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THE ANTI-INFLAMMATORY ACTIVITY OF PLANT DERIVED INGREDIENTS: AN ANALYTICAL REVIEW

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ABSTRACT: Inflammation, a protective response, can be dangerous if left untreated. The current synthetic anti-inflammatory drugs available in the market are coupled with various side effects. Plant-derived products can serve as a better alternative being cheap, easily available and having very few side effects. A sizable number of plants having anti-inflammatory activity have been studied. The crude extract of the plant is easy to obtain but it is not possible to indicate the component responsible for a particular property of the extract as it is a mixture of various components. Therein lays the importance of isolating the active principles from the crude extract and studying their mechanism of action. The present study aspires to provide an insight into the current trend of treatment of inflammation using herbal remedies by highlighting the different active principles obtained from different parts of plants, their concentrations used in specific test systems alongside underlining their molecular mode of action.

INTRODUCTION: Inflammation is defined as the response shown by the body when it is invaded by an antigen or any type of damage (physical, chemical or traumatic) occurs [1]. It is a naturally resolving process in which body fluid, proteins, and cells from the blood are transferred to the damaged tissues for their removal and resolution of the area. The inflammatory response is initiated by temporary vasoconstriction which is followed by acute vascular response due to increased blood flow leading to edema [2]. The acute cellular response occurs over the next few hours and is characterized by infiltration of neutrophils into the damaged area.

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If the damage is severe, chronic cellular response follows and is characterized by appearance of macrophages and lymphocytes. Over a few weeks, normal tissue design is restored. When the immune system is unable to restore the body to the original state because of the presence of a large amount of antigen or inaccessibility of the antigen, persistent inflammation occurs, and treatment becomes essential.

Immune Components Responsible for Inflammation: Both cells and soluble components act as mediators of inflammation. The vasoactive amines, reactive oxygen species, arachidonic acid derivatives, *etc.* are some of the mediators responsible for the propagation of inflammation. The cells include macrophages, eosinophils, neutrophils, etc. Some of the mediators are described below:

Arachidonic Acid Derivatives: Prostaglandin E2 (PGE2) is responsible for the pain and edema

which occurs during inflammation [3]. It is formed when cycloxygenase (mainly COX-2, which is inducible and plays an important role; COX-1 being constitutive) acts on arachidonic acid [4]. Cycloxygenase, in turn, is activated by nitric oxide (NO), another molecule of great importance, synthesized by inducible nitric oxide synthase (iNOS) [5]. The lipoxygenase pathway is also activated during inflammation to produce leukotrienes. Both the pathways activate various kinins, neuro-peptides, and histamine, as well as complement components, along with cytokines and free radicals.

Cytokines: Cytokines are proteins, secreted by white blood cells which play a critical role in inflammation by regulating inflammatory mediators usually secreted by other cells [6]. Pro-inflammatory cytokines aggravate inflammation while anti-inflammatory cytokines down-regulate the same. Pro-inflammatory cytokines include IL-1β, IL-6, IL-12 and TNF-α while anti-inflammatory cytokines include IL-10, IL-4, *etc*. [7]

Oxidative Status and Anti-oxidant Enzymes: Generation of reactive oxygen species (ROS) like superoxide, peroxynitrite, nitric oxide, *etc*. are greatly increased in inflammation causing damage to the cell components [8]. To minimize damage, cells have evolved enzymatic (catalase, superoxide dismutase) and non-enzymatic (glutathione) defense mechanisms but are downregulated during inflammation [9].

Signaling Pathways: NF-κB is a transcription factor which plays an important role in inflammation as it controls the expression of NO, COX-2 and pro-inflammatory cytokines [10]. It remains in the cytoplasm rendered inactive by IκB. When activated, IκB is phosphorylated and degraded, and NF-κB binds to DNA after entering the nucleus, allowing transcription of iNOS mRNA and various other pro-inflammatory cytokines. The activation of NF-κB occurs *via* the activation of mitogen-activated protein kinases (MAPKs) which include p38 MAPK (p38), extracellular signal-regulated kinases 1/2 (ERK1/2) and c-jun N-terminal kinase (JNK) [11, 12].

Current Anti-inflammatory Drugs are Associated with Side Effects: The control of inflammation includes synthetic anti-inflammatory drugs that can be given orally. They include the non-steroidal anti-inflammatory drugs (NSAIDs), steroids and disease-modifying antirheumatic drugs (DMARDs) [13]. The NSAIDs results in relief of pain by inhibiting cycloxygenases but are associated with side effects like headache, giddiness, abdominal pain, gastric ulcer, abnormal liver function, *etc.* [13]

Other than the general symptoms some drugs are associated with specific symptoms like Flurbiprofen is associated with cogwheel rigidity and Ibuprofen with agranulocytosis and aplastic anemia [14]. The major steroids used for the treatment of inflammation are glucocorticoids which reduces bone erosions but cause suppression of T cells, extreme changes in mood, headache, giddiness, extreme changes in mood, seizures, *etc.* [15] The DMARDs slows down the disease by suppression of the immune system which in itself is a disadvantage. TNF-α blocking agents are associated with increased bacterial infections.

Alternate Anti-Inflammatory Drugs from Natural Flora: As the market available drugs pose danger to the human body [16], the search for a natural product is essential as it would be less toxic but equally effective. Research is currently concentrated in this area and herein lays the importance of India being a treasure trove of medicinal plants by virtue of its being a mega diversity country. Plant products are therefore easily available and are a cheap option in India. The properties of the medicinal plants were well documented in Ancient Indian Literature and practiced in Ayurveda and other traditional forms of treatment.

MATERIALS AND METHODS: The names of the plants having anti-inflammatory properties were identified from a myriad of books on medicinal plants and also searched in an online database by entering the name of the plant along with the word "anti-inflammatory". The plants having anti-inflammatory properties were then separately searched in Pubmed, Google, Science Direct etc to see whether their active components were isolated and the mechanism of action studied. The information accumulated on the active ingredients and their mode of action were then represented in a table format.

RESULTS AND DISCUSSION:

Active Ingredients Obtained from Plants and Their Mechanism of Action: The plants manifesting anti-inflammatory properties are listed **Table 1** along with their mechanism of action. Most of the anti-inflammatory properties of plants are ascribed to phenols derived from the secondary metabolism of plants. Phenolic compounds are grouped into flavonoids, composed of two aromatic rings linked through an oxygen heterocycle, and non-flavonoids, commonly known as phenolic acids [17]. Flavonoids possess significant anti-inflammatory activity [18].

Active Ingredients: Some components namely cirsimarin (*Cirsium japonicum*) [19], eucalyptol (*Eucalyptus sp.*) [20], allylpyrocatechol (*Piper betle*) [21], curcumin (*Curcuma longa*) [22], theanine (*Camellia sinensis*)[23] *etc.* are obtained from specific one or two plants in which they are present as a major component or alongside other phenols. Most of them have various therapeutic properties. Since inflammation is associated with various diseases like rheumatoid arthritis, neurodegenerative diseases, heart diseases, gastric ulcers, cancer, *etc.*, some of these components were able to relieve the symptoms of various diseases simply by inhibiting the mediators of inflammation or by upregulating the anti-oxidant properties of the organism besides acting on specific targets of the respective diseases **Table 1**.

Animals/Cell Lines Used: Various strains of rat (Sprague Dawley, Wistar, *etc.*) and mice (ICR, C57BL/6, BALB/c, *etc.*) were the common choices as models of inflammation wherein inflammation was induced by lipopolysaccharide, pro-inflammatory cytokines or other phlogistic agents. Lipopolysaccharide was used in maximum number of cases. The drug of choice is given orally in most cases and then the plasma/tissues/cells are collected for analyzing the effect of the drug. Histological studies of the affected tissues using common stains were done in many cases to prove the efficacy of the herbal drugs. For *in-vitro* studies, mouse peritoneal cells or cell lines were used. RAW264.7 is the general choice for study of the anti-inflammatory activity of the plant product (though other cell lines like THP-1 and U937 were also used) while more specific cell types (BV2 microglial cells, human umbilical vein endothelial cells, human lung cancer cell, *etc.*) were chosen for studying the anti-inflammatory effect related to a particular disease **Table 1**.

TABLE 1: PLANTS HAVING ANTI-INFLAMMATORY PROPERTIES AND THEIR MECHANISM OF ACTION

Plant-derived product	Part of plant	Test system(s)	Concentration	Molecular mechanism(s) of action
Caffeic acid, S-allyl cysteine, and uracil from *Allium sativum*	Bulb	HR-1 hairless mice	5-20 μM	Inhibited DCFDA induced ROS production. Inhibited degradation of type1 procollagen and expression of MMP 3 and 9. Uracil inhibited COX-2 and Inos. Others inhibited NF-κB and AP-1 activity[24]
S-allyl cysteine		Wistar rats	25-100 mg/kg b.w.	Improved spatial recognition memory. Inhibited MDA and increased SOD, catalase and GSH levels.
		C2C12 myotubes	0.01- 0.1 mM	Inhibited glial fibrillary acidic protein, IL-6, IL-1β, Nox, NF-κB, IL-1 β and TLR4 activity. Upregulated Nrf2 activity[25, 26]
Alliin		3T3-L1 adipocytes	100 μmol/L	Inhibited LPS induced IL-6, MCP-1, Egr-1. Inhibited phosphorylation of ERK1/2 upregulation of genes involved in immune response[27]
Thiacremonone		ICR/(APP/ PS1) transgenic mice: attenuated cognitive impairments. BV-2 microglia cells. Cortical neuronal cells from Sprague Dawley rats	1-10 mg/kg b.w., 10 mg/L 1-5 μg/ml 1-5μg/ml	Inhibited ROS and NO, iNOS, COX-2 and GFAP expression. Inhibited amyloid β, NF-κB and ERK activity. Inhibited BACE level brains and augmented peroxiredoxin 6 (PRDX6)[28, 29]
Hirsutenone from *Alnus sp.*	Bark	Human keratinocytes HEK001 RAW264.7 cells	1 – 10 μM IC_{50}: 14.08 μM	Reduced NO, IL-1 β, IL-8, CCL17 and scavenged free radicals. Reduced activation of TLR-4, NF-κB and ERK phosphorylation[30, 31]
Antcin A from *Antrodia camphorata*	Fruiting bodies	Human lung cancer cell A549	10 mol/L	Induced nuclear migration of glucocorticoid receptor. Successfully docked to the binding cavity of GR[32]
Antrocamphin A		RAW264.7 cells	1-20 μg/ml, 20 mg/ ml	Inhibited NO, iNOS, COX-2 and superoxide. Inhibited platelet aggregation. Inhibited NF- κB activation [33, 34]
Arctigenin from *Arctium lappa*	Seed	C57BL/6 mice peritoneal macrophages C57BL/6 mice	5 mg/kg b.w. 0-20 μM 25-50 mg/kg b.w.	Inhibited IL-1β, IL-6, TNF-α, MIP-2, MCP-1, MAdCAM-1, ICAM-1, and VCAM-1 increased IL-10 and CD204 expression. Decreased MDA level but increased SOD and GSH levels. Inhibited PI3K, AKT,

				IKKβ, NF-κB and MAP kinase activity[35, 36]
3-acetyl-11-keto-β-boswellic acid from *Boswellia serrata*	Gum resin	KBM-5, RAW 264.7, H1299, HEK A293, HCC4 and MDA 1986 cells, Albino rats	10-50 µM 125-250 mg/kg	Inhibited COX-2, IL-6, and TNF-α. Reduced TNF-α induced NF- κB. Blocked NF- κB activation and increased dopamine levels [37, 38]
Cajaninstilbene acid from *Cajanus cajan*	Leaves	RAW264.7 cells U937, Zebrafish Larvae	25 -100 µg/ml 10-50µM 1.25-5 µM	Activated PPARγ. Inhibited NO, iNOS, IL-6, and TNF-α. Inhibited migration of neutrophils and macrophages. Inhibit NF-κB and MAP kinase activation [39, 40]
Epigallocatechin-3-gallate (green tea) from *Camellia sinensis*	Leaves	Fibroblast cells BALB/c mice: reduced OVA-induced nasal rubbing and sneezing	10-100 µM 25-100mg/kg b.w.	Inhibited COX-2, TNF-α, IL-4, IL-1β, and IL-6 [41, 42]
Theaflavin (black tea)		C57BL/6 mice U937 and RAW264.7 cells Gingival keratinocytes: enhanced tight junction integrity	20-40 mg/kg bw 6.25-50 µM/7.9-125 µg/ml 31.25-250 µg/ml	Inhibited NF-κB, JNK, and p38 activity. Inhibited TNF-α, IL-1β, IL-6, chemokine (C-X-C) ligand 8, MMP-3, MMP-8 and MMP-9 [43, 44]
Thearubigin (black tea)		Mice: inhibited 2,4,6-trinitrobenzene sulfonic acid (TBNS) induced colitis	40-100 mg/kg b.w.	Inhibited TBNS induced NO, iNOS. Inhibited NF-κB activation [45]
Theanine		ICR mice CD-1 mice: reduced TPA-induced erythema, vascular permeability increase, epidermal and dermal hyperplasia,	20- 40 mg/kg 5-250 mM	Decreased alanine aminotransferase, aspartate aminotransferase, SOD and MDA levels. Reduced neutrophil infiltration and PECAM-1. Decreased IL-1β, TNF-α, COX-2, iNOS, MMP-3 IFN-γ and increased IL-10. Decreased NF-κB activity [23, 46]
Capsaicin from *Capsicum sp.*	Fruit	Human THP-1 cells	10 µM	Decreased LPS induced IL-1β, TNF-α and Il-6. Increased LXRα expression through PPARγ pathway and inhibiting NF-κB activity[47]
Cirsimarin from *Cirsium japonicum*	Aerial part	RAW 264.7 cells	10-40 µM	Inhibited LPS induced NO, iNOS, COX-2, PGE2, TNF- α and IL-6. Downregulated phosphorylation of JAK and MAPK and nuclear translocation of interferon regulatory factor 3.[19]
Colchicine from *Colchicum autumnale*	Bulb like corms	Recurrent aphthous stomatitis (RAS) patients	0.5 mg	Decrease in level of neutrophil-lymphocyte ratio, white cell count and red cell distribution width. No change in mean platelet volume, Hb levels [48]
Corynoline from *Corydalis bungeana*	Whole herb	RAW264.7 cells Human umbilical vein endothelial cells	10 -100µg/ml, 1-4 µM 1-4 µM	Inhibited LPS-induced NO, iNOS, COX-2, IL-6, IL-10, TNF-α, IL-1β, VCAM-1 and ICAM-1. Increased expression of Nrf2, quinone oxidoreductase 1 and HO-1. Inhibited NF-κB, p38 and ERK[49-51]
Cudratricuxanthone A from *Cudrania tricuspidata*	Root	RINm5F C57BL/6 mice	1- 10 µM 0.058-0.294 mg/kg b. w.	Inhibited ROS, NO, iNOS, IL-6, TNF-α and NF-κB. Reduced phosphorylation of STAT-1, 3 and 5. Inhibited glucose-stimulated insulin secretion. Reduced cecal ligation and puncture (CLP)-induced creatinine, blood urea nitrogen (BUN), lipid peroxidation[52]
Curcumin from *Curcuma longa*	Rhizome	BV2 microglial cells C57BL/6 mice RAW264.7, THP-1 cells Wistar rats	10-50 µM 10 mg/kg 5 - 15 µM 0.15 -0.6 mg/ml	Inhibited NO, iNOS, TNF-α, IL-6 and IL-1β. Improved ovalbumin-induced total WBC, PLA2, TP, IgE, IL-4, IFN-γ, IFN-γ/IL-4 ratio, SOD, thiol. Inhibited NF-κB, ERK, p38 pathway and p13K/AKT pathway[22, 53, 54]
Eucaluptol (1,8 cineole) from *Eucalyptus* sp	Leaves	Murine alveolar macrophage cell line MH-S (CRL 2019) C57BL/6 and TRPM8 mice HEK293T cells	0-100% vol/vol 30-300 mg/kg b.w.	Reduced IL-1α, IL-1β, TNF-α, IFN-γ and IL-6. Downregulated TREM -1 and NLRP3 pattern recognition receptors and enhanced phagocytic activity. Inhibited JNK1/2 and ERK1/2 activity [20, 55]
Ginkgetin from *Gikngo biloba*	Leaves	Mouse bone marrow-derived mast cells, ICR mice: TPA induced ear edema	1.6- 50 µM 20—80 µg /ear/treatment	Reduced PGD2, PGE2, COX-2 and IL-1β. Inhibited leukotriene and β-hexoseaminidase[56, 57]
Alantolactone and isoalantolactone from *Inula helenium*,	roots	HaCat cells	0.6-2.4 µg/ml	Inhibited TNF-α-induced activation of NF-κB and the expression of TNF-α, IL-1, and IL-4.[58]
Scopariusols from *Isodon scoparius*	Aerial parts	RAW264.7 cells	IC_{50} value of 0.6 µmol·L^{-1}	Inhibited LPS induced NO production[59]
Kalopanaxsaponin A from *Kalopanax pictus*	Stem bark	ICR mice: inhibited weight reduction, colon shortening, inflammation and thickening peritoneal macrophages Murine BV2 microglial cell	10-20 mg/kg b.w. 5-10 µM 100-300 µM	Inhibited LPS-induced iNOS, COX-2 IL-1β, TNF-α and IL-6, ROS and upregulated IL-10. Inhibited activation of IRAK-1, NF-κB, JNK, ERK and p38 and upregulated HO-1 [60, 61]
Momordin from *Kochia scoparia*	Fruits	RAW 264.7 cells	7.5-30 µg/ml 5-80 µM	Reduced NO, iNOS, COX-2, PGE2, IL-6 and TNF-α and NF-κ [62, 63]

Thymoquinone from *Nigella sativa*	Seed	BV2 microglial cells Wistar rats: Reduced neutrophil accumulation in pleural space Human neutrophils C57BL/6: Reduced EtOH–induced gastritis, RAW264.7, and human monocyte-like U937	10 µM 10-50 mg/kg b.w. 0.1-2.5 µg/ml 0- 25 µM	Inhibited NO, iNOS, COX-2, TNF-α, IL-6, IL-1β IL-12p40/70, superoxide ion, CCL12 /MCP-5, CCL2/ MCP-1, and G-CSF, Cxcl10. Inhibited IRAK-1, AP-1, PKC, MAPK, and NF-κB. Impaired the phosphorylation on Ser-304 and Ser-328 of p47(PHOX), a cytosolic subunit of the NADPH oxidase[64-66]
Ginsenoside from *Panax ginseng*	Roots	Human airway epithelial cells A549 cells, Intestinal epithelial cells (H-29); RAW264.7 cells Sprague Dawley rats	50 µM 900 nM 1-50 µM 20mg/kg b.w.	Reduced IL-1β, TNF-α, IL-6, NO, COX-2, ROS, MDA and caspase 3. Increased GSH, p-AKT/AKT, GSK 3β, and reduced p21WAF1/CIP1 and p53 proteins. Inhibition of NF- κB activity [67-69]
Picroliv isolated from *Picrorhiza kurroa*	Roots and rhizomes	KBM 5 /H1299/A293 cells BALB/c mice	50- 150 µg/ml. 12.5 mg/kg b.w.	Downregulated IL-1β, TNF-α, and NF-κB pathway. Suppressed IAP1, Bcl-2, Bcl-xL, survivin, and TRAF2, cyclin D1 and COX-2, VEGF, ICAM-1, and MMP-9. Inhibited MPO, MDA expression and increased SOD levels [70,71]
Allylpyrocatechol from *Piper betle*	Leaves	Sprague Dawley rats: reduced paw edema. RAW 264.7 cells	10 mg/kg bw/ 20 mg/kg b.w. 2.5 and 5 µg/ml	Inhibited NO and iNOS. Inhibited IL-12p40, TNF-α, IL-6 COX-2 and PGE_2. Inhibited NF-κB activation [21, 72]
Platycodin D from *Platycodon granduflorum*	Roots	Sprague Dawley rats C57BL/6 mice bovine mammary epithelial cells (bMEC)	10-30 mg/kg b.w. 20-80 mg/kg.b.w. 5-20 µM	Attenuated cigarette smoke-induced/LPS induced MDA, NO, IL-6, TNF-α, and IL-1β. Decreased serum alanine transaminase, aspartate transaminase and total bilirubin. Attenuated cigarette smoke-induced pathological changes in lung. Down-regulated MD-2 and CD14. Attenuated TLR4, MyD88 and TRAF-6, NF-κB and upregulated LXRα expression [73-75]
Cirsitakaoside from *Premna szemaoensis*	Stem and leaves	C57BL/6J mice Mouse peritoneal macrophages and RAW264.7 cells	50mg/kg 0-75 µM	Suppressed LPS induced activation of IL-1B, TNF-α, IL-6. Inhibited iNOS and COX-2 mRNA. Inhibited NF-KB and MAPK pathway [76]
Punicalagin from *Punica granatum*	Fruit	ICR mice: prevented LPS induced memory impairment Astrocytes and microglial BV-2 cells. Bovine endometrial epithelial cells (bEEc)	1.5 mg/kg b.w. 1 µg/ml 5-20 µg/ml	Inhibits LPS induced iNOS, COX-2, production of ROS, NO, TNF-α, IL-6, IL-8, and IL-1β. Suppress NF-κB, p38, JNK and ERK activity. Downregulated APP and BACE1 expression [77, 78]
Tanshinone IIA from *Salvia miltiorrhiza*	Root	Human vascular endothelial cells (HUVEC) C57B/L mice RAW264.7 cells	0-20 µM 30-60 mg/kg b.w. 10 µM	Attenuated IL-1β, TNF-α, COX-2, fractalkine/CX3CL1, VCAM-1, ICAM-1, GMCSF and AP-1. Reduced total cholesterol, triglyceride, LDL, VLDL, MDA. Inhibited adhesion of THP-1 monocytes. Inhibited ERK1/2 and NF-κB activity [79-81]
Cryptotanshinone		A7r5 cells CD-1 mice: alleviate memory decline in $Aβ_{1-42}$-injected mice	10^{-7} to 10^{-5} M 1-10 mg/kg b.w.	Reduced expression of NO iNOS COX-2 *via* ERβ-dependent and NF-kB pathway [82, 83]
Salvianolic acid B		Wistar rats: improved cerebral ischemic injury PC-12 cells. Sprague Dawley rats: Primary cortical neurons were obtained and LPS induced depression was reduced. C57BL/6: suppressed cartilage destruction and slowed osteoarthritis development Human OA chondrocytes	30 mg/kg 200-800 ng/ml 20 mg/kg b.w. 25 mg/kg b.w. 25-100 µM	Reduced chemical and oxygen-glucose deprivation and reoxygenation (OCD/R) IL-1β, IL-6, TNF-α, NO, PGE2, INOS, COX-2, MMP-13 and ADAMTS-5. Inhibited TLR4/MyD88/TRAF6 signaling ameliorated NeuN release. Induced autophagy and decreased NLRP3 inflammasome activation. Inhibited NF-κB activity [84-86]
Saurolactum from *Saururus chinensis*	Roots	RAW 264.7 cell	1 – 10 µM	Inhibited LPS induced IL-1β, IL-6, TNF-α, iNOS, COX- 2, PGE2. Inhibited activation of NF-κB, phosphorylation of ERK, JNK and p38 kinase87
Sauchinone	Roots	Microglial BV-2 cells and cultured astrocytes. Human osteoarthritis chondrocytes	1 – 10 µM 2.5-20 µg/ml	Inhibited generation of ROS, NO, iNOS, COX-2, PGE2. Inhibited MMP-3 and MMP-13 release [88, 89] Inhibited β-secretase, STAT3, and NF- κB
Schisandrin B from *Schisandra chinensis*	Fruits	BV2 microglial cells. Human umbilical vein endothelial cells (HUVECs)	12.5 -50 µM 10 -40 µM	Inhibited LPS induced TNF-α, IL-6, IL-1β,IL-8, ICAM-1, VCAM-1, and PGE2. Downregulated NF-κB upregulated the expression of PPAR-γ, Nrf2 and HO-1 [90, 91]
Schisandrin A		RAW 264.7 cells	50 -200 µM	Inhibited Lps induced NO and PGE2 by inhibiting iNOS and COX-2 respectively. Reduced TNF-α and IL-1β. Inhibited NF-κB, MAPK, and PI3K/Akt activity. Upregulated Nrf2 and HO-1 [92]
Schisandrin C		Human dental pulp cells (HDPC)	10 -20 µM	Inhibited LPS induced TNF-α, IL-1β, ICAM-1, VCAM-1.MMP-2 and -9, NO production, ROS formation, NF-κB. Upregulated SOD, HO-1, peroxisome proliferator-activated receptor-gamma coactivator 1-α, p-Akt and Nrf2 [93]

Gomisin N	Fruits	Human periodontal ligament cells (HPDLC). C57BL/6 mice: Attenuates Ethanol-Induced Hepatic Steatosis and Liver Injury SK-HEp-1 cells HepG2 cells	0-50 µM 20 mg/kg b.w. 5-20 µM 50-100 µM	Inhibited TNF-α induced IL-6, IL-8, chemokine ligand CCL 2, and CCL20. Inhibited NF-κB, ERK and JNK pathway. Decreased MDA and CYP2E1 and increased SOD, catalase, GSH, and GPX levels. Enhances sirtuin1 (SIRT1) and phosphorylated AMP-kinase (AMPK)[94, 95]
Gomisin A		C57BL/6J peritoneal macrophages	0.01-1 ng/ml	Inhibited LPS induced COX-2, iNOS, IL-6, TNF-α and NO. Inhibited receptor-interacting protein 2 (RIP2) and NF-κB activity[96]
Taraxasterol from *Taraxacum officinale*	Aerial part and root	Wistar rats: suppressed Freunds Complete Adjuvant induced paw swelling and arthritis index, human umbilical vein endothelial cells	2-8 mg/kg b.w. 5-18µg/ml	Inhibited FCA/LPS induced TNF-α, IL-8, IL-1β, NO, iNOS, COX, PGE2, and RANKL, Increased serum OPG production. Decreased NF-κB and increased expression of LXRα[97, 98]
Triptolide from *Tripterygium wilfordii*	Leaves	BALB/c mice Sprague Dawley rats MH7A cells	5-15 µg/kg b.w. 0.2mg/kg b.w. 0.5-2 µM	Reduced LPS/ TNF-α induced leukocyte, myeloperoxidase activity, edema of the lung, Inhibited TNF-α, IL-1β, and IL-6, IL-8, iNOS, COX-2 Inhibited expression of TLR4 and NF-κB, ERK and JNK activity. Attenuated brain infarction volume, death of neuronal cells, Bcl2, Bax, caspase3 [99-101]
Zingerone from *Zinziber officinale*	Rhizome	C57BL/6 mice SW1353 cell line Wistar rats	10-40 mg/kg b.w. 10-40 µM 10-50 mg/kg b.w.	Suppressed chemically induced BUN, creatinine, lactate dehydrogenase, and reduced inflammatory cytokines TNF-α, IL-6, IL-8, and IL-1 β. Inhibited TLR4, MyD88, TRIF expression and NF-κB, p38 and JNK activation [102-104]
Gingerol		RAW264.7 cells	50-300 µg/ml	Inhibited LPS induced NO, PGE2, TNF-α, IL-1β, and IL-6. Inhibited iNOS and COX-2 mRNA expression. Inhibited NF-κB activation [105]
6-Shogaol		BV2 microglial cells		Inhibited LPS-induced TNF-α, IL-1β, IL-6, and PGE2. Inhibited NF-κB and increased PPAR-γ [106]

ADAMTS: disintegrin and metalloproteinase with thrombospondin motifs, Akt: Protein kinase B, AMPK: AMP-activated protein kinase, AP: activator protein, APP: Amyloid precursor protein, BACE: beta-site APP Cleaving Enzyme, BUN: blood urea nitrogen, CCL: chemokine ligand, CD: cluster of differentiation. COX-2: cycloxygenase2, CLP: cecal ligation and puncture, CXCL: chemokine (C-X-C motif) ligand, CYP: Cytochrome 450, DCFDA: 2',7'-dichlorodihydrofluorescein diacetate, Egr: early growth response proteins, ERβ: Estrogen receptor β, ERK: extracellular signal regulated kinase, GFAP: Glial fibrillary acidic protein, GMCSF: granulocyte macrophage colony stimulating factor, GSH: glutathione, GSK: glycogen synthase kinase, GR: glucocorticoid receptor, HO: heam oxygenase, IAP: Inhibitors of apoptosis proteins, ICAM: intercellular adhesion molecule, IFN: interferon, IKK: IκB kinase, IL: interleukin, iNOS: inducible nitric oxide synthase, IRAK: interleukin-1 receptor-associated kinase, JNK: Jun N terminal kinase, LPS: lipopolysaccharide, LXR: Liver X receptor, MadCAM: mucosal vascular addressin cell adhesion molecule, MAPK: mitogen activated protein kinase, MCP: monocyte chemoattractant protein, MD2: lymphocyte antigen 96, MDA: malondialdehyde, MIP: macrophage inflammatory protein, MMP: matrix metalloproteinase, Myd88: Myeloid differentiation primary response 88, NeuN: neuronal nuclei, Hexaribonucleotide Binding Protein, NF- κB: Nuclear factor kappa B, NLRP: Leucine rich Repeat and Pyrin domain containing, NO: nitric oxide, NOX: NADPH oxidase, Nrf: nuclear factor (erythroid derived), OCD/R: oxygen glucose deprivation and reoxygenation, OPG: osteoprotegerin, P21Waf1: Cip1/Kip1 family of cyclin-dependent kinase inhibitors, PECAM: platelet endothelial cell adhesion molecule, PGE2: Prostaglandin E2, PI3k: phosphatidylinositol 3-kinase,PKC: protein kianse C, PPAR: Peroxisome proliferator-activated receptor, PRDX: Peroxiredoxin, RIP: receptor interacting protein, ROS: Reactive oxygen species, RANKL: Receptor activator of nuclear factor kappa-B ligand, SIRT: Sirtuin, SOD: superoxide dismutase, STAT: signal transducer and activator of transcription, TLR: toll like receptor, TBNS: 2,4,6-trinitrobenzene sulfonic acid, TNF: tumor necrosis factor, TP: thromboxane, TPA: 12-O-tetradecanoylphorbol- 13-acetate, TRAF: Tumor necrosis factor receptor–associated factor, TREM: Triggering receptor expressed on myeloid cells, VCAM: vascular cell adhesion molecule, VEGF: Vascular endothelial growth factor.

Mechanism of Action: The anti-inflammatory property of many of the active plant components was exhibited by their ability to bring down the common mediators of inflammation like NO, iNOS and pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, IL-12p40, *etc*. Chemokines such as RANTES, MCP-1, *etc*. were also inhibited by certain plant products. The other important mediators of inflammation such as cycloxygenase-2 (COX-2), prostaglandins and leukotrienes, the chosen targets of the existing anti-inflammatory drugs, were also downregulated by majority of compounds derived from plants. Reduction in ROS, lipid peroxidation along with upregulation of the enzymatic (superoxide dismutase, catalase, *etc*.) and non-enzymatic (glutathione, *etc*.) defense systems were also tested as markers of anti-inflammatory activity. Inhibition of neutrophil infiltration reduced expression of cell adhesion proteins (ICAM, VCAM, PECAM, *etc*.) and metallo-proteins (MMP-3, 8, 9, *etc*.) were also taken into account. All the above-mentioned events were mainly attributed to the downregulation of signaling pathways like NF- κB pathway by the naturally derived plant products. The MAP kinase pathway (p38, ERK, and JNK pathway) was also inhibited and Nrf2 pathway activated to bring about a remission of inflammation **Table 1**.

CONCLUSION: Therapies of inflammation must inhibit one or more of the pro-inflammatory mediators released from different cells without

hampering the normal functions of the body. As the currently available drugs are yet to be perfected, researchers are looking into traditional and folk medicine in the pursuit of devising a more improved drug. The present study focuses on the role of traditional plants and their phytoconstituents in reducing inflammation along with their molecular mechanisms of action. Most of the plant's products exert their effect by reducing the known mediators of inflammation such as NO, TNF-α, IL-6, ROS, COX-2, and prostaglandins. These reductions were due to the inhibition of the signaling pathways like NF-κB pathway or MAP kinase pathways. This review attempts to present a collage of the different anti-inflammatory constituents from plants that would enable researchers to use this study as a foundation for their future experiments towards devising a more potent medicine for the treatment of inflammation.

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