves as a recurring, warning symptom that precedes various significant cardiovascular events (108). In conventional therapy, Ursodeoxycholic acid (UDCA) is utilized as a treatment option. From a chemical standpoint, it is identified as 3-,

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7-dihydroxy-5-cholan-24-oic acid. It serves to inhibit endoplasmic reticulum (ER) stress and receptor for advanced glycation end products (RAGE) signaling, thereby offering protection against the development of atherosclerosis in individuals with diabetic atherosclerosis. By reducing levels of ER stress, RAGE, and adhesion molecules, UDCA effectively prevents the formation of atheromatous plaques (109, 110). The release of adrenaline and noradrenaline by L-NAME leads to increases in blood pressure, since these substances have a beneficial effect on the contractility and heart rate of the myocardium. L-NAME treatment works by suppressing the activity of nitric oxide synthase (NOS), leading to a decrease in the presence of vasodilatory NO and facilitating vasoconstriction. Consequently, this process culminates in an elevation in systolic blood pressure. The activation of soluble guanylyl cyclase by NO results in the synthesis of cyclic guanosine monophosphate (cGMP). Additionally, the oxidation of nitric oxide gives rise to the formation of plasma nitrite (35). Heart and kidney hypertrophy was brought on by L-NAME, which also quadrupled plasma lipid peroxidation but markedly decreased plasma nitrite and glutathione concentrations (108). In severe concentric and eccentric left ventricular hypertrophy, the QT corrected interval and QT dispersion increased (111). However, Bazett's formula,(QTc = QT / RR), can be used to calculate QT corrected (112, 113). Previously it was discussed that TLRs facilitate inflammatory signals through various pro-inflammatory cytokines and mediators (27). Atherosclerosis is primarily a pathological condition involving inflammation, which is characterised by an intricate interaction of several inflammatory indicators. While these markers hold significance in patients with CAD who possess conventional cardiovascular risk factors, their impact on CAD patients devoid of these conventional risk factors remains uncertain (114).

The disturbance of cardiomyocyte homeostasis was seen when there was an increase in the severity or duration of endoplasmic reticulum (ER) stress. This disruption resulted in a decrease in cardiomyocyte proliferation and an increase in apoptosis and fibrosis (115). Herbal medicines are now recognized as a better and safer option. The use of herbal medicines in medicine dates back almost as far as human civilization, and the traditional system of medicine has identified more than a thousand different herbs for the treatment of different cardiovascular issues (116). An aromatic alkaloid known as CSS-CTF II was identified in an Indian skin extract obtained from the common murrel fish (*Channa striatus* L.). This compound was found to be toxic to male Swiss albino mice, with a lethal dose (LD_{50}) of 42.5 mg/kg when administered intravenously. When introduced into the bloodstream of cats, CSS-CTF II led to a drop in blood pressure, resulting in hypotension. Further investigation into the cardiotoxic potential of CSS-CTF II was conducted using isolated guinea pig hearts. This research revealed that CSS-CTF II induced a reduction in both heart rate and contraction amplitude, leading to an irreversible blockage. Additionally, when applied to a single guinea pig ear, CSS-CTF II caused a decrease in both the amplitude and frequency of contractions, ultimately resulting in an intractable blockage. These observations collectively suggest that CSS-CTF II-induced cardiotoxicity may arise from the inhibition of cardiac impulses (117).

Delivery of natural products:

The kingdom of plants serves as a valuable reservoir of natural goods, facilitating the identification of various pharmaceuticals and the advancement of intricate polymers, alongside the synthesis of little drug-like compounds [118]. Marine creatures, fungi, bacteria, and invertebrates (such as insects and reptiles) are some other natural sources [119]. Drug delivery is the process of transporting a medicinal material to a specified site and releasing it there at a certain rate. In recent times, there has been a notable surge in the utilization of delivery methods for the purpose of dispensing drugs aimed at addressing a diverse range of diseases. This trend has yielded considerable advancements and positive outcomes. Both tiny and big molecules, including peptides, nucleic acids, polymers, and therapeutic agents that are poorly water-soluble, can be delivered by means of drug delivery systems [120]. It has been successful to employ a variety of distribution techniques. The category of inorganic nanoparticles encompasses several types, including carbon nanotubes, quantum dots, metal-based and silica nanoparticles [121]. The most studied polymeric nanoparticles for use in conjunction with natural products include liposomes and poly (lactic-co-glycolic acid. Due to their biocompatibility, biodegradability, and simplicity of functionalization, the former are the most often employed [122]. Additionally, components have been stabilized and therapeutic action has been increased using drug delivery methods[123]. To enhance the beneficial effects of *Artemisia arborescens* essential oil against Herpes simplex virus type 1, Sinico et al. used multilamellar liposomes. It was shown that the application of oil resulted in an augmentation of the plant's active components' ability to penetrate the cytoplasmic viral barrier, thereby leading to an increase in in vitro activity (124). Compounds that are discovered to be physiologically active are frequently also highly water soluble, have limited absorption, and, in certain situations, can have high molecular weight, such flavonoids, tannins, and terpenoids. Consequently, upon in vivo evaluation, these entities exhibit limited ability to efficiently cross lipid membranes, resulting in inadequate absorption and diminished biological

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efficacy (125). Additionally, *Flammulina velutipes* sterols have been improved in terms of bioavailability and biodistribution using a micelle-based delivery strategy (126). Considerable advancements have been made in the application of drug-delivery technologies to the delivery of biotherapeutics. This approach offers potential benefits in expediting the initiation of therapeutic intervention and facilitating the administration of biomolecules by non-invasive methods, as opposed to intravenous delivery (127). For example, inhalation treatment can deliver biotherapeutics like growth hormone, glucagon, or 1-antitrypsin efficiently with the use of a suitable delivery mechanism (128). By protecting and lengthening the half-lives of highly degradable substances like peptides and proteins, drug delivery techniques can be employed to improve their pharmacokinetics. The administration of insulin via non-invasive oral or inhalation methods is a significant development. The best way to administer insulin is orally since it will reach the liver, which is where insulin acts most effectively (129). The requirement to develop therapeutic molecules of a constant quality is the fundamental difficulty in dealing with mushrooms. These include the challenge of growing mushrooms, the need for appropriate manufacturing practices in cultivation techniques, and the development of reliable techniques for isolating, purifying, identifying, and evaluating bioactive chemicals in order to clarify their modes of action (130). The absence of standards in this field of study is the biggest issue, and it has reduced the number of clinical studies that can be conducted. An area of potential relevance is around powerful naturally occurring antibiotics that have limited practicality owing to the difficulties connected with their insolubility. Novel synthesis techniques are required for these antibiotics in order to improve their bioavailability. Additionally, the use of methods of delivery is necessary to optimise targeting and minimise the development of antibiotic resistance (131).

Table 2: Represents various drug delivery approaches for different phytomolecules.

Phytochemicals	Pharmacological action	Delivery approaches	Pharmacological Outcome	Ref.
CUR	Antineoplastic and antioxidant	Liposomes and phytosomes	Long systemic residence time and high entrapment efficiency	[132] [133]
Quercetin	Anticongestion and antianxiety	Liposomes	To enhance effectiveness, optimize bioavailability, and mitigate adverse effects	[133]
Glycyrrhizic acid	IMM	Nanoparticles	To enhance blood circulation to the brain and metabolism	[134]
Wogonin	Anticancer	Liposomes	To extend the duration of activity	[135]
Embelin	Antifertility and antibacterial	Phytosomes	To increase solubility	[136]
Curcumin	AI	Micropellatization	to facilitate the controlled and prolonged release	[137]

Role of Ministry of AYUSH/India in promoting traditional system of medicine

The Ministry of AYUSH has been actively promoting research in traditional medicinal systems, specifically Ayurveda, Unani, Siddha, and Homoeopathy. This support involves allocating significant funding to various universities and research centers for research projects. Recently, the Department of Pharmaceutical Technology at Jadavpur University received a project grant focused on conducting research into the pharmacological properties and formulation optimization of Khamira Gozaban Sada (KGS). This traditional remedy contains Borago officinalis Linn. as its primary component and is traditionally used for its cardiotonic properties and in the treatment of palpitations. Additionally, the Department of Pharmaceutical Technology at Jadavpur University is also exploring Dawa-ul-Misk Motadil, another Unani formulation. Furthermore, research is also being conducted at the Department of Pharmaceutical Technology at Jadavpur University on Ayurvedic formulations such as Haridra Khanda and Mahamanjisthadi Kwatham.

Conclusion:

Natural products offer a vast repertoire of bioactive compounds with significant potential in managing inflammatory conditions. These naturally occurring substances provide potential therapeutic interventions for inflammatory illnesses such as IBD, RA, cardiovascular diseases, and dermatological disorders by modulating inflammatory mediators and signalling pathways. The future of inflammatory pharmacology lies in the exploration of synergistic combinations, the discovery of novel natural product sources, the establishment of standardized quality control measures and novel drug delivery. By harnessing the power of natural products, we can unlock nature's arsenal and develop effective interventions to combat chronic inflammation, improving the lives of millions affected by inflammatory disorders.

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Reference:

1. Barik R, Sarkar R, Biswas P, Bera R, Sharma S, Nath S, et al. 5,7-dihydroxy-2-(3-hydroxy-4, 5-dimethoxy-phenyl)-chromen-4-one-a flavone from Bruguiera gymnorrhiza displaying AI properties. Indian J Pharmacol [Internet]. 2016 [cited 2023 Jul 23];48(3):304. Available from: http://www.ijp-online.com/text.asp?2016/48/3/ 304/ 182890
2. Kundu A, Dey P, Sarkar P, Karmakar S, Tae IH, Kim KS, et al. Protective effects of Croton hookeri on streptozotocin-induced diabetic nephropathy. Food Chem Toxicol [Internet]. 2020 Jan [cited 2023 Jul 23];135:110873. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0278691519306635
3. Karmakar S, Biswas S, Bera R, Mondal S, Kundu A, Ali MA, et al. Beverage-induced enhanced bioavailability of carbamazepine and its consequent effect on antiepileptic activity and toxicity. J Food Drug Anal [Internet]. 2015 Jun [cited 2023 Jul 24];23(2):327–34. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1021949814001598
4. Pattnaik A, Sarkar R, Sharma A, Yadav KK, Kumar A, Roy P, et al. Pharmacological studies on Buchanania lanzan Spreng.-A focus on wound healing with particular reference to anti-biofilm properties. Asian Pac J Trop Biomed [Internet]. 2013 Dec [cited 2023 Jul 23];3(12):967–74. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2221169113601872
5. Ahmmed S, Mukherjee P, Bahadur S, Kar A, Mukherjee K, Karmakar S, et al. Interaction potential of Trigonella foenum graceum through cytochrome P450 mediated inhibition. Indian J Pharmacol [Internet]. 2015 [cited 2023 Jul 24];47(5):530. Available from: http://www.ijp-online.com/text.asp?2015/47/5/530/165179
6. Das PP, Rahaman SB, Shaharyar A, Rahman M, Alam K, Kazmi I, et al. Antipsychotics and Antimanics: An Insight into Mechanism of Action of Natural Compounds. In: Bioactive-Loaded Nanomedicine for the Management of Health and Disease. Apple Academic Press; 2022. p. 89–110.
7. Das PP, Rahaman SB, Shaharyar A, Bhowmik R, Mandal A, Karmakar S. Plant-Derived Anti-Psychotic Drugs: An Insight into Receptor and Phytoconstituent Interaction. In: Bioactive-Loaded Nanomedicine for the Management of Health and Disease. Apple Academic Press; 2022. p. 111–37.
8. Sahu KB, Banerjee M, Ghosh S, Maity A, Mondal S, Paira R, et al. I2 catalyzed Friedel–Crafts alkylation reaction of substituted anilines with ninhydrin: formation of novel products and their antimicrobial evaluation. Med Chem Res [Internet]. 2013 Apr [cited 2023 Jul 26];22(4):2023–37. Available from: http://link.springer.com/10.1007/s00044-010202-z
9. Nagchaudhuri A, Karmakar S, Roy D, Pal S, Pal M, Sen T. AI activity of Indian black tea (Sikkim variety). Pharmacol Res [Internet]. 2005 Feb [cited 2023 Jul 23];51(2):169–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661804001902
10. Baishya R, Nayak DK, Chatterjee N, Halder KK, Karmakar S, Debnath MC. Synthesis, Characterization, and Biological Evaluation of ^{99m}Tc(CO)$_3$ -Labeled Peptides for Potential Use as Tumor Targeted Radiopharmaceuticals. Chem Biol Drug Des [Internet]. 2014 Jan [cited 2023 Jul 23];83(1):58–70. Available from: https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12166
11. Sarkar L, Bhuvaneswari N, Samanta SK, Islam MdN, Sen T, Fukui H, et al. A report on anti-oedemogenic activity of Byttneria herbacea roots – Possible involvement of histamine receptor (type I). J Ethnopharmacol [Internet]. 2012 Mar [cited

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

2023 Jul 23];140(2):443–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874112000268

12. Mani Senthil Kumar KT, Gorain B, Roy DK, Zothanpuia, Samanta SK, Pal M, et al. AI activity of Acanthus ilicifolius. J Ethnopharmacol [Internet]. 2008 Oct [cited 2023 Jul 23];120(1):7–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874108004017
13. Charlier C, Michaux C. Dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal AI drugs. Eur J Med Chem [Internet]. 2003 Jul [cited 2023 Jul 23];38(7–8):645–59. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0223523403001156
14. Karmakar S, Prakash P, Chattopadhyay A, Dutta D. Zinc Sulphate and Vermicompost Mitigate Phytotoxic Effects of Arsenic by Altering Arsenic Uptake, Biochemical and Antioxidant Enzyme Activities in Wheat (Triticum aestivum L.). Russ J Plant Physiol [Internet]. 2021 Jul [cited 2023 Jul 23];68(S1):S72–81. Available from: https://link.springer.com/10.1134/S1021443721070062
15. Roy DK, Kumar KTMS, Zothanpuia, Karmakar S, Pal S, Samanta SK, et al. Pharmacological studies on Indian black tea (leaf variety) in acute and chronic inflammatory conditions. Phytother Res [Internet]. 2008 Jun [cited 2023 Jul 23];22(6):814–9. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ptr.2375
16. Sen T, Abdulsalam CA, Pal S, Sen S, Karmakar S, Saravanan KS, et al. Effect of amitriptyline on gastric ulceration. Fundam Clin Pharmacol [Internet]. 2002 Aug [cited 2023 Jul 23];16(4):311–5. Available from: http://doi.wiley.com/10.1046/j.1472-8206.2002.00092.x
17. Shill MC, Das AK, Itou T, Karmakar S, Mukherjee PK, Mizuguchi H, et al. The isolation and synthesis of a novel benzofuran compound from Tephrosia purpurea, and the synthesis of several related derivatives, which suppress histamine H1 receptor gene expression. Bioorg Med Chem [Internet]. 2015 Nov [cited 2023 Jul 23];23(21):6869–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0968089615300742
18. Sarkar L, Bera R, Sen T, Karmakar S. Comparative study of the fractions of a relatively unexplored plant Byttneria herbacea on histaminergic inflammation. Int J Pharm Pharm Sci. 2013;5(3):862–6.
19. Shill MC, Mizuguchi H, Karmakar S, Kadota T, Mukherjee PK, Kitamura Y, et al. A novel benzofuran, 4-methoxybenzofuran-5-carboxamide, from Tephrosia purpurea suppressed histamine H1 receptor gene expression through a protein kinase C-δ-dependent signaling pathway. Int Immunopharmacol. 2016;30:18–26.
20. Shill MC, Mizuguchi H, Karmakar S, Kadota T, Mukherjee PK, Kitamura Y, et al. A novel benzofuran, 4-methoxybenzofuran-5-carboxamide, from Tephrosia purpurea suppressed histamine H 1 receptor gene expression through a protein kinase C-δ-dependent signaling pathway. Int Immunopharmacol [Internet]. 2016 Jan [cited 2023 Jul 23];30:18–26. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1567576915301892
21. Banerjee M, Kumar S, Paira R, Ghosh S, Karmakar S, Mondal N. Synthesis and Characterization of Furo[3,2-h]Quinoliniums as Potent Non-Detergent Spermicides. Lett Drug Des Discov [Internet]. 2013 Nov 31 [cited 2023 Jul 24];11(1):104–13. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1570-1808&volume=11&issue=1&spage=104
22. Barik R, Sarkar R, Biswas P, Pattnaik A, Samanta SK, Manisenthilkumar K, et al. Inhibition of arachidonic acid metabolism and PRO-Icytokine production by Bruguiera gymnorrhiza leaf. Orient Pharm Exp Med [Internet]. 2013 Mar [cited 2023 Jul 23];13(1):41–9. Available from: http://link.springer.com/10.1007/s13596-013-0103-9
23. Sarkar A, Saha S, Paul A, Maji A, Roy P, Maity TK. Understanding stem cells and its pivotal role in regenerative medicine. Life Sci [Internet]. 2021 May [cited 2023 Jul 25];273:119270. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0024320521002551
24. Goswami S, Sarkar R, Saha P, Maity A, Sarkar T, Das D, et al. Effect of human placental extract in the management of biofilm mediated drug resistance – A focus on wound management. Microb Pathog [Internet]. 2017 Oct [cited 2023 Jul 23];111:307–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0882401017301390
25. Halder S, Yadav KK, Sarkar R, Mukherjee S, Saha P, Haldar S, et al. Alteration of Zeta potential and membrane permeability in bacteria: a study with cationic agents. SpringerPlus [Internet]. 2015 Dec [cited 2023 Jul 23];4(1):672. Available from:

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JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

http://www.springerplus.com/content/4/1/672

26. Veerabadhran M, Chakraborty S, Mitra S, Karmakar S, Mukherjee J. Effects of flask configuration on biofilm growth and metabolites of intertidal Cyanobacteria isolated from a mangrove forest. J Appl Microbiol [Internet]. 2018 Jul [cited 2023 Jul 23];125(1):190–202. Available from: https://academic.oup.com/jambio/article/125/1/190/6714245
27. Biswas N, Roy D, Karmakar S, Bhowmik R, Mazumdar H, Banerjee A, et al. Differential expression of TLR4 in patients of coronary artery disease with and without traditional cardiovascular risk factors. Eur Heart J [Internet]. 2023 Jan 25 [cited 2023 Jul 24];44(Supplement_1):ehac779.137. Available from: https://academic.oup.com/eurheartj/article/doi/10.1093/eurheartj/ehac779.137/7000587
28. Das K, Kundu A, Karmakar S, Ghosh M. Novel structured diacylglycerol (DAG) rich oleo formulations activate the Nrf2 pathway and impedes NF-κB translocation to mitigate pre-clinical conditions of hypertension. J Funct Foods [Internet]. 2020 Jan [cited 2023 Jul 24];64:103650. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1756464619305742
29. Mandal A, Bhowmik R, Anand MASK, Mandal P, Akhtar J, Karmakar S, et al. THE PROTECTIVE ACTION OF EARTHWORM PROTEIN POWDER/MWCO 50 KDA FRACTION ON EXPERIMENTAL HEPATIC DAMAGE: AN INVIVO/INVITRO APPROACH INVOLVING INFLAMMATORY TNF-A AND IL-6.
30. Ghosh B, Karmakar S, Prasad M, Mandal AK. Praja1 ubiquitin ligase facilitates degradation of polyglutamine proteins and suppresses polyglutamine-mediated toxicity. Olzmann J, editor. Mol Biol Cell [Internet]. 2021 Aug 15 [cited 2023 Jul 26];32(17):1579–93. Available from: https://www.molbiolcell.org/doi/10.1091/mbc.E20-11-0747
31. Bera R, Kundu A, Sen T, Adhikari D, Karmakar S. In Vitro Metabolic Stability and Permeability of Gymnemagenin and Its In Vivo Pharmacokinetic Correlation in Rats – A Pilot Study. Planta Med [Internet]. 2016 Feb 25 [cited 2023 Jul 26];82(06):544–50. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0042-101032
32. Sarkar A, Paul A, Banerjee T, Maji A, Saha S, Bishayee A, et al. Therapeutic advancements in targeting BCL-2 family proteins by epigenetic regulators, natural, and synthetic agents in cancer. Eur J Pharmacol [Internet]. 2023 Apr [cited 2023 Jul 25];944:175588. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299923000997
33. Xia X, Wang X, Wang H, Lin Z, Shao K, Xu J, et al. Ameliorative effect of white tea from 50-year-old tree of Camellia sinensis L. (Theaceae) on kidney damage in diabetic mice via SIRT1/AMPK pathway. J Ethnopharmacol [Internet]. 2021 May [cited 2023 Jul 17];272:113919. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874121001458
34. Karmakar S, Prakash P. Ameliorative effect of zinc and vermicompost on physiological and yield attributes in wheat (Triticum aestivum L.) under arsenic toxicity. J Pharmacogn Phytochem. 2019 Jun 1;
35. Shaharyar MdA, Bhowmik R, Afzal O, Altamimi ASA, Alzarea SI, Almalki WH, et al. Anti-Hypertensive Activity of Some Selected Unani Formulations: An Evidence-Based Approach for Verification of Traditional Unani Claims Using LC-MS/MS for the Evaluation of Clinically Relevant Blood Parameters in Laboratory Rats. J Clin Med [Internet]. 2022 Aug 8 [cited 2023 Jul 24];11(15):4628. Available from: https://www.mdpi.com/2077-0383/11/15/4628
36. Roy M, Das R, Kundu A, Karmakar S, Das S, Sen P, et al. Organic Cultivation of Tomato in India with Recycled Slaughterhouse Wastes: Evaluation of Fertilizer and Fruit Safety. Agriculture [Internet]. 2015 Sep 16 [cited 2023 Jul 24];5(3):826–56. Available from: http://www.mdpi.com/2077-0472/5/3/826
37. Mandal A, Das P, Bhowmik R, Mazumdar H, Shaharyar MdA, Kumari R, et al. An insight into the agents used for immunomodulation and their mechanism of action. In: How Synthetic Drugs Work [Internet]. Elsevier; 2023 [cited 2023 Jul 23]. p. 503–28. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323998550000221
38. Sarkar R, Kumar A, Divya L, K. Samanta S, Adhikari D, Karmakar S, et al. Antioxidant Properties of Kalanchoe blossfeldiana – A Focus on Erythrocyte Membrane Stability and Cytoprotection. Curr Tradit Med [Internet]. 2017 Jun 13 [cited 2023 Jul 23];3(1). Available from: http://www.eurekaselect.com/148719/article
39. Kundu A, Dey P, Bera R, Sarkar R, Kim B, Kacew S, et al. Adverse health risk from prolonged consumption of formaldehyde-preserved carps in eastern region of Indian population. Environ Sci Pollut Res [Internet]. 2020 May [cited 2023 Jul 24];27(14):16415–25. Available from: http://link.springer.com/10.1007/s11356-020-07993-0

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

40. Manna A, Behera A, Jena J, Manna S, Karmakar S, Kar S, et al. The antiulcer activity of Pterospermum acerifolium bark extract in experimental animal. J Pharm Res. 2009;2(5):785–8.
41. Manna AK, Jena J, Behera AK, Roy DC, Karmakar S, Kar SK. EFFECT OF PTEROSPERMUM ACERIFOLIUM BARK EXTRACT ON OXIDATIVE DAMAGES IN THE GASTRIC TISSUE DURING ALCOHOL INDUCED ULCERATION. In 2009.
42. Picchianti-Diamanti A, Rosado MM, D'Amelio R. Infectious Agents and Inflammation: The Role of Microbiota in Autoimmune Arthritis. Front Microbiol [Internet]. 2018 Jan 16 [cited 2023 Jul 23];8:2696. Available from: http://journal.frontiersin.org/article/10.3389/fmicb.2017.02696/full
43. Sarkar R, Chaudhary SK, Sharma A, Yadav KK, Nema NK, Sekhoacha M, et al. Anti-biofilm activity of Marula – A study with the standardized bark extract. J Ethnopharmacol [Internet]. 2014 May [cited 2023 Jul 23];154(1):170–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378874114002712
44. Sarkar R, Mondal C, Bera R, Chakraborty S, Barik R, Roy P, et al. Antimicrobial properties of *K alanchoe blossfeldiana* : a focus on drug resistance with particular reference to quorum sensing-mediated bacterial biofilm formation. J Pharm Pharmacol [Internet]. 2015 Jun 11 [cited 2023 Jul 23];67(7):951–62. Available from: https://academic.oup.com/jpp/article/67/7/951-962/6128281
45. Mandal P, Pal TK, Chakraborty S, Bera R, Saha C, Karmakar S. DETERMINATION OF OXACEPROL (FED AND FASTING PERIOD) BY VALIDATED LC-MS/MS METHOD IN INDIAN HEALTHY HUMAN PLASMA AND ITS APPLICATION TO IN-VIVO COMPARATIVE PHARMACOKINETIC STUDY. 2021;
46. Das B, Bhardwaj PK, Sharma N, Sarkar A, Haldar PK, Mukherjee PK. Evaluation of Mollugo oppositifolia Linn. as cholinesterase and β-secretase enzymes inhibitor. Front Pharmacol [Internet]. 2023 Jan 4 [cited 2023 Jul 25];13:990926. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2022.990926/full
47. Lee YM, Son E, Kim SH, Kim OS, Kim DS. AI and anti-osteoarthritis effect of *Mollugo pentaphylla* extract. Pharm Biol [Internet]. 2019 Jan 1 [cited 2023 Jul 25];57(1):73–80. Available from: https://www.tandfonline.com/doi/full/10.1080/13880209.2018.1557700
48. Biswas K, Bhattarcharya D, Saha M, Mukherjee J, Karmakar S. Evaluation of antimicrobial activity of the extract of Streptomyces euryhalinus isolated from the Indian Sundarbans. Arch Microbiol [Internet]. 2022 Jan [cited 2023 Jul 23];204(1):34. Available from: https://link.springer.com/10.1007/s00203-021-02698-5
49. Das B, Kar A, Bhowmik R, Karmakar S, Tripathy S, Matsabisa MG, et al. Quality Related Safety Evaluation of a South African Traditional Formulation (PHELA®) as Novel Anti-Biofilm Candidate. Molecules [Internet]. 2022 Feb 11 [cited 2023 Jul 23];27(4):1219. Available from: https://www.mdpi.com/1420-3049/27/4/1219
50. Sen T, Karmakar S, Sarkar R. Evaluation of Natural Products against Biofilm-Mediated Bacterial Resistance. In: Evidence-Based Validation of Herbal Medicine [Internet]. Elsevier; 2015 [cited 2023 Jul 23]. p. 321–38. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128008744000155
51. Bishop P, Pitts ER, Budner D, Thompson-Witrick KA. Chemical Composition of Kombucha. Beverages [Internet]. 2022 Aug 5 [cited 2023 Jul 23];8(3):45. Available from: https://www.mdpi.com/2306-5710/8/3/45
52. Tomilova SV, Globa EB, Demidova EV, Nosov AM. Secondary Metabolism in Taxus spp. Plant Cell Culture In Vitro. Russ J Plant Physiol [Internet]. 2023 Jun [cited 2023 Jul 23];70(3):23. Available from: https://link.springer.com/10.1134/S102144372270008X
53. Choudhury H, Gorain B, Karmakar S, Biswas E, Dey G, Barik R, et al. Improvement of cellular uptake, in vitro antitumor activity and sustained release profile with increased bioavailability from a nanoemulsion platform. Int J Pharm [Internet]. 2014 Jan [cited 2023 Jul 23];460(1–2):131–43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378517313009861
54. Choudhury H, Gorain B, Tekade RK, Pandey M, Karmakar S, Pal TK. Safety against nephrotoxicity in paclitaxel treatment: Oral nanocarrier as an effective tool in preclinical evaluation with marked in vivo antitumor activity. Regul Toxicol Pharmacol [Internet]. 2017 Dec [cited 2023 Jul 23];91:179–89. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0273230017303380

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

55. Choudhury H, Gorain B, Karmakar S, Pal TK. Development and Validation of RP-HPLC Method: Scope of Application in the Determination of Oil Solubility of Paclitaxel. J Chromatogr Sci [Internet]. 2014 Jan 1 [cited 2023 Jul 24];52(1):68–74. Available from: https://academic.oup.com/chromsci/article-lookup/doi/10.1093/chromsci/bms206
56. Senthil Kumar KTM. The Gastroprotective Role of Acanthus ilicifolius – A Study to Unravel the Underlying Mechanism of Anti-Ulcer Activity. Sci Pharm [Internet]. 2012 [cited 2023 Jul 23];80(3):701–17. Available from: http://www.mdpi.com/2218-0532/80/3/701
57. Seth M, Khan H, Bhowmik R, Karmakar S, Jana S. Facile fabrication of fluorine free zirconium zinc stearate based superhydrophobic and superoleophilic coating on cotton fabric with superior antibacterial property. J Sol-Gel Sci Technol [Internet]. 2020 Apr [cited 2023 Jul 23];94(1):127–40. Available from: http://link.springer.com/10.1007/s10971-019-05079-z
58. Lodi A, Saha A, Lu X, Wang B, Sentandreu E, Collins M, et al. Combinatorial treatment with natural compounds in prostate cancer inhibits prostate tumor growth and leads to key modulations of cancer cell metabolism. Npj Precis Oncol [Internet]. 2017 Jun 5 [cited 2023 Jul 24];1(1):18. Available from: https://www.nature.com/articles/s41698-017-0024-z
59. Shaharyar MA, Rahman M, Alam K, Beg S, Anand K, Hossain CM, et al. Nanomedicines for the Treatment of Gastric and Colonic Diseases. In: Nanomedicine for the Treatment of Disease. Apple Academic Press; 2019. p. 239–70.
60. Gupta MS, Shaharyar MA, Rahman M, Anand K, Kazmi I, Afzal M, et al. Ursolic Acid: A Pentacyclic Triterpene from Plants in Nanomedicine. Biomark Target Herb Drug Discov Pharmacol Approach Nanomedicines. 2021;65.
61. Anand K, Ray S, Rahman M, Shaharyar A, Bhowmik R, Bera R, et al. Nano-emulgel: Emerging as a Smarter Topical Lipidic Emulsion-based Nanocarrier for Skin Healthcare Applications. Recent Patents Anti-Infect Drug Disc [Internet]. 2019 Oct 21 [cited 2023 Jul 24];14(1):16–35. Available from: http://www.eurekaselect.com/173587/article
62. Anand K, Rahman M, Ray S, Karmakar S. Insights into the Approach, Fabrication, Application, and Lacunae of Nanoemulsions in Drug Delivery Systems. Crit Rev Ther Drug Carr Syst [Internet]. 2020 [cited 2023 Jul 24];37(6):511–51. Available from: http://www.dl.begellhouse.com/journals/3667c4ae6e8fd136,7df5d48a29269388,248565d2066ab778.html
63. Biswas E, Kumar Banerjee K, Karmakar S, Karmakar S, Kumar Pal T. Preparation and Evaluation of Eprosartan Mesylate loaded PLGA Nanostructures. Res J Pharm Technol [Internet]. 2022 Jan 25 [cited 2023 Jul 24];103–12. Available from: https://rjptonline.org/AbstractView.aspx?PID=2022-15-1-18
64. A. P, S. M, R. S, S. H, B. Sa, A. M, et al. EHydrogel Formulation of Buchanania lanzan Spreng-A Focus on Rheological Properties. Int J Drug Deliv Technol [Internet]. 2015 Sep 30 [cited 2023 Jul 24];5(3). Available from: https://www.myresearchjournals.com/index.php/IJDDT/article/view/8879
65. Karmakar R, Sadhu T, Hazra A, Sahana S, Karmakar S. A Comparative Study of Multiple Sequence Alignments. 2017;
66. Gorain B, Chakraborty S, Pal MM, Sarkar R, Samanta SK, Karmakar S, et al. Arylamine N-acetyl Transferase (NAT) in the blue secretion of Telescopium telescopium: xenobiotic metabolizing enzyme as a biomarker for detection of environmental pollution. SpringerPlus [Internet]. 2014 Dec [cited 2023 Jul 24];3(1):666. Available from: https://springerplus.springeropen.com/articles/10.1186/2193-1801-3-666
67. Purwaningsih S, Handharyani E, Ananda W. Hepatoprotective activity of mangrove snail (*Telescopium* sp.) extract in *sprague dawley* rats induced by paracetamol. IOP Conf Ser Earth Environ Sci [Internet]. 2019 Mar 28 [cited 2023 Jul 24];241:012022. Available from: https://iopscience.iop.org/article/10.1088/1755-1315/241/1/012022
68. Paul A, Maji A, Sarkar A, Saha S, Janah P, Maity TK. Recent Approaches in the Synthesis of 5-Arylidene-2,4-thiazolidinedioneDerivatives Using Knoevenagel Condensation. Mini-Rev Org Chem [Internet]. 2023 Feb [cited 2023 Jul 25];20(1):5–34. Available from: https://www.eurekaselect.com/202912/article
69. Mandal P, Chakraborty S, Bera R, Karmakar S, Pal TK. Internal Standard an Important Analyte Use in Drug Analysis by Liquid Chromatography Mass Spectrometry- An Article. Int J Pharm Bio Med Sci [Internet]. 2022 Jan 11 [cited 2023 Jul 24];2(01):10–7. Available from: https://ijpbms.com/index.php/ijpbms/article/view/56
70. Mandal P, Dan S, Ghosh B, Barma S, Bose R, Pal T. SIMULTANEOUS DETERMINATION AND

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

QUANTITATION OF METFORMIN AND TENELIGLIPTIN IN HUMAN PLASMA BY LC-ESI-MS/MS WITH AN APPLICATION TO PHARMACOKINETIC STUDIES. Indian Drugs. 2018;55(4).

71. Mandal P, Chakraborty S, Bera R, Saha C, Pal TK, Ghosh B, et al. A NOVEL VALIDATED BIO-ANALYTICAL METHOD DEVELOPMENT FOR AZELNIDIPINE (DIHYDROPYRIDINE) IN INDIAN HUMAN PLASMA BY LIQUID CHROMATOGRAPHY QUADRUPLE TANDEM MASS SPECTROMETRY (LC-ESI-MS/MS, API-4000) WITH AN APPLICATION TO IN VIVO PHARMACOKINETIC AND BIOEQUIVALENCE STUDY. Indian Drugs. 2022;59(5).
72. Pal M, Dan S, Ghosh B, Das A, Das D. Bioanalytical method development and validation of letrozole by LC-ESI-MS/MS in human plasma. J Anal Pharm Res. 2017;4(1):00093.
73. Maity S, Kundu A, Karmakar S, Sa B. In Vitro and In Vivo Correlation of Colon-Targeted Compression-Coated Tablets. J Pharm [Internet]. 2016 Feb 17 [cited 2023 Jul 24];2016:1–9. Available from: https://www.hindawi.com/journals/jphar/2016/5742967/
74. Sarkar A, Saha R, Saha S, Bhowmik R, Chatterjee A, Paul A, et al. Transesterification, GC-MS profiling, and in vitro antimicrobial potential of oil obtained from seeds of Citrus maxima (Burm.) Merr. Ind Crops Prod [Internet]. 2022 Dec [cited 2023 Jul 23];189:115764. Available from: https://linkinghub.elsevier.com/retrieve/pii/S092666902201247X
75. Bera R, Ahmed SKM, Sarkar L, Sen T, Karmakar S. Pharmacokinetic analysis and tissue distribution of andrographolide in rat by a validated LC-MS/MS method. Pharm Biol [Internet]. 2014 Mar [cited 2023 Jul 24];52(3):321–9. Available from: http://www.tandfonline.com/doi/full/10.3109/13880209.2013.836544
76. Ghosh B, Mandal P, Chakraborty S, Bera R, Saha C, Poddar S, et al. Determination and quantitation of benzofuran, Indole and piperazine containing selective serotonin reuptake inhibitor vilazodone hydrochloride in human plasma by LC-ESI-MS/MS with an application to pharmacokinetic study under the frame work of bioequivalence study. J Anal Pharm Res [Internet]. 2021 Feb 8 [cited 2023 Jul 24];10(1):1–12. Available from: https://medcraveonline.com/JAPLR/determination-and-quantitation-of-benzofuran-indole-and-piperazine-containing-selective-serotonin-reuptake-inhibitor-vilazodone-hydrochloride-in-human-plasma-by-lc-esi-msms-with-an-application-to-pharmacokinetic-study-under-the-frame-work-of-bioequivalence-study.html
77. Mandal P, Khanam J, Karmakar S, Pal TK, Barma S, Chakraborty S, et al. An Audit on Design of Pharmaceutical Packaging. J Packag Technol Res [Internet]. 2022 Oct [cited 2023 Jul 25];6(3):167–85. Available from: https://link.springer.com/10.1007/s41783-022-00141-8
78. Mandal P, Dan S, Chakraborty S, Ghosh B, Saha C, Khanam J, et al. Simultaneous Determination and Quantitation of Diosmetin and Hesperetin in Human Plasma by Liquid Chromatographic Mass Spectrometry With an Application to Pharmacokinetic Studies. J Chromatogr Sci [Internet]. 2019 May 1 [cited 2023 Aug 6];57(5):451–61. Available from: https://academic.oup.com/chromsci/article/57/5/451/5365612
79. Mandal P, Dan S, Bose A, Bag S, Biswas A, Khanam J, et al. LC-MS/MS method development and validation of an antihistaminic, calcium channel blocker, di-phenyl-methyl-piperazine group containing cinnarizine in human plasma with an application to BA/BE studies in Indian volunteer. Pharm Pharmacol Int J. 2018;6:475–82.
80. Zhang XY, Tan YL, Chen DC, Tan SP, Malouta MZ, Bernard JD, et al. Serum IL-18 level, clinical symptoms and IL-18-607A/C polymorphism among chronic patients with schizophrenia in a Chinese Han population. Psychoneuroendocrinology. 2016;68:140–7.
81. Yasmina Hernandez-Santana, Irwin N, Walsh P. IL-36: A therapeutic target for ulcerative colitis? 2022;
82. Hahn M, Frey S, Hueber AJ. The novel interleukin-1 cytokine family members in inflammatory diseases. Curr Opin Rheumatol. 2017;29(2):208–13.
83. Mencej S, Albagha O, Janez Prezelj, Kocjan T, Marc J. Tumour necrosis factor superfamily member 11 gene promoter polymorphisms modulate promoter activity and influence bone mineral density in postmenopausal women with osteoporosis. 2008;40(6):273–9.
84. Smeets E, Meiler S, Lutgens E. Lymphocytic tumor necrosis factor receptor superfamily co-stimulatory molecules in the pathogenesis of atherosclerosis. Curr Opin Lipidol. 2013;24(6):518–24.
85. Wu H, Chen S, Liu M, Xu X, Ji X, Gao K, et al. Molecular characterization and evolutionary analysis of horse BAFF-R, a tumor necrosis factor receptor related to B-cell survival. Int Immunopharmacol [Internet]. 2014 [cited 2023 Jan 1];18(1):163–8. Available from:

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

https://www.sciencedirect.com/science/article/pii/S1567576913004700

86. Sun B, Skjæveland I, Svingerud T, Zou J, Jørgensen J, Robertsen B. Antiviral Activity of Salmonid Gamma Interferon against Infectious Pancreatic Necrosis Virus and Salmonid Alphavirus and Its Dependency on Type I Interferon. J Virol. 2011;85(17):9188–98.
87. Casanova JL, Abel L. Human genetics of infectious diseases: Unique insights into immunological redundancy. Semin Immunol. 2018;36:1–12.
88. Hillyer P, Mane V, Schramm LM, Puig M, Verthelyi D, Chen A, et al. Expression profiles of human interferon-alpha and interferon-lambda subtypes are ligand- and cell-dependent. 2012;90(8):774–83.
89. Davidson AJ, Freeman S, Crosier KE, Wood CR, Crosier PS. Expression of Murine Interleukin 11 and its Receptor α-Chain in Adult and Embryonic Tissues. STEM CELLS. 1997;15(2):119–24.
90. Wang Q, Bing C, Al-Barazanji K, Mossakowaska DE, Wang XM, McBay DL, et al. Interactions Between Leptin and Hypothalamic Neuropeptide Y Neurons in the Control of Food Intake and Energy Homeostasis in the Rat. Diabetes. 1997;46(3):335–41.
91. Yamasaki K, Taga T, Hirata Y, Yawata H, Kawanishi Y, Seed B, et al. Cloning and expression of the human interleukin-6 (BSF-2/IFN beta 2) receptor. Science. 1988;241(4867):825–8.
92. Jung M, Weigert A, Tausendschon M, Mora J, Oren B, Sola A, et al. Interleukin-10-Induced Neutrophil Gelatinase-Associated Lipocalin Production in Macrophages with Consequences for Tumor Growth. Mol Cell Biol. 2012;32(19):3938–48.
93. Gallagher G, Dickensheets H, Eskdale J, Izotova LS, Mirochnitchenko OV, Peat JD, et al. Cloning, expression and initial characterisation of interleukin-19 (IL-19), a novel homologue of human interleukin-10 (IL-10). Genes Immun [Internet]. 2000 [cited 2023 Jan 1];1(7):442–50. Available from: https://www.nature.com/articles/6363714
94. Andoh A, Zhang Z, Inatomi O, Fujino S, Deguchi Y, Araki Y, et al. Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. Gastroenterology [Internet]. 2005 [cited 2022 Jan 1];129(3):969–84. Available from: https://pubmed.ncbi.nlm.nih.gov/16143135/
95. Purchio AF, Cooper JA, Brunner AM, Lioubin MN, Gentry LE, Kovacina KS, et al. Identification of mannose 6-phosphate in two asparagine-linked sugar chains of recombinant transforming growth factor-beta 1 precursor. J Biol Chem. 1988;263(28):14211–5.
96. Zhao Y, Chegini N, Flanders KC. Human fallopian tube expresses transforming growth factor (TGF beta) isoforms, TGF beta type I-III receptor messenger ribonucleic acid and protein, and contains [125I]TGF beta-binding sites. J Clin Endocrinol Metab. 1994;79(4):1177–84.
97. Sutter K, Dickow J, Dittmer U. Interferon α subtypes in HIV infection. Cytokine Growth Factor Rev. 2018;40:13–8.
98. Cao M, Wang N, Yan X, Yang N, Fu Q, Zhang X, et al. Structures, evolutionary relationships and expression profiles of the tumour necrosis factor superfamily and their receptors in black rockfish (Sebastes schlegelii). Dev Comp Immunol [Internet]. 2022 [cited 2023 Jan 1];132:104405. Available from: https://www.sciencedirect.com/science/article/pii/S0145305X22000672
99. Cayrol C, Girard JP. Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family. Immunol Rev. 2017;281(1):154–68.
100. Shaharyar MA, Rahman M, Anand K, Hossain CM, Kazmi I, Karmakar S. Rosmarinic Acid: A Boon in the Management of Cardiovascular Disease. Biomark Target Herb Drug Discov Pharmacol Approach Nanomedicines. 2021;229.
101. Banerjee A, Roy D, Mazumdar H, Bhowmik R, Karmakar S, Roy A, et al. MICRORNA 126 AS A SURROGATE MARKER FOR PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE ACROSS DIFFERENT AGE GROUPS IN SUSCEPTIBLE POPULATION. J Am Coll Cardiol [Internet]. 2022 Mar [cited 2023 Jul 24];79(9):3466. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109722044576
102. Banerjee A, Roy D, Mazumdar H, Karmakar S, Bhowmik R, Biswas N, et al. MicroRNA 155:145 ratio as a marker of atherogenic tilt manifested across different age groups and risk factor profiles. Eur Heart J [Internet]. 2022 Feb 4 [cited 2023 Jul 24];43(Supplement_1):ehab849.063. Available from: https://academic.oup.com/eurheartj/article/doi/10.1093/eurheartj/ehab849.063/6521109
103. Shaharyar MdA, Bhowmik R, Al-Abbasi FA, AlGhamdi SA, Alghamdi AM, Sarkar A, et al. Vaccine Formulation Strategies and Challenges Involved in RNA Delivery for Modulating Biomarkers of Cardiovascular Diseases: A Race from Laboratory to Market. Vaccines [Internet]. 2023 Jan 21 [cited 2023 Jul 24];11(2):241.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

Available from: https://www.mdpi.com/2076-393X/11/2/241

104. Gorain B, Choudhury H, Kundu A, Sarkar L, Karmakar S, Jaisankar P, et al. Nanoemulsion strategy for olmesartan medoxomil improves oral absorption and extended antihypertensive activity in hypertensive rats. Colloids Surf B Biointerfaces [Internet]. 2014 Mar [cited 2023 Jul 24];115:286–94. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0927776513007649
105. Bhowmik R, Shaharyar MdA, Anand K, Mazumdar H, Mandal A, Mandal P, et al. Mechanism of action of drugs used in hypertension. In: How Synthetic Drugs Work [Internet]. Elsevier; 2023 [cited 2023 Jul 24]. p. 349–67. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323998550000154
106. Banerjee A, Roy D, Mazumdar H, Bhowmik R, Karmakar S, Manna K, et al. MICRO RNA 155:126 RATIO AS A MARKER OF CLINICALLY MANIFEST ATHEROSCLEROSIS ACROSS DIFFERENT AGE GROUPS AND RISK FACTOR PROFILES. J Am Coll Cardiol [Internet]. 2022 Mar [cited 2023 Jul 24];79(9):1008. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109722019994
107. Nandi U, Karmakar S, Das AK, Ghosh B, Padman A, Chatterjee N, et al. Pharmacokinetics, pharmacodynamics and toxicity of a combination of metoprolol succinate and telmisartan in Wistar albino rats: Safety profiling. Regul Toxicol Pharmacol [Internet]. 2013 Feb [cited 2023 Jul 24];65(1):68–78. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0273230012002206
108. Karmakar S. Insights into the mode of action of antianginal and vasodilating agents. Synth Drugs Work Insights Mol Pharmacol Class New Pharm. 2022;329.
109. Mukherjee JR, Choudhury H, Karmakar S, Pal TK. Comparative Pharmacokinetic and Relative Bioavailability Study of Ursodeoxycholic Acid Tablets in Healthy Indian Volunteers. In 2013.
110. Chung J, An SH, Kang SW, Kwon K. Ursodeoxycholic Acid (UDCA) Exerts Anti-Atherogenic Effects by Inhibiting RAGE Signaling in Diabetic Atherosclerosis. Hudson BI, editor. PLOS ONE [Internet]. 2016 Jan 25 [cited 2023 Jul 25];11(1):e0147839. Available from: https://dx.plos.org/10.1371/journal.pone.0147839
111. Kunisek J, Zaputovic L, Cubranic Z, Kunisek L, Butorac MZ, Lukin-Eskinja K, et al. Influence of the left ventricular types on QT intervals in hypertensive patients. Anadolu Kardiyol Derg Anatol J Cardiol [Internet]. 2015 Jan 22 [cited 2023 Jul 24];15(1):33–9. Available from: https://www.anatoljcardiol.com//en/influence-of-the-left-ventricular-types-on-qt-intervals-in-hypertensive-patients-136502
112. Karmakar S, Padman A, Swamy Mane N, Sen T. Hypokalemia: A potent risk for QTc prolongation in clarithromycin treated rats. Eur J Pharmacol [Internet]. 2013 Jun [cited 2023 Jul 24];709(1–3):80–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299913002562
113. Karmakar S, Ali MA, Bera R, Mazumdar H, Sen T. QT prolongation by ranitidine in hypokalemia and arrhythmogen provoked rat heart. Vasc Dis Ther [Internet]. 2017 [cited 2023 Jul 24];2(4). Available from: http://www.oatext.com/QT-prolongation-by-ranitidine-in-hypokalemia-and-arrhythmogen-provoked-rat-heart.php
114. Biswas N, Roy D, Karmakar S, Bhowmik R, Banerjee A, Roy A. DIFFERENTIAL EXPRESSION OF HIGHLY SENSITIVE C-REACTIVE PROTEIN IN PATIENTS OF CORONARY ARTERY DISEASE WITH AND WITHOUT TRADITIONAL CARDIOVASCULAR RISK FACTORS. J Am Coll Cardiol [Internet]. 2023 Mar [cited 2023 Jul 24];81(8):2044. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109723024889
115. Das S, Mondal A, Dey C, Chakraborty S, Bhowmik R, Karmakar S, et al. ER stress induces upregulation of transcription factor Tbx20 and downstream Bmp2 signaling to promote cardiomyocyte survival. J Biol Chem [Internet]. 2023 Apr [cited 2023 Jul 24];299(4):103031. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021925823001631
116. Anand K, Ray S, Shaharyar MA, Rahman M, Bhowmik R, Karmakar S, et al. Delivery of Herbal Cardiovascular Drugs in the Scenario of Nanotechnology: An Insight. Biomark Target Herb Drug Discov. 2021;133–54.
117. Karmakar S, Das T, Ghosh A, Dasgupta SC, Biswas AK, Gomes A. Isolation and partial structural evaluation of a cardiotoxic factor from Indian common murrel (Channa striatus L.) skin extract. Indian J Exp Biol. 2004 Mar;42(3):271–8.
118. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 2015;33(8):1582–614.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 129-155 | ISSN:2251-6727

119. Cragg GM, Newman DJ. Natural product drug discovery in the next millennium. Pharm Biol. 2001;39(sup1):8–17.
120. Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. Curr Opin Solid State Mater Sci. 2002;6(4):319–27.
121. Pelaz B, Alexiou C, Alvarez-Puebla RA, Alves F, Andrews AM, Ashraf S, et al. Diverse applications of nanomedicine. ACS Nano. 2017;11(3):2313–81.
122. Watkins R, Wu L, Zhang C, Davis RM, Xu B. Natural product-based nanomedicine: recent advances and issues. Int J Nanomedicine. 2015;6055–74.
123. Sherry M, Charcosset C, Fessi H, Greige-Gerges H. Essential oils encapsulated in liposomes: a review. J Liposome Res. 2013;23(4):268–75.
124. Sinico C, De Logu A, Lai F, Valenti D, Manconi M, Loy G, et al. Liposomal incorporation of Artemisia arborescens L. essential oil and in vitro antiviral activity. Eur J Pharm Biopharm. 2005;59(1):161–8.
125. Bonifacio BV, da Silva PB, Ramos MA dos S, Negri KMS, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. Int J Nanomedicine. 2014;1–15.
126. Radwan FF, Perez JM, Haque A. Apoptotic and immune restoration effects of ganoderic acids define a new prospective for complementary treatment of cancer. J Clin Cell Immunol. 2011;004.
127. Sung JC, Pulliam BL, Edwards DA. Nanoparticles for drug delivery to the lungs. Trends Biotechnol. 2007;25(12):563–70.
128. Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol. 1998;85(2):379–85.
129. Ramineni SK, Cunningham LL, Dziubla TD, Puleo DA. Competing properties of mucoadhesive films designed for localized delivery of imiquimod. Biomater Sci. 2013;1(7):753–62.
130. El Enshasy HA, Hatti-Kaul R. Mushroom immunomodulators: unique molecules with unlimited applications. Trends Biotechnol. 2013;31(12):668–77.
131. Brooks BD, Brooks AE. Therapeutic strategies to combat antibiotic resistance. Adv Drug Deliv Rev. 2014;78:14–27.
132. Bhattacharya S. Phytosomes: emerging strategy in delivery of herbal drugs and nutraceuticals. Pharma Times. 2009;41(3):9–12.
133. Li DC, Zhong XK, Zeng ZP, Jiang JG, Li L, Zhao MM, et al. Application of targeted drug delivery system in Chinese medicine. J Controlled Release. 2009;138(2):103–12.
134. Hou J, Zhou S. Formulation and preparation of glycyrrhizic acid solid lipid nanoparticles. J Third Mil Med Univ. 2003;
135. Chen Y, Lin X, Park H, Greever R. Study of artemisinin nanocapsules as anticancer drug delivery systems. Nanomedicine Nanotechnol Biol Med. 2009;5(3):316–22.
136. Naik SR, Panda VS. Hepatoprotective effect of Ginkgoselect Phytosome® in rifampicin induced liver injurym in rats: Evidence of antioxidant activity. Fitoterapia. 2008;79(6):439–45.
137. Verma H, Prasad SB, Yashwant SH. Herbal drug delivery system: A modern era prospective. Int J Curr Pharma Rev Res. 2013;4:88–101.