



Traditional Uses and Anti-Inflammatory Activities of Different Medicinal Plants: A Systematic Review

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Abstract

A considerable preponderance of population throughout the globe has consistently manipulated medicinal plants as pioneer informant of health protection to oppose contagious and non-contagious diseases. The bulk of these pharmaceutical plants have scientific affirmation to be contemplated in prevailing application. Inflammation is the crucial problem interconnected with copious infection. Every living creature can sense sick, feverish and weak as our body struggle to over through the infection and recuperates itself. Inflammation is absolutely important to conserve us healthy. However, sometimes the inflammatory response of our body can be a bit overenthusiastic, not arrest when it is expected to; which can cause numerous complications and even condition of disease. To completely comprehend and be able to competently treat these disorders, we require a more desirable and satisfactory comprehension of how and why these long lasting chronic infection happens. Now in present time, inflammation is rehabilitated by NSAIDS. These drugs unfortunately accomplish appalling possibilities of blood clots leading to strokes and cardiac arrest. Therefore, the essential universal products are currently under applications in order to develop the dynamic anti-inflammatory drugs. For the rehabilitation of various disease linked with inflammation, the essential crude products from important medicinal plants performs a decisive factor. To get rid of the side effects of present day drugs, there is a necessity for the development of advance drugs with minor or no secondary responses. The current review designed towards gathering of particular information on auspicious curative plants especially experimented in inflammatory model manipulating accurate scientific experimental system.

Key words: Inflammation, Cytokines, NF- κ B, MAPK and anti-inflammatory activity.

Abbreviations

TNF- α , tumor necrosis factor-alpha; IL-1, interleukin-1; IL-1 β , interleukin 1-betta; NF- κ B, nuclear factor – kappa B; LPS, lipopolysaccharide; MAPK, mitogen associated protein kinase; JNK, C-Jun N terminal kinase; ICAM-I, intracellular adhesion molecules-I; GM-CSF, Granulocyte monocyte-colony stimulating factor; COX, cyclooxygenase; ROS, reactive oxygen species; CFA, Complete Freund's adjuvant.

1. Introduction

1.1 Inflammation

Inflammation is a conservative retroaction of organism accomplished by pathogens or damage tissue through the assemblage of immune cells like microphages and microglia eradicating pernicious stimuli¹. Multiple substances are released during the tissue injury which is whether caused by heat, chemicals, bacteria, trauma, or any other phenomenon and causes remarkable secondary changes in the neighbouring

tissues. The whole complex of changes in tissue is called inflammation. It is described by (a) an increase in local blood flow due to the vasodilation of the blood vessels, (b) allowing the accumulation of large abundance of fluid in the interstitial space due to increased permeability of the capillaries, (c) clotting of fluids occurs in the interstitial space due to the increased in the concentration of clotting factors like fibrinogen and other proteins discharging from the capillaries, (d) movement of large quantity of monocytes and granulocytes into the tissue (e) swelling. Prostaglandins, serotonin, histamines, lymphokines released by T cells, reaction outcome of complement and blood clotting system causes these reaction. Walling –Off is the first result of inflammation to separate the surrounding tissues from the area of injury. Macrophage is the First Line of Defense and the phagocytic potential of macrophage is maximum among all phagocytes. They are activated by Interferon-gamma (IFN- γ) secreted from CD₄ T helper₁ cells. Activated macrophages performs following functions:-

Greatest phagocytotoxicity.

Oxidative burst and hydrolytic cleavage of pathogens

Antigen presentation by MHC II to CD₄ TH cells.

Neutrophil invasion to the site of injury is the Second Line of Defense. They have transmembrane receptor. Inflammatory cytokines (IL-1, TNF) and others biochemical products cause increased utterance of adhesion molecules like selectin and ICAM-1 on the surface of endothelial cells and venules. Due to the reaction of adhesion molecules with integrin Neutrophil sticks to the venule& capillary walls in the inflamed region. They also causes chemotaxis of the neutrophil towards the infected region. Intrusion of second macrophage into the effected tissue is the Third Line of Defense. Along with the neutrophil, monocytes are discharged to the inflamed region from the blood and activated by INF- γ to become macrophage. The fully matured macrophage can plays a decisive role in beginning of antibodies development. It can also phagocytize far larger particle and bacteria. Due to the stimulation of monocytes and granulocytic progenitors, there is an increase in production of monocytes and granulocytes in the infected area by the bone marrow is the Fourth Line of Defense. Colony stimulating factors mainly GM-CSF, stimulates the production of monocytes and granulocytes from the marrow ².

1.2. Types of Inflammation

1.2.1. Acute Inflammation

It is a temporary process and it starts in less than a minute or hours after the tissue injury. The sign of acute inflammation are erythema, pain, edema and heat. It is designated by the leakage of plasma proteins, fluids as well as migration of white blood corpuscle towards the inflamed region. The neutrophils are the first cells which are recruited in large concentration to the region of inflammation. The aim of acute inflammatory response is to kill the virus, parasite and bacteria to repair the wound ³. **Fig. 1**

1.2.2. Chronic Inflammation

Over utterance and secretion of cytokines plays a decisive factor in the pathogenesis of autoimmune disorders, joint diseases, chronic inflammatory diseases and bone resorption ⁴. Being an efficacious paracrine molecules, TNF- α can urge others pro-inflammatory cytokines like GM-CSF and IL-1 β and play a decisive factor in the origination and development of inflammatory disorders and RA. It can lasts for several month even years, refers to chronic inflammation and it results from:

Incompetent to eradicate whatsoever was accomplishing an acute inflammation.

An autoimmune disease that affect conventional normal tissue, mistaking it for a pathogen that executes disease.

Revelation to an inconsequential particular irritant, such as an industrial chemical, lasting for a considerable time.

Although mutilated tissue cannot recuperate without inflammation, chronic inflammation can ultimately accomplish multiple diseases and conditions implicating some cancers, rheumatoid arthritis, hay fever, periodontitis, and atherosclerosis. Inflammatory condition in human like rheumatoid arthritis, autoimmunity and sepsis are designated by an imbalance of the pro-inflammatory and anti-inflammatory cytokines prescribed by multiplication and stimulation of Th₁ and Th₂ cells. In the origination and development of autoimmune, depression, obesity and allergic disorder, these immune imbalance performs a decisive factor. These disorders are accounted to the deteriorative countenance of cytokines namely IL-6 and TNF- α ⁵. **Fig.2**

1.3. Mediators of Inflammation

Histamines is released from cells during inflammation is one of the best known chemical mediators, which causes vascular permeability and vasodilation. It is released immediately after the cell injury. Prostaglandins are synthesized from arachidonic acid. Except RBC all mammalian cells produce prostaglandins. The enzymes cyclooxygenase (COX) catalyze this reaction. There are two isozymes of COX present in mammals, COX-1 & COX-2. Prostaglandins causes vasodilation in the local area and chemotaxis⁶. NF- κ B, which inculcates in the whole mechanism of inflammation, is one of the most significant redox –sensitive common universal transcription factors that switch on the countenance of those genes which are inculcated in inflammation, procreation of cells and endurance⁷. Among the mediators of inflammation, NO formed from L-arginine in the presence of enzyme NO synthase act both as 1⁰ and 2⁰ messenger. The function of NO as primary messenger is the signaling to the secretion of vasodilators in the area of NO action. The function as secondary messenger is the activation of guanylate cyclase in smooth muscles of body. However the excess of NO production leads to damage of normal tissue⁸. Reactive oxygen species (ROS) are essential in conventional cells for many biological process because it act as second messenger in cell signaling⁹. In the pathogenesis of inflammatory disorder Reactive oxygen species plays a pivotal role,¹⁰ and are inculcated in the countenance of the inflammatory genes by arbitrating the activation of the cyclooxygenase (COX-2) and nuclear factor- κ B signaling pathways¹¹. ROS is significant in defense mechanism in the course of respiratory burst. Activated NADPH Oxidase also known as PHOX enzyme is present on the outer membrane of leucocytes produces excessive concentration of superoxide which forcefully destroy the pathogens. Antioxidant are accountable for perpetuating the right amount of ROS for signaling and other physiological activities. When this stability is imbalanced and large amount of ROS have generated or decrease the amount of antioxidant, oxidative stress occurs. Oxidative stress has been broadly inculcated in many inflammatory diseases. ROS also causes oxidative damage to lipid, protein, deoxyribonucleic acid. Oxidation is a frequent natural energy accomplishing reaction, oxidative stress is a disastrous to cell, because the oxidation's yields such as reactive oxygen species and free radicals destroy the cell system and leads to different diseases¹². **Fig.3**

2. Plants and their compounds as natural anti-inflammatory agents

In this study, we explored the biological activities especially the anti-inflammatory activity of various medicinal plants. The data provides considerable confirmation of anti-inflammatory activity of plants.

Dilodendronbipinnatum

Dilodendronbipinnatum is an indigenous plant from South America. It is broadly spread in Amazon, Atlantic rain forest, carrado Peru, North of Paraguay. It is commonly known as “Maria pobre”, “dry-flour” and “poor-Mary”. The decoction and maceration form of stem bark has been historically used for the treatment of various diseases. Specifically, the bark of inner stem of *Dilodendronbipinnatum* is used for the treatment of bone fractures, dermatitis, general pain and uterine inflammation. In RAW 264.7 triggered with LPS, hydro ethanolic extract of *Dilodendronbipinnatum* (HEDB) lowers the activation of P38 MAPK, countenance of COX-2 proteins, P-JNK, assemblance of ROS, depolarization of mitochondrial membranes

and translocation of NF- κ B. In the cell supernatant HEDB showed an augment in the utterance of MKP-1 and diminish in the concentration of PGE₂ and pro-inflammatory cytokines. It is investigated that blocking of macrophage P38, ERK, and JNK pathways also lowers the COX-2 countenance, production of TNF- α and IL-1 β during the course of inflammation. Extract shows strongest anti-inflammatory activity by elevating the MPK-1 countenance and diminishing mitochondrial destabilization, assemblance of ROS, and also diminishing P38, MAPK and JNK consequencing in attenuating the activation of NF- κ B, which in turns suppressing the transactivation of genes such as IL-1 β , TNF- α and COX-2 in a model of LPS mediated RAW 264.7 cell¹³.

Pittacantusplagiophyllus

Pittacantusplagiophyllus appertains to the family Loranthacea. In the folk medicine it is broadly practice around the world. For the treatment of stomach problems like (gastritis and ulcer) & inflammation, the leaves of the *P. plagiophyllus* are used in the folk medicine. The preliminary studies with the extract of leaves of this species shows that it has edema inhibiting capacity and gastro protective capacity in rats without urging acute toxicity. The aqueous extract of *P. plagiophyllus* (AEPp) downregulated the mediators including the early and late phase of edema formation. AEPp also reduced paw edema developed in the rat model mediated by dextran in dose dependent manners. AEPp extract enables the great reduction of neutrophil migration in the carrageenan induced air pouch inflammation model. It is efficacious in diminishing the exudate secretion and recruitment of leukocytes particularly neutrophil. Because of some phenolic compounds, it has capability to downregulate the synthesis of eicosanoids, interrupt the assemblance of pro inflammatory cytokines, enhance the expression of genes which are inculcated in the inflammatory responses and act on the action of inflammatory cells directly or indirectly, Such as NK cells, monocytes, lymphocytes, mast cells, neutrophil and macrophages and exhibits anti-inflammatory activity¹⁴. AEPp extract also shows greatest antioxidant activity, which is assigned predominately to their phenolic compounds. Therefore AEPp, due to its higher phenolic content exhibited noticeable *in vitro* anti-oxidant and *in vivo* anti-inflammatory activity.

Artemisia herba-alba

Artemisia herba-alba is a perennial dwarf greenish-silver shrub nurture in the arid and semi-arid climate. It is found in the deserts and stapes of Spain, North, Middle East Africa, spreading into northern western Himalayas. In traditional medicine this plant has been manipulated for the rehabilitation of diarrhea, hypertension, bronchitis and diabetes. *Artemisia herba alba* depicted substantial anti-inflammatory activity in an IFN- γ /LPS mediated RAW 264.7 due to the subsistence of phenolic compounds in the methanol extract, it also manifested greatest inhibition of NO. The *A. herba-alba* extract depicts anti-oxidant activity evaluated by using particular *in vitro* assays ABTS/DPPH radicals scavenging activity and AAPH. The extract also exhibits a high anti-cancerous activity, by specifically targeting the carcinoma cell lines (RT112) human laryngeal carcinoma cells (HEP2) human myelogenous leukemia (K562). It may be concluded that the methanol extract of *A. herba-alba* depicted higher anti-oxidant and anti-inflammatory activity associated with appreciable anti-cancerous activity. The anti-inflammatory response of *A. herba-alba* extract is presumed due to the influence of extract on the mediators of the inflammation and prostaglandin synthesis pathway. Isolation of flavonoids from medicinal plants have been evidence to have anti-inflammatory effect. It is therefore conceivable that anti-inflammatory effect of *A. herba-alba* extricate is due to the inhabitation of rich source of flavonoids such as cirsilineol and hispidulin in it¹⁵.

Moringaoleifera

Moringaoleifera appertains to mono-generic family, "moringaceae" is the most cultivated species nurture to the sub-Himalayan tract of India, Bangladesh, Pakistan and Afghanistan. In traditional medicine

Moringaoleifera is one of the most comprehensively used plant. All parts of *Moringaoleifera* have medicinal attributes, but the leaves is the most useful part due to its extreme abundance of biologically active phyto-constituents. The ethanol extract of *Moringaoleifera* leaves manifests greatest anti-inflammatory activity. In both acute and chronic phases of complete Freund's adjuvant (CFA) urged arthritis, the *Moringa* leaves extract depicted high percent of inhibition especially at chronic stages which is higher than the reference indomethacin. Another exploration by Sudha et al also accounted that methanol extricate of *M. leaves* was highly competent in immune modulatory effect in mice. The group of animals either treated with *Moringaleaves* extract or indomethacin depicted less arthritic and inflammatory symptoms, indicated that leaves extract is efficacious in arresting the RA progression. The extract illustrates a substantial anti-nociceptive activity in the arthritic rat by an effective convalesce, suggesting that the extract is more effective to decrease the inflammatory related pain and the inhibition of prostaglandin arbitrated action of bradykinins. The methanol extract of combined root and leaves also shows the same activity¹⁶. In regards of above, it is revealed that methanol extract has a contemplable effect in intercepting development or enhance arthritic disease severity.

Saussureaheteromalla

The genus *Saussurea* appertains to family Astraceae, is an indigenous of cooler area of North America, Asia and Europe encompassing of about 410 species with the stupendous diversity in the central Asia and Himalayas. *Saussureaheteromalla* is abundant in the shivalik region of Himalayas. The natural ethanoic extricate (extract) of the plant alleviated inflammation and several mediators of inflammation are also alleviated by the sesquiterpene fragments of extract. The ethyl acetate extricate of *S.heteromalla* influentially hindrance the fabrication of TNF- α and IL-6. The natural extract depicts 100% inhibition of TNF- α and IL-6. Chlorojanerin, which is a pure component of *S. heteromalla* inhibit cytokines fabrications in LPS mediated THP-1 cells and in RA synovial tissue. Chlorojanerin depicts diminishing of TNF- α and IL-6 by arresting the countenance of the transcriptional unit NF- κ B. Transcription profiling of human monocytes cell lines mediated by LPS exposed that Chlorojanerin depicts its anti-inflammatory activity by blocking the utterance of 8 genes which are inculpates in transcriptional unit activation NF- κ B. Another species *S.lappa* and its major constituents including sesquiterpene lactones particularly dehydrocostus lactones and costonolide exhibits numerous biological activities including anti-inflammatory, anti-ulcer, anti-tumor and anti-microbial. Ethanolic extricate of *S.lappa* was examined at a dose dependent manner in rat. The result of this examined process concluded that the plant extract depicted substantial values for anti-inflammatory animation in carrageenan mediated paw edema & peritonitis model. The anti-inflammatory activity of costonolide was observed by blocking of proteins and m-RNA utterance of IL-1b¹⁷.

Garcinia mangostana

Garcinia mangostana appertains to Guttiferae family and is also known as the "Queen of fruits".It is a tropical tree indigenous to India, Malaysia, Myanmar, Sri Lanka and Philippines. For the rehabilitation of wounds and skin diseases, themangostana fruits pericarp has been manipulated since ancient time as a medicine. Methanol extract and xanthones extracted from *Garcinia mangostana* depicted anti-oxidant activity by manipulating following methods: ferric thiocyanate method, 2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonate (ABTS) assay and 2,2, diphenyl-1- picrylhydrazyl (DPPH) radical scavenging assay. There is a confirmation regarding anti-inflammatory and anti-allergic responses of *Garcinia mangostana* in various *in vitro* models. A-Mangostin extracted from the mangosteen diminished immunocytoadherence and systemic anaphylaxis in rats and guinea pigs and primary and secondary activities of adjuvant mediated arthritis in rat. Ethanol extract of GML mangosteen fruit diminish the liberation of histamines in RB-L-2H3 cell urged by IgE. In C6 rat's glioma cells, the ethanol extract of GML

influentially obstructed PGE₂ liberation urged by A23187. Against the carrageenan mediated paw edema in mice, the anti-inflammatory response of α and γ mangostins were interpreted. α -Mangostin has substantial anti-inflammatory response than γ -Mangostin. In various allergic reactions, the discharge of histamines, which is an inflammatory mediators occurs due to transduction of intra cellular signaling mediated by IgE receptors. Xanthones extracted from mangosteen (α , β and γ mangostins) restricted the degranulation in basophilic leukemia RBL-2H3 cells of rats. This inhibitory action of degranulation by xanthones was chiefly ascribed to inhibition of SYK/PLC γ s/PKC pathways¹⁸.

Achilleamillifolium

Achilleamillifolium appertains to family Astraceae is an everlasting herb which is indigenous to Europe and in herbal remedies it is highly accepted for its anti-inflammatory characteristics. For the rehabilitation of burns, irritated, swollen skin and wounds the plant has been manipulated traditionally externally. The aqueous extract of *Achilleamillefolium* depicted remarkable effect in shielding the gastric mucosa against the acute gastric lesion caused by indomethacin and ethanol. It also depicted healing activity in chronic gastric lesion mediated by acetic acid. The aqueous extract of *A. millefolium* strongly suppressed the NO assemblance and also downregulated the iNOS protein utterance in dose dependent manner. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-10 secretion was also decreased. The anti-inflammatory activity of plant extract is mainly attributed with the suppression of the transcriptional factors NF- κ B activation and P38 signaling. The extract has an ability to decrease the concentration of intracellular ROS and free radical scavenging activity. Isoprenoid and phenolic compounds are the two secondary metabolites mainly attributed to the anti-inflammatory action. In traditional medicine the alcoholic and aqueous extracts of *A. millefolium* are manipulated internally for the betterment of gastro-intestinal and hepato-biliary diseases and also used as an anti-phlogistic drug. The sesquiterpene depicted anti-inflammatory activity by the restriction of metabolism of arachidonic acid. Rutin, luteolin-7-o-glucoside and aspigenin-7-O-glucoside are three flavonoids present in the natural extract and the two fractions decorated in the flavonoid and dicaffeoyquinic acid hindrance human neutrophil elastase and metalloproteinase, which are inculcated with the anti-inflammatory activity¹⁹.

Aconitum heterophyllum

Aconitum heterophyllum appertains to family Ranunculaceae. It is an important medicinal plant native to India mostly in western Himalayas and inhabitant in Kashmir, uttarakhand and Sikkim. *A.heterophyllum* is familiar to have a variety of curative effects. Ayurveda, traditional treating system of India, this plant has been used in some formulation traditionally since ancient times. The chemical examination of this plant depicted that the different parts of plants contains carbohydrates, proteins, amino acids, saponins, alkaloids, Quinone, glycosides, terpenoids, flavonoids etc. The plant *A.heterophyllum* has been investigated to have diuretic, anti-diarrheal, hepato-protective, analgesic, anti-pyretic, anti-oxidant activity^{20, 21}. It is also used for the medication of disease of digestive system, nervous system and rheumatism. Alkaloids, sterols, flavonoids and glycosides are present in the Ethanolic root extract of *A.heterophyllum*. Plant with these classes of chemical compounds has been accounted to execute extensive anti-inflammatory activity through the downregulation of prostaglandin pathway. To estimate the proliferative and secretive component of chronic inflammation, the cotton pellet mediated granuloma has been extensively used. *A.heterophyllum* extract administration has been perceived to reduce the wet cotton pellet weight in dose dependent manner. Its higher concentration depicted hindrance of inflammation comparatively to the obstructory effectuate of diclofenac sodium. It has been narrated in literature that plant extract has ability to control sub-acute inflammation by the suspension of arachidonic acid assimilation²².

Bacopamonnieri

Bacopamonniera appertains to family Scrophulariaceae is commonly known as “Brahmi”. It is a renowned and ancient medicinal plant with important applications. Numerous phytochemicals such as betulinic acid, brahimine, hersaponin, herpestine, β -sitosterol, saponin-d-mannitol, bacosides A and B are accounted in plant. The plant depicted substantial cardio protective and anti-ulcerogenic activities. Methanolic extract of *B.monnierea* greatly reduced the formation of carrageenan and histamine mediated edema. The ability of extract as free radical scavenging and anti-inflammatory activities may be particularly due to the occurrence of phytoconstituents like tannins, saponin and flavonoids²³. In India and Pakistan *B. monnieri* anciently used as a digestive aid to ameliorate respiratory function in the instances of Broncho constrictor. The plant depicted anti-inflammatory response on rat paw edema mediated by carrageenan by inhibitory effect of 82% as compared to indomethacin. *B. monnieri* also substantially block the activities of COX-2 and Lipoxxygenase²⁴. The plant fraction comprising of Bacosides and Triterpenoids inhibited the discharge of pro-inflammatory cytokines particularly IL-6 and TNF- α . This was examined *in vitro* using peripheral blood mononuclear cells and peritoneal secretory cells activated by LPS. Thus *B. monnieri* exhibit anti-inflammatory activity by inhibiting the secretion of proinflammatory mediators²⁵.

Eiseniabicyclis

Eiseniabicyclis belongs to the family Laminareaceae, is a perennial brown algae, which is widely spread in the middle pacific coast around Japan and Korea. Brown algae *E-bicyclis* derived phorotannin have been demonstrated to be concerned with the inhibitory activities of hyaluronidase, lipoxxygenase, phospholipase A₂ and COX enzymes which all are associated in the inflammatory reaction. Phlorotannins which are the secondary metabolites of *Eiseniabicyclis*, executes anti-inflammatory activity by the inhibition of COX-2 and iNOS expression and downregulation the activity of matrix metalloproteinase (MMPS) by upregulating the Mitogen activated protein kinase pathway. The MeOH extricate of *E-bicyclis*, its dichloromethane (CH₂ Cl₂), ethyl acetate fractions and its constituents Fucosterol and Phlorotannins exhibited noticeable anti-inflammatory activity that can adulterated the LPS mediated NO assemblance, iNOS and COX-2 protein levels and ROS generated by tetra-butylhydroperoxide (t-BHP) in RAW 264.7 murine macrophage cells. Fucosterol depicted remarkable dose dependent inhibitory activities on NO production urged by LPS in RAW 264.7 cells²⁶.

Yucca schidigera

Yucca schidigera appertains to Lily family is herbaceous plant indigenous to the northern Mexico and south-western United States deserts. Native Americans used this plant in traditional medicines for rehabilitation of the numerous diseases encompassing arthritis. In numerous applications *yucca* products are used in present days²⁷. It has depicted anti-inflammatory and anti-arthritic activity. It comprises of numerous physiological active phytochemicals. It is also an abundant reservoir of saponins, which have substantial biological activity. It has been suggested that saponin have anti-arthritic activity by restricting intestinal protozoa, which performs key process in joint inflammation. The anti-inflammatory activity of *yucca* plant is due to the subsistence of polyphenolic compounds, such as resveratrol and variety of stilbenes (yaaccols A, B, C, D and E). Nitric oxides are the inflammatory agent which are formed by the synthesis of iNOS stimulated by NF- κ B. These phenolic compounds present in the *yucca* plant are the suppressor of NF- κ B. By inhibiting ROS, the *yucca* phenolic depicted great free radical scavenging and anti-oxidant activity. Platelet aggregation is the main feature of inflammation. Against aggregation of platelets during inflammatory process, *yucca* phenolic depicted great inhibitory response²⁸.

Odinawodier

Odinawodier resides to Anacardiaceae family. It is indigenous to Indian sub-continent, commonly known as “Rhusolina”. Traditionally it was manipulated for different ailments. Plant bark is relevance for heart

disease, rheumatism, ulcer, gout, wound healing and different skin infections. *O. woder* bark (OWB) extract alleviated the paw edema urged by carrageenan and dextran in rat. This alleviation in both carrageenan and dextran mediated inflammation by plant extract indicated its capability to block the liberation of inflammatory mediators such as histamine, serotonin and kinin. Although OWB extricate significantly inhibited the granuloma formation mediated by cotton pellet, depicted its anti-inflammatory ability possibly by alleviating the fibroblasts concentration with mucopolysaccharides and collagen synthesis. OWB and its chief constituent Chlorogenic acid (CA) quenched synthesis of PGE₂ by blocking COX-2, followed by hindrance of NO assemblance attributed to lowers iNOS mRNA utterance in LPS urged macrophage cell. Also OWB and CA application substantially alleviated the countenance of IL-1 β , IL-6, IL-12 and INF- α in LPS urged macrophages. Further the utterance of TLR4, MYD88, NF- κ B65 and COX-2 molecules were alleviated by OWB and CA ²⁹.

Albizialebeck

Albizialebeck is an unbranched and tall plant appertains to Mimosaceae family usually called as “Sirisa” and is dispersed allover India. For the rehabilitation of different inflammatory disorders like arthritis, bronchitis, allergies, fractures, asthma, tooth ache and gingivitis different parts of tree have been manipulated in traditional system. *A. lebeck* has been known by its capability of producing more than one effect such as immunomodulatory, anti-inflammatory, anti-oxidant, anti-arthritic and anti-tumor activities. The aqueous and ethanol extract of *A. lebeck* substantially inhibited the formation of edema in both phases. In first phase, the anti-edematous response of *A. lebeck* is possible due to the downregulation of signaling of histamine and transcription of histidine decarboxylase gene or due to downregulation of NF- κ B. Reduction of edema by *A. lebeck* in second phase is mainly due to blocking of liberation or response of prostaglandin and kinin. Aqueous and Ethanol extract of *A. lebeck* also lowers the granuloma dry weight considerably due to its capability in alleviating fibroblasts concentration, intercepting angiogenesis and quenching of T-helper₁ T lymphocytes pathway. Phytochemical analysis of *A. lebeck* leaves depicted the subsistence of flavonoids, tannins, alkaloids, terpenoids and saponins. The anti-inflammatory response of *A. lebeck* could be accounted due to the subsistence of flavonoids and saponins³⁰.

Acacia ferruginea

Acacia ferruginea is a deciduous and drought resistant tree appertains to Mimosoideae family, is indigenous to India. Traditionally the plant bark is manipulated to heal ulcer, blood related disease, itching, urinary tract related disease, eyes and liver associated diseases. Ethanolic extricate of *A. ferruginea* leaves explored to have anti-ulcer hepato-protective and anti-tumor properties. Secondary metabolites of *A. ferruginea* encompasses flavonoids, alkaloids, phenols, terpenoids and tannins. Analgesic response of hydro alcoholic extract of *A. ferruginea* leaves and bark in comparison to reference drug Tramadol, significantly alleviated the thermal stimulation by blocking prostaglandin synthesis. The hydro alcoholic extricate also substantially hinder the edema formation in both phases induced by carrageenan. The extract of *A. ferruginea* leaves depicted highly considerable acute inflammatory responses in comparison of bark extract ³¹.

Lychnophorapasserina

It is commonly called as “Arnica” appertains to Asteraceae family. Traditionally it was manipulated to rehabilitate inflammation, anti-nociceptive, rheumatism, pain and insect bite. Ethanolic extract (EE) of plant and its methanol and ethyl acetate fractions depicted considerable anti-inflammatory response in J774.A1 macrophage urged by LPS *in vitro* by blocking secretion of inflammatory arbitrators such as NO and TNF- α and initiation of secretion of anti-inflammatory cytokines IL-10. The plant extract significantly alleviated the paw edema urged by carrageenan in comparison to diclofenac. Consequently the substantial *in vivo* response of EE may be accounted to collaborative activity of various biological active molecules. The response of

various substance on many inflammatory condition, and the probability to enhance the biological availability of molecules may contributed in a potent response of crude extricate³². Therefore the manipulation of aerial parts of *L. passerine* in traditional culture during inflammatory process could be effective to heal tropical inflammatory state.

Portulacaoleracea

Portulacaoleracea appertains to Portulacaceae family. It has been broadly manipulated in folk medicines in different countries. *Portulacaoleracea* has evinced different pharmacological activities accommodating analgesic, anti-bacterial, wound healing and skeletal muscles relaxant. In the course of inflammation, plentiful concentration of PGE2 and Nitric oxide are liberated by different tissue and cells. *Portulacaoleracea* evinced a substantial activity against inflammation by blocking NO production and PGE2 level. *Portulacaoleracea* also blocks the LPS mediated proteins utterance level of iNOS. It hindrance the secretion of LPS mediated pro-inflammatory cytokines in RAW 264.7 such as PGE2, NO, TNF- α and IL-6. *P. oleracea* manifest anti-inflammatory potency and could restricted the macrophage urged inflammatory encouragement³³.

Byrsonima intermedia

Byrsonima intermedia is broadly disperse through tropical America and it appertains to Malpighiaceae family. The chief constituent of *Byrsonima* bark is tannins. *B. intermedia* evinced anti-hemorrhagic, anti-inflammatory and anti-diarrhea properties. Most popularly the tea of *Byrsonima* stem bark are manipulated as anti-inflammatory and anti-fungal responses and against diarrhea. *B. intermedia* aqueous extract(BIAE) manifested considerable hindrance of Paw edema induced by carrageenan. Moreover BIAE substantially alleviated the migration of leukocytes towards peritoneal cavity, also depicted that extract of *Byrsonima intermedia* possibly accommodates active anti-inflammatory factors. Additionally BIAE diminished the wet and dry weight of cotton pellet, which is possibly due to alleviation of fibroblast concentration as well as mucopolysaccharides and collagen synthesis, which are the main proliferative factors inculcated in the granuloma formation³⁴.

Cuscutareflexa

Cuscutareflexa appertains to Convolvulaceae family. It is distributed mostly throughout India. It grows on other plants as a parasite twinner. In ancient time, *Cuscutareflexa* has been manipulated for the rehabilitation of different diseases, such as cough, liver disorder and itching. The natural extract of *Cuscutareflexa* depicted anti-inflammatory response by substantially preventing the damage of erythrocytes. The anti-inflammatory action of *Cuscutareflexa* extricate can be accounted to the flavonoids subsistence. Anti-inflammatory response of water extricate of *C. reflexa* was explored *in vitro* in RAW264.7 macrophages cell line induced by LPS. The extricate depicted anti-inflammatory response in RAW 264.7 cell line by inhibited LPS urged over utterance of TNF- α and COX-2, by arrested NF- κ B binding to its receptor, by depicted the utterance of pro-apoptotic genes BAX and P53 and quenched the countenance of anti-apoptotic genes BCL-2 and Survivin³⁵.

Juniperuscommunis

Juniperuscommunis appertains to Cupresaceae family and is distributed throughout the cold temperate northern hemisphere. Traditionally the chief oil of *Juniperus* is manipulated against the vast array of diseases and also for flavoring purposes. The essential oil and its vital constituent alpha-Pinene have been greatly explored for anti-inflammatory, anti-fungal, anti-cancer and anti-microbial activities. In mouse macrophage and Human Peripheral Blood Mononuclear Cell (HPBMC), alpha-Pinene exhibits potent anti-inflammatory responses by inhibited nitric oxide, MAPK, TNF- α and IL-1 β . Another examination has revealed that chief component alpha-Pinene reduced the inflammation by inhibiting the over utterance of

COX-2. The methanolic extract of *Juniperus communis* has been accounted to accomplish anti-inflammatory response in an arthritic rat model. *Juniperus* essential oil substantially hinders the excessive assemblance of two pro-inflammatory chemokines IFN- γ induced protein and IFN- inducible T-cell alpha chemoattractant and depicts anti-inflammatory response³⁶.

Pinus roxburghii

Pinus roxburghii is commonly known by the name of "chir" and pertains to Pinaceae family. It is indigenous to Kashmir, Tibet, Nepal, Sikkim, Butan and other northern regions of India. It is the only tree with both ornamental and medicinal properties. It is significant in rehabilitation of inflammation, eye and ear related disorder, liver and skin diseases. Its wood is anti-helminthic, diuretic, digestive and hemostatic³⁷. In the carrageenan induced paw edema, the alcoholic extract of *Pinus roxburghii* substantially hinders the paw edema by blocking cyclooxygenase synthesis. The subsistence of flavonoids in extract of *P. roxburghii* could be accountable for the anti-inflammatory response in rats. The capability of flavonoids to hinder eicosanoids like prostaglandin which are implicated in many immunological reactions and in the output of lipoxygenase and cyclooxygenase pathways. Flavonoids also reduce the liberation of arachidonic acid by preventing the degranulation of neutrophils. The aqueous stem bark extract of *Pinus roxburghii* restricts the formation of cotton pellet induced granuloma which is usual representative of an initiated chronic inflammatory action³⁸.

Lophiraprocera

Lophiraprocera belongs to Ochnaceae family. It is found in damp forest in Africa. The plant has been traditionally used in several pathological treatments, especially the bark of this plant is used in lotions which are used in ulcers, breast cancer, the evil of kidney, rheumatoid arthritis. The anti-inflammatory exertion of *lophiraprocera* was investigated by using protein denaturation method with albumin from fresh chicken egg. Water extract depicts considerable anti-inflammatory activity by protein inhibition (albumin) as compared to the reference molecules which is diclofenac sodium. Therefore the water extract of *lophiraprocera* can intercept the discharge of lytic enzymes and inflammatory mediators and also prevent the production of auto antibodies by inhibiting the protein denaturation. The aqueous extract of *lophiraprocera* also shows strong anti-angiogenic activity by blocking angiogenesis and it also shows strong anti-oxidant activity³⁹.

Oenanthecrocata

Oenanthecrocata is found in Mediterranean region and it is a perennial species. In traditional medicine for the rehabilitation of dermatological infections and brain related disorders, leaves and flowers of *oenanthecrocata* have been used for a long time. The anti-inflammatory activity of the essential oil of *oenanthecrocata* was assessed by measuring the assembly of NO and iNOS expression on LPS stimulated macrophage. The macrophage incubated with the LPS and IFN- γ consequence in a remarkable increase in nitrite production, whereas the production of nitrite was reduced without affecting cell viability in the presence of oil. Sabinene (pure compound) alone also reduced the production of NO similar to oil, therefore this compound may be engaged for the anti-inflammatory activity of oil. It inhibited pro-inflammatory cytokines such as TNF α , IL-1 β and IL-6 and also has greatest scavenging capacity to inhibit iNOS expression. Due to the scavenging and inhibitory activity of iNOS expression it shows important anti-inflammatory activity⁴⁰.

Ocimum basilicum

Ocimum basilicum is an odoriferous (aromatic) plant used especially for pasta and flavoring sauce cooking. It has been revealed that the chief oil of this plant has the habit of monoterpenes (linalool) and phenyl-propanoids (estragole) which showed greatest anti-nociceptive and anti-microbial activities.

Ocimum basilicum essential oil (OBEO) showed anti-inflammatory activity in mice by reducing all types of paw edema. The conjugated complex of OBEO & β -CD (β -Cyclodextrin) showed notable reduced paw edema formation induced by carrageenan /dextran showed that the complex (OBEO & β -CD) have anti-edematogenic effect in mice. In the carrageenan mediated peritonitis model, the OBEO & β -CD complex also showed notable anti-inflammatory activity by inhibiting the recruitment of leukocyte to the site of inflammation in model. The OBEO & beta -CD complex shows anti-edematogenic and anti-inflammatory activities ⁴¹.

Urticadiocia

Urticadiocia appertains to Urticaceae family and has been anciently manipulated for the rehabilitation of vast array of diseases. It is indigenous to the temperate zone of America, Asia, Europe and certain region of Africa. Although it has been explored that juice of plant triggers the function of digestive system and flow of milk in nurturing mother, gives consolation from pain and also rehabilitating diabetes ⁴². The aqueous leaves extricate of *Urticadiocia* was explored to considerably hindrance the inflammation mediated by Formalin. This anti-inflammatory response of plant extricate is possible due to existence of secondary metabolites such as flavonoids, saponins, alkaloids and tannins. HEUD and its fraction HF2 substantially depicted the anti-inflammatory response by blocking the synthesis or discharging of histamine and prostaglandins activators in carrageenan induced edema in rats ⁴³.

Datura stramonium

Datura stramonium appertains to family solanaceae having pale green and hairy leaves and herbaceous stem. For the rehabilitation of inflammatory disease, infection of skin and dental pain whole plant are manipulated in Africa. Dried leaves are used for the healing purposes. Ethanol leaves extract of *Datura stramonium* were administered to explore the anti-inflammatory activity in rat. Ethanolic extract of *Datura* leaves depicted substantial anti-inflammatory response in proportional to the specific drug diclofenac sodium in case of carrageenan urged paw edema in rats. In the albumen urged rat model, the chief oil obtained from the crumbled seed and leaves of *D. Stramonium* depicted considerable anti-inflammatory response ⁴⁴.

Cassia siamea

Cassia siamea appertains to Fabaceae family and is broadly spread food and medicinal plant, indigenous to Africa and Southeast Asia. Traditionally *Cassia siamea* has been manipulated for the rehabilitation of many diseases such as malaria, jaundice and constipation. Chemical constituents of *cassia siamea* includes flavones, glycosides, sterols, antheraquinones and various hydrocarbon. Flavones, sterols and glycosides are believed to important as anti-oxidant and anti-inflammatory factors. The ethanolic extract of *C. siamea* significantly alleviated the swelling urged in rat paw by carrageenan ⁴⁵.

Table: Enumeration of Plants depicting anti-inflammatory activities.

S.No	Plant Name	Family Name	Plant Part	Type Of Extract	Test method	References
1	<i>Acacia ferruginea</i>	Mimosoideae	Bark leaves	Hydro alcoholic	Paw edema urged by carrageenan.	³¹
2	<i>Adhatodavasica</i>	Acanthaceae	All parts	Aqueous	Carrageenan-induced paw edema assay, Formalin-induced paw edema assay in	⁴⁶

					albino rats.	
3	<i>Albizzialebbeck</i>	Mimosaceae	Leaves	Aqueous, Ethanol	Cotton pellet induced granuloma model and carrageenan induced paw edema.	³⁰
4	<i>Artemisia herba alba</i>	Asteraceae	Leaves	Methanol	INF- γ /LPS induced RAW 264.7 macrophage cell.	¹⁵
5	<i>Acanthus ilicifolius</i> Linn	Acanthaceae	Leaves	MeOH	Carrageenan induced paw edema, COX (1&2) and 5-LOX activity.	⁴⁷
6	<i>Azardirachta indica</i>	Meliaceae	Leaves	Hydro-alcohol	Carrageenan-induced paw edema model	⁴⁸
7	<i>Aconitum heterophyllum</i>	Valeraneaceae	Root	Ethanol	Cotton pellet induced granuloma in rat.	²²
8	<i>Bacopamonneri</i>	Scrophulariaceae	Whole plant	Methanol	Carrageenan induced rat paw edema, LPS activated PBMNC and peritoneal exudates cells <i>invitro</i> .	²⁵
9	<i>Bryophyllumpinnatum</i>	Crassulaceae	Leaves	Methanol	Fresh egg albumin-induced paw edema model	⁴⁹
10	<i>Barringtonia racemose</i> Linn	Lecythidaceae	Leaves	Ethanol, hexane	Inhibition of nitric oxide formation in RAW 264.7 cell by Griess assay.	⁵⁰
11	<i>Byrsonima intermedia</i>	Malpighiaceae	Bark	Aqueous	Paw edema induced by carrageenan.	³⁴
12	<i>Cassia siamea</i>	Fabaceae	Aerial parts	Ethanol	Paw edema induced by carrageenan.	⁴⁵
13	<i>Caesalpiniamimosoides</i>	Leguminosae	Fruit	CH ₂ Cl ₂ and acetone.	Inhibition of LPS induced nitric oxide production in RAW 264.7 cells.	⁵¹
14	<i>Cuscutareflexa</i>	Convolvulaceae	Whole plant	Crude	Inhibition of LPS urged over utterance of TNF- α and COX-2 in RAW 264.7	³⁵

					macrophage.	
15	<i>Calophyllum</i>	Clusiaceae	Nut kernal	Ethanol	Carrageenan and formalin induced paw edema and cotton pellet implantation.	52
16	<i>Datura stramonium</i>	Solanaceae	Leaves	Ethanol	Albumen urged and carrageenan induced paw edema model.	44
17	<i>Dilodendron bipinnatum</i>	Sapindaceae	Stem Bark	Hexane	Downregulation of MAPKp38/JNK/NF- κ B pathways and COX-2 in LPS mediated RAW 264.7 macrophage cells.	13
18	<i>Eiseniabicyclis</i>	Laminareaceae	Whole	Methanol	Inhibition of production of LPS induced NO, tetrabutylhydroperoxide induced ROS and downregulation of iNOS and COX-2 in RAW 264.7 macrophage cells.	26
19	<i>Garcinia mangostana</i>	Guttiferae	Fruit	Methanol	Paw edema induced by carrageenan.	18
20	<i>Hederarhombea</i>	Araliaceae	Leaves	Butanol	Paw edema induced by carrageenan.	53
21	<i>Juniperus communis</i>	Cupresaceae	Oil	Methanol	HPBMC and CFA induced arthritis in rat model.	36
22	<i>Lophiraprocera</i>	Ochnaceae	Bark	Water	Protein denaturation method with albumin from fresh chicken egg.	39
23	<i>Lychnophora passerine</i>	Asteraceae	Aerial parts	Ethanol	Carrageenan induced paw edema.	32
24	<i>Moringaolifera</i>	Moringaceae	Root Flower	Methanol, Aqueous	CFA-urged arthritis in rat.	16
25	<i>Melaleuca leucadendron L.</i>	Myrtaceae	Bark leaves	Butanol	LPS induced NO and PGE2 production and COX-2 expression in RAW 264.7 macrophage.	63
26	<i>Ocimum basilicum</i>	Magnoliaceae	Oil	Ethanol	Carrageenan	41

					induced paw edema and cotton pellet induced granuloma.	
27	<i>Odinawodier</i>	Anacardiaceae	Bark	Methanol	Dextran and carrageenan induced paw edema in rat.	29
28	<i>Pongamiapinnata (L) pierre</i>	Fabaceae	Leaves	Ethanol	Carrageenan, prostaglandin E-2, histamine and cotton pellet granuloma models.	54
28	<i>Pluchea indica</i>	Asteraceae	Root	Chloroform	Carrageenan, histamine, serotonin, hyaluronidase and sodium urate induced paw edema.	55
29	<i>Pinus roxburghii</i>	Pinaceae	Stem bark	Aqueous Alcoholic	Cotton pellet induced granuloma & carrageenan induced paw edema.	38, 39
30	<i>Piper ovatum</i>	Piperaceae	Leaves	Hydro alcoholic	Carrageenan-induced pleurisy in rats and croton oil-induced ear edema in mice	[56]
31	<i>Piper longum</i>	Piperaceae	Roots	Aqueous	Carrageenan-induced right hind paw edema method.	57
32	<i>Portulacaoleracea</i>	Portulacaceae	Leaves, shoot	Ethanol	Inhibition of iNOS and pro-inflammatory cytokines in LPS mediated RAW 264.7 macrophage cell.	33
33	<i>Psittacanthus plagiophyllus</i>	Loranthaceae	Leaves	Aqueous extract	Dextran and carrageenan induced paw edema model in rat.	14
34	<i>Rheum emodi</i>	Polygonaceae	Rhizome	Methanol	Paw edema induced by carrageenan.	65
34	<i>Ricinus communis</i>	Euphorbiaceae	Roots and Leaves	Methanol, ether	Carrageenan induced paw edema.	58
36	<i>Rubus ellipticus</i>	Rosaceae	Root	Ethanol	Carrageenan induced paw edema.	64
35	<i>Saussurea heteromalla</i>	Asteraceae	Whole plant	Ethanol	Carrageenan mediated paw	17

					edema and peritonitis model.	
36	<i>Sesbaniasesban</i>	Leguminosae	Leaves, Bark	Methanol	Carrageenan induced paw edema.	⁵⁹
37	<i>Sidacordifolia</i>	Malvaceae	Whole plant	Water	Carrageenan induced paw edema.	⁶⁰
38	<i>Swertiachirata</i>	Gnetaceae	Aerial parts	Benzene	Carrageenan induced paw edema.	⁶¹
39	<i>Thespesiapopulnea</i>	Malvaceae	Leaves, Bark	Ethanol	Paw edema induced by carrageenan.	⁶²
40	<i>Urticadiocia</i>	Urticaceae	Leaves	Aqueous	Carrageenan mediated paw edema model in rat.	⁴³

3. Conclusion

The aim of this review was to enlighten the substantial manipulation of important plants species. These plants sustains potent nutritional and medicinal properties for human and animals. The literature was examined to gather the pharmacological properties of substantial plants, which declare that these plants are an important home of phytochemicals and pure compounds having medicinal importance for the rehabilitation of different diseases. Across the world vast mass of human population is getting influenced by inflammation associated disease. Against the inflammatory disease majority of herbal species have been manipulated in traditional medicines. Larger number of them have been examined experimentally and explored to be greatly efficacious anti-inflammatory factor. In the past two decades there is an extraordinary advances of research for the characteristic drug discover, which led to the recognition and designing of variety of medicinal plants with significant anti-inflammatory activities. This type of study will assigned to the welfare of population health care. Further research is needed to dictate which ingredients are significant which will impart relevant clues for researching and developing anti-inflammatory drugs in the future.

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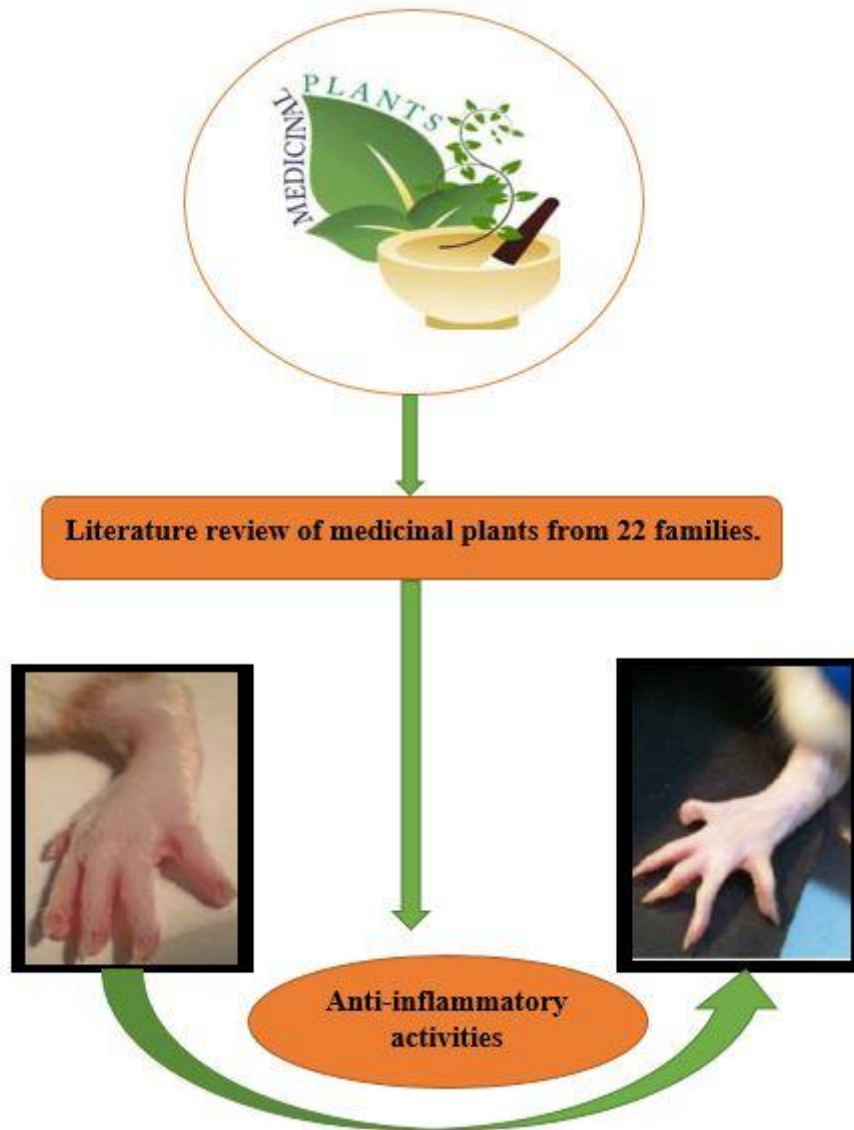
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Graphical Abstract

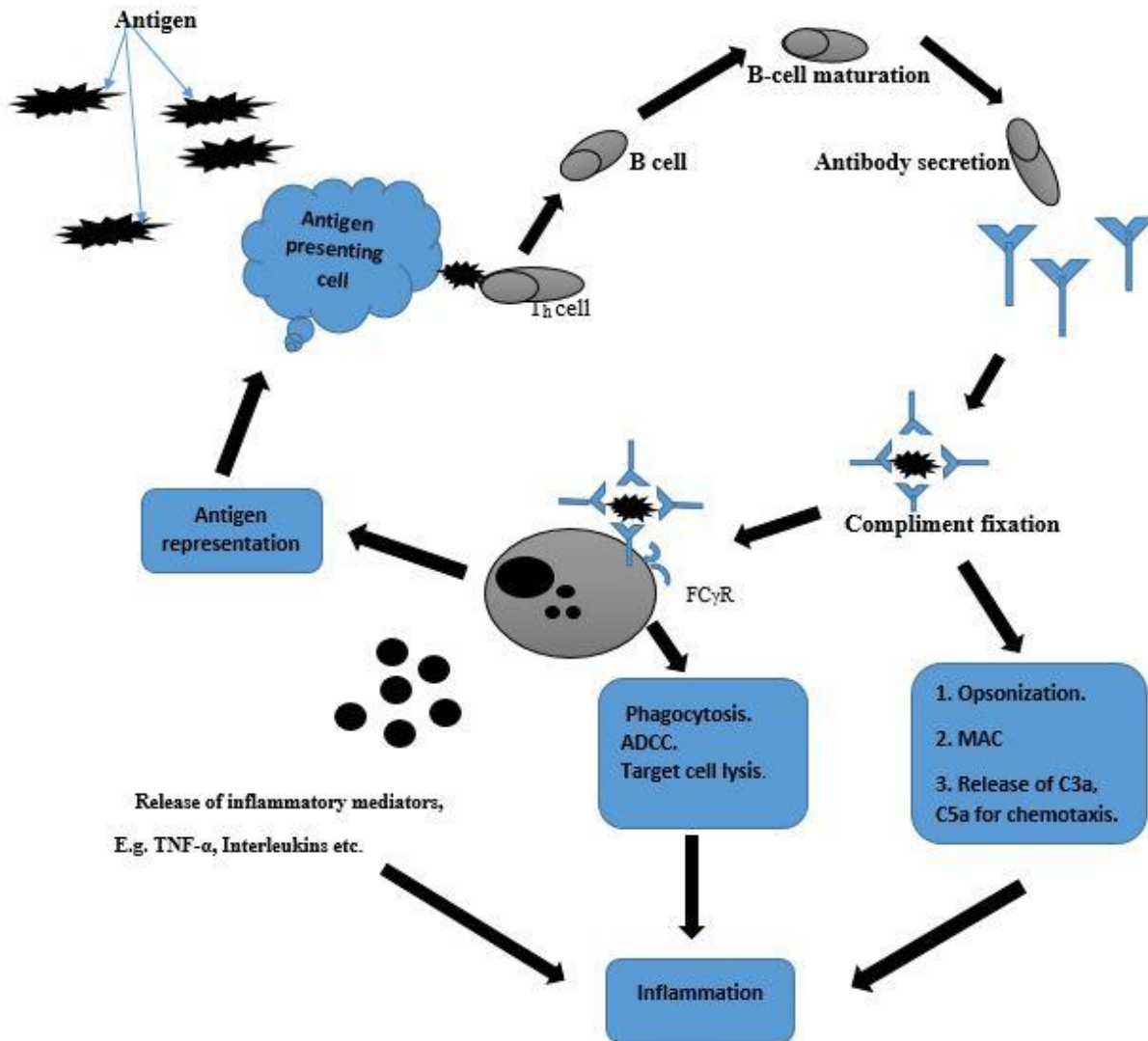


Fig. 1 Antigen presentation, B-Cell maturation, Complement fixation and Inflammation.

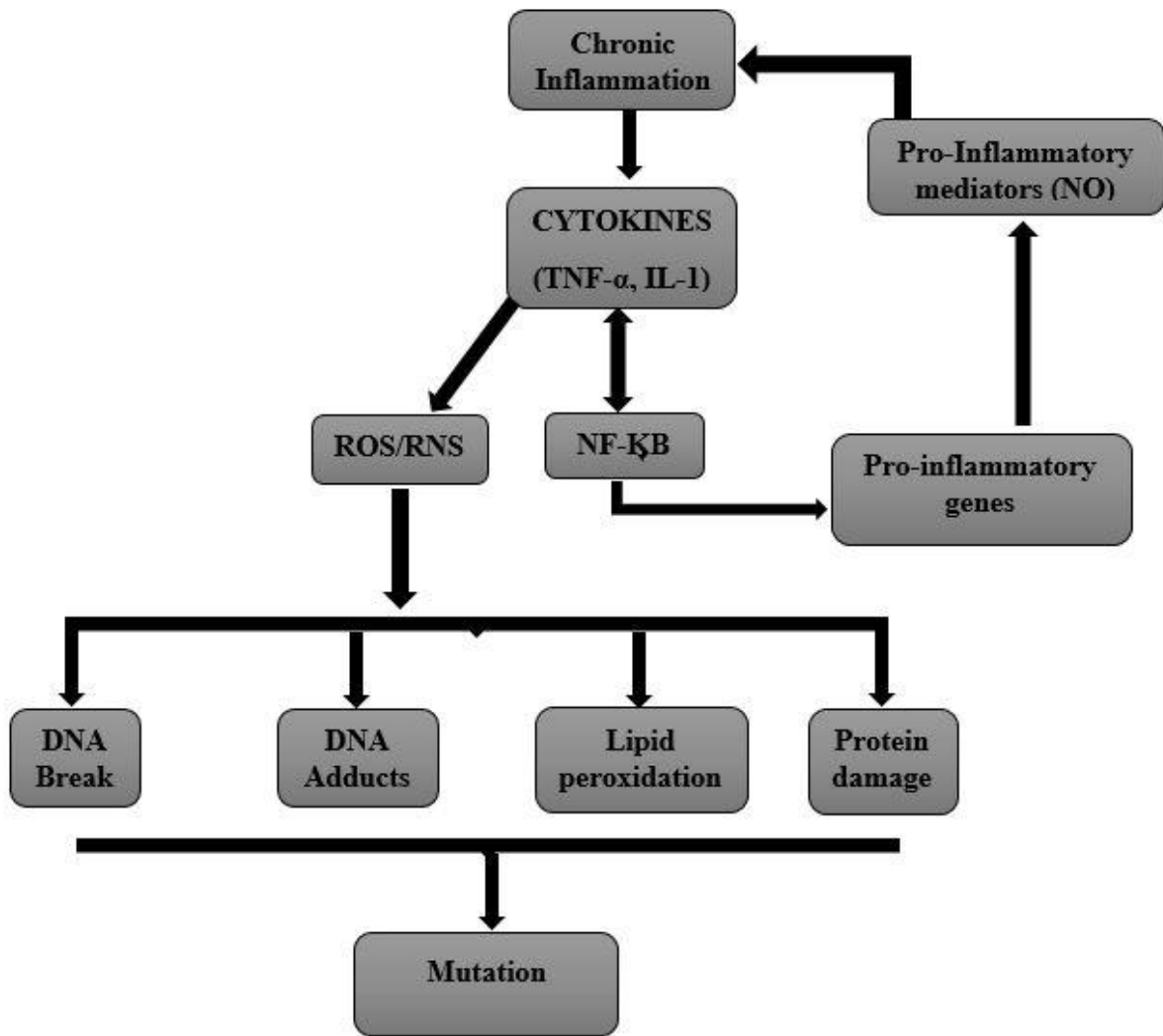


Fig.2 Mechanism of Chronic Inflammation.

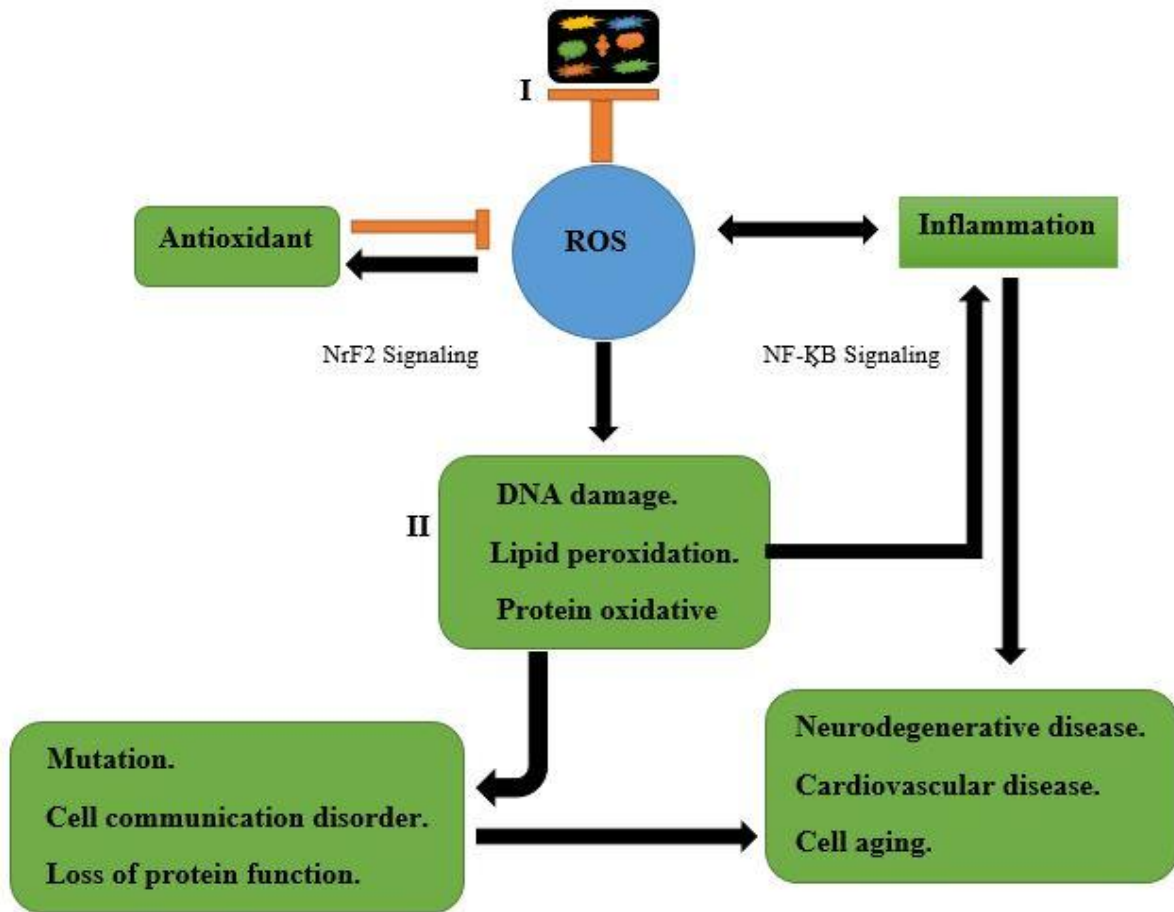


Fig 3 The diverse role of ROS in inflammation.