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# Pharmacology and biochemistry behind the use of natural herbs to control arthritis – A review

Sankar P. Mitra

Integrated Pharmaceuticals Inc. 310, Authority Drive, Fitchburg, MA- 01420, USA

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The article provides information regarding pharmacological and biochemical aspects of few herbs (Turmeric, Ginger, Capsicum, Devils' claw, Meadowsweet, Willow, Evening primrose, Juniper, Nettle and Boswellia) that are commonly used in treating arthritis and associated inflammations. All of them have substantialability to reduce pain and inflammation without the side effects. Distinctively, the herbs synthesize multiple phyto-chemicals that are chemically categorized as terpenes, flavins and tannins offering irrefutable impact on the patients providing significant relief. Advantageously, due to less side effects, the presence of multiple anti-inflammatory components insists patients to rely on herbs as a viable alternative in place of commercial therapeutic drugs available to control the arthritis. Many also use herbs as a supplement for additional therapeutic measure. It is proven that naturally occurring terpenes, sterols, flavins and polyphenols exert significant immune modulatory function to inhibit the inflammatory processes normally observed owing to the eruption of arthritis. So, by preventing the actions of NF–κβ and other associated factors these herbs control the arthritic problems. The co-presence of numerous ingredients in a single species often synergize the anti-inflammatory encounter while also preventing the generations of free radicals/ ROS which normally accelerate the inflammatory process. Intermittent assistance is occasionally provided by the few fatty acids within some herbs for their metabolic conversion to PGE1 or TXA1 adding additional preventive role. So less side effects along with the traditionally proven positive records ensure many to use herbs while managing the arthritic problems.

**Keywords:** Anti-inflammatory actions, Arthritis, Flavins, Herb, Tannins, Terpenes.

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## Introduction

In early days, apothecaries, the ancient medical professionals used herbs to treat various ailments. In reality, those are the precursors of modern medicines. The practice originated from the age of Ayurveda in ancient India which was noticed also during the Greek civilization of 2500 BC[1]. The interests proliferated from those ancient scholars and afterward relayed by their successor leads to the wondrous innovations of modern day chemistry and pharmacology directed to heal the ailing people. Today, scientists across the world have revealed innumerable organic compounds from the herbs and identified their physiologic roles that further prioritize the modern medicine. But despite that fabulous successes, the practice of alternative medicines using natural herbs have retained its popularity throughout the ages around the globe. The underlying reason could be the inadequacy of finding any precise cure. In a way, the exact logic behind this popular behavior stays in mystery. It is noticed that a single herb contains multiple medicinal components and among them quite a few are suitable to cure the specific illnesses. Admittedly, some impose adversarial effects, although seen relatively in minor occasions. Whereas majority indeed offers positive effects. Factually they provide long irrefutable track records which in essence offer high confidence in favor of their use. Presumably, the added effects of multiple equitable components enhance the superiority in terms of effectivity rather than a single entity used in the regular treatment procedure. Additionally, judging the centuries of human-trials for being accepted as folk medicines cater much confidence, legitimacy as well as the selectivity to allow continue the practice. But despite the time honored facts, judicious approach is still necessary before selecting any one for the use. Usually, most of them wield positive effects toward the chronic illnesses like in the present crisis of arthritis and gout management[2]. Advantageously, its frequent use does not show adverse effects. Statistically they are

*Correspondent author
Email: smitra3554@gmail.com

seen well tolerable. Individually majority of the components are accounted to be beneficial and they target same but following the different pathways to prevent progression of the disease (Table 1). In current day therapies, it is not so unprecedented to use multiple regimens to combine in a single pill. The combination often provides added advantages.

The herbs are usually used in the form of solids, liquids, tea-bags or extracts. Occasionally, ointments are also prepared for topical applications to reduce the local pain or swelling. The solid doses are offered in the form of capsules, tablets, lozenges or even as freeze-dried powders. Liquid doses are introduced by diluting the tinctures that are prepared by pulping and percolating the materials with alcohol. The extracts are concentrated by distilling off the extra alcohol to make a tincture which is shelved for necessary dilution during use. The use of dried form as tea is also a common practice. For that, the dried stems, barks, roots or rhizomes are normally used. Commercially, a specific amount is sealed inside a bag which is soaked in a cup of hot/ boiling water before sipping[3].

Interest regarding the involvement of inflammatory pathways particularly at cellular and molecular level is greatly increased, which in effect helps design numerous drugs for treating the inflammatory diseases like arthritis/ gout[4,5]. A long list of inflammatory pain mediators like, kinins or cytokines are known to act on specific targets causing the release of other intermediary ingredients at the inflamed sites exacerbating the problems[6]. The herbal components tend to block any of their actions to inhibit the propagating pathways.

The herbs that are discussed here to ease the pain or inflammation during arthritis are: Devil's Claw, Capsicum, Evening Primrose, Ginger, Juniper, Meadowsweet, Nettle, Turmeric, Willow and Boswellia. Table 1 briefly displays the nature and course of their biochemical actions. Even though they may belong to the different categories, but as a common measure, their actions are primarily targeted to block any inflammatory pathways. Along with the more active one, a single herb provides several supportive ingredients. As for example, various forms of terpenes are present in most of them, which are recognized to be the strong anti-inflammatory agents. Additional actions are assisted by the flavonoids. In turmeric, curcumin (diarylheptanoid) blocks many pro-inflammatory factors produced during the inflammation. Additionally, the presence of few essential oils (ar– turmerone, α– turmerone, β–turmerone and others) synergize that anti-inflammatory process[7]. The flavonoids or curcuminoids are known to trap the ROS generated during the invasion of macrophage or leucocytes at the sites of inflammation[8]. Thus by trapping, they assist further to prevent the progression of inflammation. In certain herbs, like in the Meadow Sweet and others, the presence of salicylic acid or any of its derivatives directly interact to alleviate the arthritic or gouty inflammation (Table 1)[9]. In that course, the presence of vicinal flavonoids offers an extra help[7]. It is also noticed that some components often offer different extra benefits eg, the compound ZT (E-8p – 17 epoxylabd – 12 ene – 15, 16 – dial) a terpenoid in Ginger, though not counted to be anti-inflammatory but enables to lower the serum cholesterol by inhibiting HMG-CoA[10]. So, the existence of multiple compounds is certainly beneficial for procuring versatile aids.

**Role of herb in arthritis**

From the ancient times, herbs are used to prevent inflammation[11]. They express numerous ingredients that have verified-effects toward healing acting concertedly but with lesser magnitude of side effects providing fewer harshness. It is long known that arthritis is a chronic inflammatory joint disease developed as a consequence of the activation of innate immune system producing redness, swelling and pain which frequently results in the loss of functionality. The incidence of OA although does not initiate at the beginning due to self-activation of body's immune network as in the case of RA, but it converges to the same painful inflammatory condition at certain stage. The hardening of synovium due to elevated level of calcification accompanied by the breaking down of proteoglycans inside synovium triggering the loss of cushioning performance within bone joint and subsequent tearing of the synovium membrane by virtue of it, initiates the painful inflammatory process[4]. As per the knowledge, all inflammatory processes follow complex order of pathways. In innate immune responses, the increased activation of NF- κβ is seen to be primarily liable to carry out the task of inflammatory process[12, 13]. There are ample of recognized reasons behind it that include microbial attack, production of ROS and generation of inflammatory eicosanoids etc[14]. Interestingly, often by practicing special diets it can be controlled to a certain extent. It is recognized that a proper diet enables to regulate the activation of NF- κβ. Along that path, essential fatty acids have definitive

Table 1 — List of few medicinal herbs used in controlling arthritis. It also provides the list of ingredients and their particular role in course of treatment concerning various physiologic actions including arthritis as well as the underlying mechanisms

| Herb | Terpene | Flavin | Tannin | Miscellaneous |
|---|---|---|---|---|
| Juniper | Monoterpene - 1, 4 Cineole, Terpin – 4-ol, Sabinene, Limonene Sesquiterpene- Caryophylline, Cadinene, Elemene | Rutin, Isoquercitin, Quercitin | Pro-anthocyanins, Gallotannins | Not fully determined |
| Meadow sweet | α – Pinene, β - Myrcene | Rutin, Hyperoside, Spireoside, Kaempferol, Coumarins | Hydrolysable tannins | Salicylates, Gaultherin, Salicin, Salicylic acid |
| Ginger | β-bisabolane, Zingeberene, Zingiberol | Gallic acid and Quercitin | Tannins of different molecular sizes | Oleoresins – Gingerols, Shogaols, Zingerone |
| Turmeric | Turmerone, Zingeberene, Bisabolane, Guaiane, Curlone. | Curcumin | Tannins and its Glyco-conjugates | Oleoresin |
| Devils' Claw | Iridoid Glycosides – Harpagide, Harpagoside, Procumbide | Kaempferol, Luteolin | | |
| Willow | | Flavins - 0.2 – 1.5% Catechin, Isoquercitin, Naringin, Quercitin, Isorhammelin | Condensed tannins | Chalcone, Isosalipurposide |
| Capsicum | Luteolin, Carotein, Capsanthin | Capsacin, Dihydrocapsacin, Homodihydrocapsacin | Low level of tannin compared to others | Vitamin – A & C. |
| Nettle | Sterols - Sitosterol | Isoquercitin, Rutin, Kaempferol, Quercitin | Tannins | Histamine, Acetyl Choline, Serotonin. Malic acid, Formic acid, salicylic acid, carbonic acid. Lectin, Lignan |
| Evening Primrose | Undetermined | Undetermined | Undetermined | Cis-Linoleic acid, γ – Linolenic acid, Oleic acid, Stearic acid, Palmitic acid |
| Boswellia/ Frankicense | Boswellic acid, 3 – oxo – TA (tri-terpenes), Pinenes, Sabinene, limonene, Bisabolane, Cembrene Verticiol | Not fully determined | Not fully determined | Poly saccharides and terpene alcohols |

roles[15]. For example, AA, the ω - 6 fatty acid activates it by acting as a pro-inflammatory agent whereas the EPA, or ω – 3 does not[16,17]. Endogenously AA is produced by the action of $PLA_2$ on phospholipid molecules. AA is the precursor of bioactive eicosanoids[18]. A majority of them are pro-inflammatory and activate the NF-κβ[12]. Additionally, extracellular cytokines like IL or TNF also can activate by binding to the cell surface receptors[12,19]. Activation also occurs through the stimulation of Toll-like Receptors (TLR[20]. Interestingly, TLR - 4 is activated by binding with the saturated fatty acids which is inhibited by the presence of ω-3 or EPA[21,22]. Research also indicates that ROS generation activates NF-κβ to initiate the inflammation episode[23]. By quenching it, antioxidants can prevent the detrimental role[24,25]. Essentially, the active components within herbs counteract with one or more pathways to inflammation (Fig.1).

The factor, NF–κβ is regarded as one of the most important immune regulators in the process of inflammation. It is a ubiquitous factor and highly conserved in most of the living species[26]. In normal unstimulated cells, it is locked and blocked by the various inhibitory proteins[27]. But if stimulated by any extracellular signals (ROS, mitogens, cytokines etc) those inhibitory proteins undergo phosphorylation and subsequent degradation by the enzymes which in turn frees the factor allowing translocate it into the nucleus. It then binds with the promoter regions of various genes expressing the TNF – α, IL - 1β, COX – 2, iNOS, MMPs etc which influences various cellular actions, like cell proliferation, apoptosis, cell adhesion, stress response and immune / inflammatory events[12–15,27,28]. The genes that are involved in the inflammatory pathways are, cytokines (IL – 1α, IL - 1β, LT – α & β, TNF – α, IFN – β & γ) and Chemokines (Eotaxin, Gro

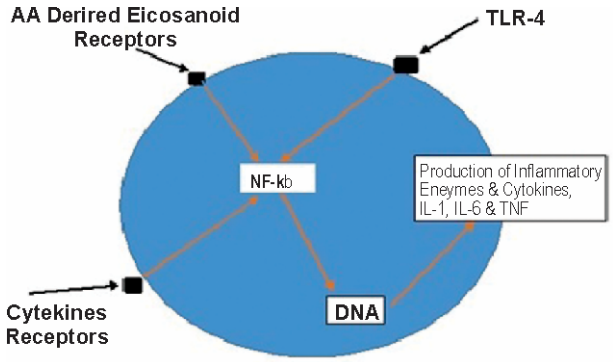


Fig. 1 — Model showing cellular inflammation by the activation of NF–κβ and concomitant production of inflammatory components. The initial production of NF–κβ takes place due to the receptor mediated interactions of various Eicosanoids, antigen interaction with Toll like receptor -4 (TLR – 4) or involvement of cytokines on the individual receptor which eventually leads to the synthesis of number of inflammatory enzymes, cytokines, IL-1, IL -6 and TNF.

– 1, MCP – β, MIP - 1β, 2 & 3α, RANTES, TCA – 3) and several stress response components like, COX, LOX, iNOS, Angio II and SODs[27, 28].

Among the herbal ingredients, terpenoids show much prominence in treating arthritis or gout. They can regulate the NF–κβ signaling pathways to inhibit its activation[29]. Besides terpenes, flavonoids also exert anti-inflammatory role by trapping the ROS generated alongside[30-32]. In that way, it adds extra benefit since ROS is also an activator of NF–κβ for the advancement of inflammation. The other components salicylates or gluco-corticoids are can inhibit the activation process also[33,34]. It is recorded that, salicylate prevents PG production, which in turn attenuates the events to create inflammation[35]. Since the entire process of inflammation follows multiple routes. In that perspective, a single herb having numerous medicinal compounds may be suitable to control that painful episode.

**ROS generation and blocking by the herbal components**

It is established that high level of disproportionate ROS generation often exacerbates the inflammation[36] Although they are generated for the purpose of physiologic protection and defense but they can exert adverse effects also by actively participating in the course to intensify inflammation. ROS is generated by virtue of the oxidative stress which occurs due to imbalance between its systemic production and system's inability to properly detoxify the reactive intermediates produced from it[37]. In other words, the disruptions in intracellular redox affairs produce excessive amounts of peroxides, superoxide ($\cdot O_2^-$) and free radicals ($OH^{\cdot}$, $:CH_2$, NO) which in turn damage the cellular components like lipids, proteins, DNA etc. Regarding basic chemistry, reduction of molecular $O_2$ produces super oxide anion ($O_2^-$) which is considered to be the precursor of ROS[38].

$O_2 + e^- \rightarrow \cdot O_2^- + \cdot O_2^-$

$2H^+ + \cdot O_2^- \rightarrow H_2O_2 + O_2$

[Dismutation of $\cdot O_2^-$ produces $H_2O_2$]

$H_2O_2 \rightarrow \cdot OH + \cdot OH$

[It is then reduced partially to reactive hydroxyl radical]

The exogenous ROS generation is caused by the ionizing radiations on $H_2O$ molecules during the course of radiolysis. Since human body consists of ~60 % of $H_2O$ so it enhances the possibility of undergoing radiolysis while facing any surrounding ionizing radiations even the UV light. Whereas its endogenous production is caused by NADPH oxidase inside the mitochondria, ER and cell membranes. Once generated, the free radicals initiate various chain reactions imposing cellular damages. The enzymes associated with the respiratory bursts responsible for this event normally exist within phagocytes or other cells and tissues. Normally, the common ROS are $^1O_2$, $O_2^-$, $\cdot OH$[38].

In normal situation $O_2$ molecule exists in the ground state carrying two unpaired electrons having parallel spin thereby making it paramagnetic and chemically inert. Activation occurs by absorbing the outside energy (UV, X - ray, heat) that reverses the spin of one of the unpaired electron creating a singlet state oxygen molecule ($^1O_2$) having electrons of the opposite spin making it more reactive. The formation and subsequent quick conversion of high energy $^1\sum_g$ singlet state (37.5 Kcals / mole higher than normal) to lesser $^1\Delta_g$ species (22.5 Kcals / mole over normal) is required to react with the biomolecules. In that way $^1\Delta_g$ ($t_{1/2}$ ~ 1μs) is needed more for its greater stability than the less stable $^1\sum_g$ state ($t_{1/2}$ ~ 0.001μs)[39].

The conversion to singlet state ($^1\Delta_g$) removes away spin restriction. So, $^1O_2$ can participate in reactions involving simultaneous transfer of two electrons (divalent reduction) making it highly reactive toward the organic compounds producing endoperoxides. The $t_{1/2}$ of $^1O_2$ ranges from 1–50 μs in aqueous media therefore it can diffuse quite a distance in the physiologic environment enabling to inflict damage to any biomolecules. The $t_{1/2}$ in human plasma is ~1.0 μs even in presence of number of antioxidants. It also has the free moving ability through the lipid–water

interface and tends to act as strong electrophile having high affinity to interact with the electron dense regions of the biomolecules. In that way oxidative damages occur to the lipid, protein or nucleic acids. The $^1O_2$ is generated also by the enzymic actions of dioxygenases, lactoperoxidases, myeloperoxidases, cytochromes, tryptophan pyrrolases and lipoxygenases. A huge generation of $^1O_2$ over the requisite level occurs during respiratory bursts due to lysosomal enzymic reactions like myeloperoxidase by the PMNs during bacterial invasions. This excessive production creates toxicity. $^1O_2$ reacts with the unsaturated fatty acids generating lipid-hydro peroxide which eventually breaks up to several other products. These hydro-peroxides participate in the redox reactions thus causing injury to the cell membranes. The damaging effect on protein by singlet oxygen generates sulfoxides and endoperoxides whereas for the nucleic acids there are strand breaks and the formation of altered bases[40,41]. These deleterious actions could be prevented either by preventing the formation or to quench the generated $^1O_2$ by using quenchers. The later step is easier to follow and effective so the practice is continued in its favor. The works showed that carotenoids quench by the energy transfer mechanism having higher rate constants ($K$~$10^9$ -$10^{10}$ $M^{-1}s^{-1}$) whereas phenolic compounds like flavonoids or other analogs work by following the way of electron / charge transfer means, having relatively lower rate constants ($K$~$10^6$–$10^8$ $M^{-1}$ $s^{-1}$). Normally all the quenchers possess low oxidation potential so that it could react with any strong oxidizing agents[42]. Under those conditions, the compounds like carotenoids, tocopherols or plasto-quinones quench the $^1O_2$ and subsequently protect the cells or tissues from toxicity. Considering the nature, all medicinal herbs possess quenchers thus enabling them to control or prevent any endogenous inflammatory episodes. It is therefore beneficial to include them in the daily diet. The most notable and common one is β–carotene. Fig. 2a shows the quenching of $^1O_2$ and the subsequent oxidation of β – carotene to β – carotene 5,6 epoxide.

Like carotenoids, similar quenching phenomena are also observed in the presence of flavonoids. They are also efficient anti-oxidants producing quinones (Fig. 2b) whose further oxidation leads to the production of tannins adding astringency to various fruits and vegetables. Since flavins/flavonoids are poly-phenolic compounds so they have strong tendency to be readily oxidized in the presence of oxidizing agents resulting the formation of quinones. If the oxidation process lingers for a longer time then the generated quinones are polymerized to various types of polymeric tannins, soluble and insoluble by nature.

It is established that free radicals can damage the joint cartilages by several ways: 1) They help degrade the proteoglycans, 2) The production of $H_2O_2$ inhibits proteoglycan synthesis in chondrocytes by interfering ATP synthesis via the inhibition of glyceraldehyde–3–phosphate dehydrogenase, 3) Production of NO promotes apoptosis in chondrocytes, 4) The ROS also activates NF–κβ and AP -1 to produce various inflammatory factors[4,43].

Tannins belong to the more complex category of polyphenolic compounds. It also has the ability to participate in quenching events, identical to other antioxidants. They exist in hydrolysable and non-hydrolysable forms[44]. All vegetables possess the both types to a different extent. Besides its anti-oxidant role, tannins also act as antiseptic, prevent septicemia, stop bleedings, block diarrhea and work as a strong anti-inflammatory agent[45,46].

The dismutation of superoxide by various endogenous superoxide dismutases (SOD1, SOD2 and SOD3) also acts as antioxidant defense for the cells[47]. They are metallo enzymes and their respective genes are located within the chromosomes of 21, 6 and 4. These enzymes catalyze the dismutation of superoxides resulting in the formation of molecular $O_2$ and $H_2O_2$. SOD1 having $Cu^{+2}$ in center exists within the cytoplasm whereas SOD2 carrying $Zn^{+2}$ locates inside the mitochondria and SOD3 with $Mn^{+3}$ resides extracellularly[48].

$$M^{(n+1)+}\text{- SOD} + O_2^{-} \rightarrow M^{n+}\text{ - SOD} + O_2$$
$$M^{n+}\text{ - SOD} + O_2^{-} + 2\ H^{+} \rightarrow M^{(n+1)+}\text{ - SOD} + H_2O_2$$

M = Cu [n=1], M = Zn [n=1], M = Mn [n=2]
(The oxidation state of metals lies within n and n=1).

Catalase, another enzyme having $Fe^{+3}$ at the center located within peroxisomes can destroy the generated $H_2O_2$ while breaking down to $H_2O$ and molecular $O_2$ [49]. Identical reactions are produced by the Glutathione peroxidase and various peroxiredoxins enzymes which usually control the cytokine induced peroxide generations[50,51]. So, the role of anti-oxidants is assigned to remove the generated ROS or its intermediates during the course of reaction while inhibiting the oxidation process. In fact the anti-oxidants are the reducing agents. In biology, they are signified as flavins, tannins, various poly-phenolic

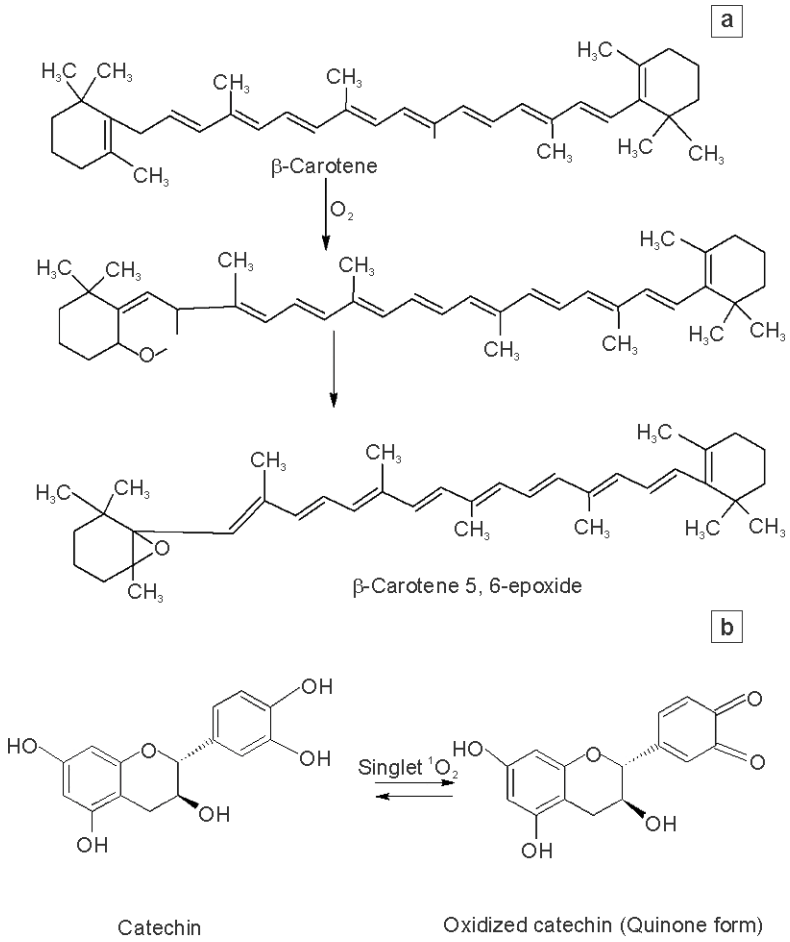


Fig. 2 — Chemical reactions involved during quenching of ROS a) Quenching of singlet oxygen($^1O_2$) by the β – Carotene and b) Quenching of singlet oxygen by the flavonoid (Catechin). Prolong oxidation leading to the creation of more complex poly-phenols like tannins.

components, thiols or vitamin C which are normally found in the herbs.

**The biochemical significance of herbs**

Herbs that are used in treating the arthritis or gout, possess the compounds, which could be best classified in three basic categories; terpenoids, flavonoids and tannins (Table 2). Obviously there are others also which are beneficial along the line of treatment. Considering the biochemical roles, terpenoids as discussed above have the ability to inactivate the NF–κβ to control the inflammation[29]. The others exert effects via their anti-oxidant role. It is noted that oxidative stress is immensely involved in numerous chronic illnesses[52,53]. The generation of ROS and its subsequent reactions with biological molecules is liable for the many harmful effects. By depleting them, anti-oxidants control the deleterious consequences. Arthritis is also benefited from such acts. Considering its preventive role, in current days publics are advised to consume more anti-oxidant enriched food. It is thus logical to presume that it would be much effective to use herbs/spices or fruits enriched with high level of various anti-oxidants to prevent the possibility of prevalence of chronic ailments like arthritis.

Products from the plants contribute multiple therapeutic agents (Table 1). In circulating plasma they also receive protection for longer survival while binding with the native albumin[54]. The ingredients work directly or indirectly to regulate the inflammatory mediators; for example, NF–κβ, proto-oncogenes and pro-inflammatory molecules (iNOS, COX, LOX, $PLA_2$), cytokines (IL-1β, TNF – α) etc[55,56]. Normally, the processes leading to inflammation is initiated by the numerous stimuli like, virus, chemicals, ROS, NOS etc. Additionally, the uncontrolled NF–κβ activation helps continue the chronic inflammatory diseases like arthritis[57]. It is proven that numerous phyto-ingredients can modulate any of the pathways in order to keep control the perils of arthritis. Terpenes or terpenoids

Table 2 — List categorizes about the major bio-active chemical ingredients and each of their physiological actions which are often used in normal practices and found in the herbs

| Bioactive compounds in herbs / spices | Physiologic actions | Compounds act on arthritis | Mechanism of action against arthritis | Normal uses |
|---|---|---|---|---|
| Salicylates, Salicin, Vanillin, Benzaldehyde, Flavins, Tannins, Coumarin, Ascorbic acid, Mucilage. | Analgesic, anti-inflammatory toward arthritis also shows anticoagulant and fibrinolytic action. Topical cream works against Squamash cell carcinoma in cervix which also reduces cervical and vaginal dysplasia | Salicylates and Gaultherin are the main compounds acting against arthritis | Salicylates itself or produced from Gaultherin prevents COX -2 action reducing inflammation and pain. Flavins and tannins assist the process. But coumarin produces anticlotting effect | Commonly used to control rheumatic problems |
| Curcumin | Hepatoprotection, Wound healing, Antiseptic, Antimicrobial, Anticancer, Neuroprotection, Anti-inflammatory effective against joint pain and chronic or acute phase of arthritis. | Responsible compound is Curcumin | Regulates MMPs, TNF – α, reduces C – reactive proteins, inhibits pre-apoptotic effect of OA synovial adherent cells, potentiates the action of Celecoxib effect | Used in Asian cooking, wound dressings. Capsules are used for anti-inflammatory and arthritis reasons |
| Capsaicin | Analgesic, enhances gastric acid secretion, inhibitor of platelets and cholesterol in the blood also increases fecal secretion, strong anti-inflammatory, lowers pain | Responsible compound is Capsaicin | Analgesia works by depleting SP from the peripheral nerve and spinal cord, specifically for unmyelinated type C nociceptive neurons | Culinary uses, diabetic neuropathy, post herpetic neuralgia and cardio-vascular tonic |
| Terpenes (Mono, Di and Sesquiterpenes) | Anti-inflammatory diseases like, Arthritis, Asthma, GI problems | The active compounds are Boswellic acid (Pentacyclic triterpene) and 3 – oxo – TA (tetracyclic triterpene) | Strong anti-inflammatory, inhibits LT synthesis and induces apoptosis in cancer cells. At low doses exerts hepatoprotection | Normally used for controlling RA, OA, Asthma, fever and pain |
| Monoterpenes (1,4 Cineole, Terpin – 4 – ol, Sabinene), Sesquieterpenes (Caryophylline, Cadinene, Elemene), Tannins (Pro-anthocyanin, Gallotannin), Flavins (Rutin, Isoquercitin, Quercitin), Vitamin – C, Di-terpenes, Glucuronic acid, Juninone | Treatment for arthritis, urinary tract cystitis, showing di-uretic properties | Anti-arthritic role is due to terpenes, flavins and tannins | Terpenes inhibit production of PGE2, TNF – α, IL -1β, LTB4 and other inflammatory mediators. Flavins and tannins blocks ROS assisting the anti-inflammatory process | Used for anti-inflammatory, antiseptic and diuretic actions |
| Mono and sesquiterpenes in oxygenated versions, lactones and Zingiberene | Blocks stomachache acting as carminative, flavoring agent, prevents nausea, vomiting, diarrhea, anti-carcinogenic, anti-oxidant, anti-fungal, anti-microbial, anti-inflammatory and effective against arthritis | The responsible compounds are Gingerol, Shogaols, Zingiberene, Bisabolane and others | Suppresses inflammatory arthritis by reducing iNOS, LT synthesis and blocking ROS actions | Used normally for culinary purposes. |

*Contd…*

Table 2 — List categorizes about the major bio-active chemical ingredients and each of their physiological actions which are often used in normal practices and found in the herbs (*Contd…)*

| | | | | |
|---|---|---|---|---|
| Flavonoids (Isoquercitin, Quercitin, Rutin). Sterol (Sitosterol) and Tannins. | Used to treat RA and Gout, Hay fever, joint pain and BPH. | Effective agents are flavonoids and sterols. | Inhibits inflammatory mediators and ROS actions. | Used for culinary and medicinal reasons acting against RA and muscle pain. |
| Cis Linoleic acid, Cis – γ –linoleic, Oleic, Palmitic and Stearic acid. | Used against RA, MS and Sjorgen's syndrome. | Cis – LA and Cis – γ – LA are the most effective agents. | LA and GLA are converted to DGLA which is precursors of PGH1, PGE1 and TXA1. They are beneficial for RA, gout, MS and other inflammatory diseases. | Helps during PMS, mastalgia, endometriosis and dementia. |
| Phenolic glycosides (Salicin, Salicortin), Tannins, Flavins (Catechin and other poly-phenols). | Effective against OA, RA and gout also lowers fever, pain and inflammation. | The responsible agents are Salicin, Salicortin, secondary tannins and flavins. | Salicin and Salicortin releases Salicylic acid preventing the mRNA for COX-2 expression. Flavins and tannins assist by blocking the ROS. | Normally used for body-ache, pain, fever and arthritis. |
| Iridoid glycosides (mono-terpenes), Chlorogenic acids, Luteolin, Kaempferol and Flavins. | Lowers pain and inflammation of RA, OA and gout. Helps GI complaints like dyspepsia/ digestive upsets also expresses anti-cancer property. | The effective compounds are Harpgide, Harpagoside and Procumbide acting against inflammation and arthritis. The Flavins work by trapping the ROS. | The release of Monoterpenes similar to "Celecoxib" by the β – Glucosidase inhibits COX – 2 by binding to its active site thus preventing the inflammations. Kaempferol and Luteolin prevents the action of ROS which also enhances the anti-inflammatory process. | Mostly used in relieving the pain and inflammations of arthritis. |

produced by the plants are originally the same. As per differences, the latter could have slight structural modifications. The molecular skeletons are built by the conjugation of multiple and identical isoprene units ($CH_2$= C ($CH_3$)-CH=$CH_2$). In that way they are nomenclatured as monoterpene (with two isoprene units), sesquieterpenes (with three units), Di-terpenes (with four units) etc. They are the primary constituents of essential oils of plants and flowers. They are also frequently used in perfumery and occasionally for the alternative medicines or food additives (vitamin–A). Characteristically, majority of them possesses typical smell and are grown inside the plants for self-protection. As mentioned earlier that they can inactivate the action of NF-κβ liable for inflammatory processes[29]. They bear strong medicinal potential and its anti-inflammatory actions is also due to the ability to modulate important cell signaling pathways involved in inflammation. In that regard the expression of NF–κβ also plays a significant role. Perhaps it is the reason why terpenes are the biggest target in recent drug discovery event[29,58]. Its anti-oxidant property also plays a beneficial role to inhibit the lipid peroxidation. By scavenging the free radicals, they inhibit harmful events averting the chronic illnesses, like LDL oxidation which is perhaps the leading cause of atherosclerosis[59]. Interestingly, some lipophilic/lipid soluble terpenes can synergize the effect of other anti-oxidants. For example, the γ–terpinene in association with rutin synergizes the inhibition of $Cu^{+2}$ induced LDL oxidation[60]. Considering the overall aspects, it is somewhat definite that herbs enriched with multiple ingredients offer valuable effects.

One of the major reasons behind the manifestation of chronic inflammatory diseases could be the lack of anti-inflammatory micro-nutrients in daily diet which in fact could help control the ailments. It is noticed that the prevalence of OA is somewhat less within the Asian and Mediterranean population compared to their Western counterparts[5]. Asides from genetic makeup, one of the liable factors is the differences in food habit. The fat enriched food within Western European diet

creates severe fatty acid imbalances which is commonly seen in many chronic arthritis patients[61]. The OA affected joints often show increased levels of AA and lipids which increases according to the severity of disease. The AA level in subchondral bone is seen 50–90 % higher in the case of OA patients[62,63]. Whereas in Asian diets, the higher consumption of vegetables offering more flavonoids help maintain the balance while preventing the formation of AA or any of its harmful derivatives like PGE2 or LTs[5,30,64-66].

Arthritis: It is a chronic disease at the inflamed joints. Numerous treatments are available now for its control but no exact cure is found yet. Often the treatments are very harsh. It is the reason why many patients often seek alternative medicines for help since those are less severe and much tolerable showing lesser side effects.

Under normal conditions, inside a joint when two bones move, twist or flex, they require smoothness for maintaining the functional flexibility (Fig. 3). During the movement, ligaments act as elastic bands to hold the bones together in the same place. The cartilage tissue that covers the bone surfaces prevent them from direct friction providing smoothness in course of the movement. In that path of normal maneuvering, no pain arises since no friction occurs. At the onset of disease, at first the cartilage damage starts, which initiates the bone erosion. Additionally, the joint cavity which is normally filled with synovial fluid produced due to the secretion from the cells aligned on synovium attached to the ligaments providing a cushioning effect ceases during arthritis. So there is a steady loss of the synovial fluid. This allows direct contact with the opposite bones raising friction and pain. So, the pain and suffering starts owing to the faulty joint which consists of, a) cartilage damage, b) shortage of synovial fluid, c) autoimmune attack, and d) infection. The disease is versatile by nature, among them OA and RA are the predominant[5].

Numerous reasons are hypothesized behind the episode of OA which includes genetic predisposition, trauma, diet, inflammation, repetitive motion of the limb and obesity as well. The biochemical role of diet, nutrition and life style are seen to be deeply linked to the damage and repair mechanism of articular cartilage and subchondral bone of the joint. It is hypothesized that the tissue injury, associated to stiffness and pain is originated by the endogenous production of AA from the metabolism of ω–6 fatty acid, whose major sources are the processed foods. The event may possibly occur

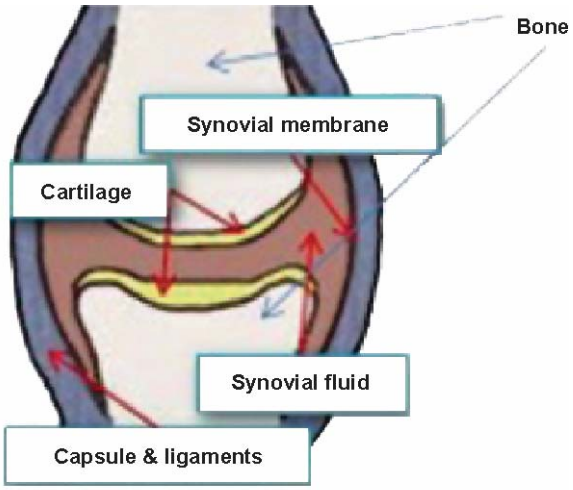


Fig. 3 — Picture of the bone joint

also due to insufficient intake of anti-inflammatory ω–3 fatty acids and other micro-nutrients like flavonoids which usually resists the inflammatory process by preventing any oxidative damages at the joint cartilages[63-66]. OA appears when cartilage starts to show damage due to the increasing rate of developing stiffness thereafter subsequent loss of the elasticity. The reason behind the development of stiffness is not well understood. It is hypothesized that the incidence could be partially age related. But the OA attack comprises of several events: a) the breaking down of proteoglycans and collagen - the lowering of proteoglycans and collagen ratio marks the progression of disease. b) Deposition of $CaPO_4$ crystals – the excessive deposition of $Ca^{+2}$ owing to uncontrolled mineralization creates deviation from normal endochondral ossification. There are numerous causes behind this effect, aging, metabolic disorders, degenerative joint diseases, physical disturbances which also set the conditions for uncontrolled calcification. The high deposition level of $Ca^{+2}$ in the form of calcium pyrophosphate di-hydrate [$Ca_2$ ($PO_3$ – O – $PO_3$)$_4$, $2H_2O$] or hydroxy apatite [$Ca_5$ ($PO_4$)$_3$ (OH)] or basic calcium phosphate [$CaPO_4$] is seen to be liable for setting the course of OA[5,67,68]. But whichever mechanism may be involved, due to the manifestation of stiffness it can no longer function as a shock absorber. The continuing erosion produces more stretching of the cartilage, causing relentless pain. As the symptom advances with rise of frictions within joint, more inflammation sets in along with the increasing order of pain and simultaneous erosion of bones. As an outcome, bones start to rub on each other intensely raising severe agony and suffering. The

condition worsens with time at the appearance of biting inflammation, which creates further harm to the affected joints. Patients feel extreme pain during and after the joint movement. There is always an aching sensation in each move and sudden move provides agonizing sensations. So the development of stiffness is a common indication of the initiation of OA. Afterward there appears hard lumps or bone spikes at the affected joints. OA generally attacks at the knees, hands, hips and spines. Any attempts to lower the inflammation at any of the stages would put a brake providing also a relief in the progression of OA[5].

In case of RA which is a recognized inflammatory disease, the synovium membrane becomes inflamed by the auto-immune attack that brings stiffness, swelling, pain and at final stage the affected joint undergoes deformity. The incidence occurs almost three times more within women than the men between the ages of 40–60, but rarely found among the children. The inflamed joints, if touched, patients feel tenderness showing red puffy colors at the affected areas. The disease enables to strike at multiple places simultaneously. It is often noticed at the wrists, necks, elbows, shoulders, knees, hips and finger joints. Interestingly, it starts to spread from smaller to the larger joints. The actual trigger remains unknown. Often environmental factors or genetic predisposition are thought to be liable. Whichever may be the stimulus, malfunctioning of immune system plays a significant role[5,69]. In that regard, B and T lymphocytes have their dominant functions. In RA, it is noted that both T and B lymphocytes become overactive. According to animal models, the T–cells alone can promote the synovitis. Reports show that T–cells in close proximity to the macrophages within cellular aggregates in synovial membrane involves in inter-cellular cross-talking which leads to their activations through the local release of various cytokines via the presentation of auto-antigens or co-stimulation or both. It is reported that T–cells can modulate the actions of other immune cells just by the direct contact which usually occurs due to the activation by cytokines. It is also noticed that the activation by IL-2, IL-1β and TNF–α of resting $CD45RO^+$ and $CD4^+$ T– lymphocytes are able to stimulate more cytokine production from the B– cells without T–cell ligation[70-72]. This insists to hypothesize that the role of T– cells in synovium is to activate the others by contact. Possibly an imaginary autocrine loop becomes established where the membrane anchored and secreted cytokines in addition to adhesion molecules control the production of both pro- and anti-inflammatory cytokines[5]. It is noticed that T– cells undergo activation by interacting with the cells of endothelia due to its contact during transmigration. Experiments show that $CD45RO^+$ cells from the circulation get activated during migrating through the endothelia. This shows the important role of adhesion molecules and cytokines expressed on the endothelial cell surface. This could be a model behind the possible cause of inflammation in synovium. Besides cytokines, the role of HLA is also an important concerned factor due to genetic effectivity[71-73]. Several HLAs are identified eg, HLA-DRB1 or HLA-DR4 alleles. They are identified as RA – shared epitope but not directly involved in causing the disease, only used for the identifications[72]. Inheriting two copies of HLA alleles would significantly increase the risk of RA. This epitope helps designing the anti-RA drugs[5].

Gout also falls into the category of arthritis but uniquely it affects the bone joints only at the faraway places, like toes. It is seen more among the men than women but equalizes after women reach at the menopausal stage, evidently supporting a strong role of estrogen. Gout is caused by the deposition of uric acid (UA)/urate crystals within the joints like toes, ankles or fingers inducing painful inflammation. The faulty purine-metabolism created either by the hyperuricemia or mal-excretion of UA for impaired kidney filtration is the key factors to elevate the serum UA level that ultimately results in the urate crystal deposition while inflicting pain and inflammation. The genetic predisposition plays a significant role in gout. The disease is also undisputedly viewed as chronic inflammatory by nature. The ingredients present within herbs have immense therapeutic potentials either preventing the disease or reducing inflammation[73].

Several herbs can be taken up for daily use to prevent or treating the gout. Among the notables are; Devil's Claw, Burdock Root, Sour Cherries, Lemon juice and celery seeds[74]. Alfalfa sprouts are also recommended but it often raises a controversy for the high Purine content[75,76]. On the other hand, Devil's Claw gains much higher ground perhaps top on the list for managing the gout. It has high level of several anti-inflammatory ingredients which inhibits COX – 2 enzyme that lowers inflammation at the affected joints[77] (Table 1). The next effective one is Burdock root. Usually, that plant is harvested and eaten as vegetable to provide good amount of dietary fibers. It is diuretic and also contains several blood purifying

agents. The extract has high level of xanthine oxidase inhibitors which are natural flavonoids like; kaempferol, myrcetin and quercetin[78-82]. Besides, the presence of inulin also helps diabetes without provoking the insulin secretion[83]. The other herb/fruit that lowers the risk of gout flare is cherries[85]. It has also high level of antioxidants. About 50 % of the risk can be avoided if 10 cherries are consumed on a daily basis. The high concentration of anthocyanins (Cyanidine) are detected to be the underlying cause.

The other herb often used in treating gout or rheumatism is the celery seeds[85]. In addition to its culinary use the seeds are used for muscle relaxation, headache, lowering the blood pressure and blood sugar. Its inherent anti-blood clotting property is due to the existence of Coumarin. Further, the existence of 3 – n – Butylphthalide provides diuretic property by stimulating the kidneys to flush out the uric acid in the blood as well as alkalizing it. Additionally, the enhanced level of Linoleic acid and flavonoids offer strong anti-inflammatory role which may alleviate the joint pain in gout and rheumatism. However, its use occasionally causes few allergic manifestations and miscarriages for pregnant women. People undergoing various drug treatments should aware of those facts before using it[86].

In addition to those, patients suffering from the gout or rheumatism also use apple ciders, lemon juice and baking sodas. These also help by easing or lowering the risk of attack. The anti-oxidants in lemon or apple and perhaps the alkalizing ability of soda are thought to be responsible for the effect[74].

**Herbs selected for treating the arthritis**

Turmeric (*Curcuma longa*): It is routinely used in South Asian cooking but, its medicinal application is noticed within the ancient Chinese and Indian Ayurvedic medicines for treating inflammatory diseases, liver disorders, bruises or colic. In present days, turmeric powder is also used in treating the joint inflammation or sports injuries. It is even used as antiseptic in dressing wounds. Recently its use in western foods becomes popular after acknowledging the role to protect liver and kidney from the environmental toxins. Its yellow color is due to a chemical component called Curcumin which carries immense pharmacological properties[82]. Besides curcumin, there are other ingredients eg, sesquieterpenes (zingiberene, bisabolane, turmerone, guaiane), common sugars (glucose, fructose, arabinose), resins, vitamins, minerals and few proteins[78,83]. The terpenes are already described for their various beneficial roles in physiology especially in controlling the inflammation like RA[29,30]. It is reported that daily use of ~1200 mg of curcumin decreases the symptoms of RA providing flexibility to the joints at a time reducing the pain and swelling. It is evaluated that ~400 mg of curcumin offers equal anti-inflammatory effect that is comparable to ~100 mg of Phenyl butazone in animals[86]. Below is the several commercially available NSAIDs commonly used by the arthritic patients to control the inflammatory action. The overall anti-inflammatory effect of turmeric is by virtue of its combined actions of curcumin plus other ingredients in the root.

Numerous hypothesis are built regarding its anti-inflammatory role like, a) effect on adrenal cortex, b) inhibition of cortisone metabolism in the liver, c) increment of cortisone in circulation, d) inhibiting 5 – LOX, e) inhibition of pyrogen induced production of TNF and IL-1β[11-14]. Report also indicates that it inhibits the LPS induced activation of NF-κβ[55]. Further, curcumin alone stimulates the stress induced expression of HSP 27, αB Crystallin and HSP 70 in both adrenal and liver signifying its potent anti-inflammatory role which can be compared with the salicylate, indomethacin and nor-dihydro-guaiaretic acid[87,88]. It is recorded also that curcumin/turmeric lowers the cortisone level in case of chronic stress[89]. It also blocks the lowering of Brain derived neuro-trophic factor (BDNF) and reduces the phosphorylated cAMP response element-binding protein in hippocampus and frontal cortex of the animals under chronic stress[90]. Perhaps this is an indication that turmeric can exert positive behavioral influence in regulating the chronic stress[91]. It is further known that turmeric provides relief during gastric pain in ulcerative condition[93]. It often protects the liver from toxin induced damage and also helps the bile flow and secretion[94]. The anti-cancer role of turmeric has been well established. It blocks the crucial pathway, like the action of NF-κβ to develop any cancers[94]. In that role, it inhibits the superoxides by acting as strong anti-oxidant. The spice suppresses ACTH secretion from the pituitary tumor cells involved in Cushing's disease. Additionally, it prevents the growth and also simultaneously induces the cell death in various tumors. It has been shown that unlike salicylic acid, curcumin does not lower $PGI_2$ synthesis but still inhibits the aggregation of platelets[11]. It also possesses the nematocidal, antifungal and anti-

bacterial property[95,96]. It is why it is used in wound dressing in the rural areas of many Asian countries. So far, no significant adverse effects of curcumin / turmeric has been reported.

Ginger (*Zingiber officianale)*: Throughout the world it majorly used for culinary purposes. The fresh or dried rhizomes/roots are normally used. Syrups and candies are often prepared commercially using the extract. Ginger root has a long medicinal history. Traditionally, fresh chopped roots act as digestive aid helping dyspepsia, gastrointestinal upsets, blocking motion sickness, nausea and vomiting[97]. The spice also offers strong anti-inflammatory role toward the OA and RA and even toward any myalgias[98,99]. The active components are – Gingerols, Shogaols and Zingerone. In addition to those there are few volatile oils like β – bisabolane, Zingeberene, Zingeberol. The matrix composition of ginger root is – 50 % starch plus amino acids and lecithins[100].

Its digestive action is suspected to be due to increased salivary secretion[101]. On the other hand it inhibits the stomach acid secretion with 1/3 potency of cimetidine while also enhancing the pH of gastric juice. Possibly in that way, it offers the gastro-protective effect. Additionally, it enhances the lipase secretion offering further help in digestion[101]. The anti-cholestermic action of ginger is highly pronounced[102, 103]. The presence of compound ZT (E-8p – 17 epoxylabd – 12 ene – 15, 16 – dial) inhibits the HMG – CoA reducing the cholesterol synthesis[9].

Considering its manifold physiologic role, the extract provides anti-aggregation effect of platelets which could be ascribed due to the inhibition of thromboxane or PG synthesis[104]. Reportedly, the strong anti-inflammatory role is owing to the prevention of eicosanoid production which particularly helps the arthritic patients. It is recorded that Gingerols and some oleoresins decrease the level of inflammatory mediators by inhibiting the enzymes COX and LOX thereby preventing both PG and LT productions[105]. Additionally, a few aromatics in ginger also inhibit the pyrogen initiated inflammation caused by the IL-1[100].

Ginger is famous for its strong anti-inflammatory role in ancient Indian Ayurvedic medicine. Its ingestion helps lower pain and swelling of arthritis and also in myalgias. The continued use of ginger (50 gm fresh or 4 gm powder) for ~3 months shows notable relief from pain and swelling of the chronic arthritic patients[99]. No adverse reaction is reported even after 2.5 years of daily use. Its efficiency (170 mg dried extract) is counted to be slightly less than the ibuprofen (400 mg) for controlling pain among the OA patients when tested for a period of about one week.

The extract has anti-emetic effect and also prevents motion sickness, nausea caused either by the anesthesia or pregnancy. The mechanism is not so clear. But it is reported that it can antagonize several 5 – $HT_3$ receptors which exist in the walls of GI track and brain. Some even suggest that anti-nausea role is due to decreasing effect of tachygastric action while preventing the elevation of vasopressin induced by the circular motion[106,107].

Capsicum: It is commonly known as chili pepper which is used mostly for the culinary purposes. About fifty different species are known so far and ~1/3 of world's population uses it on daily basis during cooking by adding either the fresh or dry fruits or in dried powder form. The use is recorded since few millennia BC among the South East Asian nations also in Mexico and Peru. The major constituents are capsaicin and its analogs (dihydro-capsaicin, nor-dihydro-capsaicin, homo – capsaicin, homo-dihydro-capsaicin) plus few carotenes (capsanthin, lutein) and vitamin A and C[108,109].

Among them, capsaicin is studied as being the most physiologically active ingredient. It behaves as a painful stimulus. Its interaction occurs through the sensory neurons of TRPV1 receptor subtype permitting cations to pass through the cell membrane causing a depolarization thereby signaling the brain to release endorphin[110-112]. The capsaicin binding to its receptor(s) produces sensation of heat, pain or burning although not physically[113]. But it is an irritant to skin. The other members of its family not always produce same degree of hotness during ingestion although behave similar way. The role of capsanthin or lutein are different. They act as anti-oxidants[114,115]. Capsaicin also offers strong analgesic effect providing substantial relief to the patients suffering from diabetic neuropathy, various arthritis or cluster headaches but not showing any anti-inflammatory property[116,117]. Numerous reports indicate that besides lowering the pain it (0.025 % cream) can markedly reduce the joint tenderness in many OA patients[118]. Its analgesic action is partly due to the depletion of Substance P (SP), a major pain mediator that often transmits pain sensation from the peripheral to spinal-cord neurons[119]. The *in vitro* data indicate the defunctionalization of various neurons that involves during pain[120]. The action may comprise several steps, a) SP is released from the

central or peripheral terminals, b) the conditions of SP containing fibers could be worsened, c) the axoplasmic SP transport is inhibited, and d) the depletion of SP lingers for a while. In that act, neuronal damages occur which is seen in both myelinated and unmyelinated δ – fibers. But no *in vivo* data is ever provided in this regard especially when taken as a food. As per additional behavior, capsaicin enhances the gastric acid secretion and acts as a potent inhibitor of platelet aggregation[121,122]. Since, the release of catecholamine has been noticed therefore caution should be taken for those undergoing any treatment with Monoamine oxidase inhibitor or hypertensives[123]. It is commercially available in the form topical creams. But its major use is noticed for the purpose of cooking. About 50–150 mg of capsaicin can be safely ingested if no prior gastrointestinal problems would exist.

Devil's Claw (*Harpagophytum*): It is a popular herb found mainly in the Southern African region but currently used also in the western world. The dried roots are used in the form of tea or tonic. Its application is directed mainly for managing the inflammatory joint diseases like OA, RA or gout although occasionally used in treating minor GI complaints like dyspepsia, or digestive upsets. The major constituents are: a) Iridoid glycosides (monoterpenes) – harpagide, harpagoside and procumbide; b) phenolic acids – chlorogenic acids, cinnamic acid; c) flavonoids – kaempferol, luteolin[124,125]. Among those, harpagoside is the ingredient of major interest. It resides in the root but not in fruits, flowers or stems. The whole plant extracts seems to offer better therapeutic effect than the ingredients from isolated parts[126]. Evidences indicate that its use is perhaps the most effective treatment of OA due to anti-inflammatory and pain relieving effects[127]. The extract increases the SOD, catalase and glutathione peroxidase actions with simultaneous reduction of *in vivo* lipid peroxidation[128]. Obviously, this provides the anti-oxidant effect. Further studies indicate that in addition to inhibit the inflammatory mediators it prevents the cartilage destructive agents like MMPs and others[129-131]. The chondroprotective action is due to suppressive role on NF-κβ activation. The extract is safe if used in moderate dosages. The side effects are limited to minor GI upsets, dyspepsia and loss of tastes. No toxicity or drug-interactions are ever reported. The main active ingredients are the Iridoid alkaloids of which harpagoside plays a dominant role[124]. Several studies prove its high efficacy regarding the treatment of OA and RA.

Hydrolysis of iridoid glycosides: It is noticed that hydrolysis by β-glucosidase results in the formation of H-harpgide which is considered to be the actual active component having a potency like Celecoxib. It bears a slight structural resemblance and inhibits COX-2 by binding at its active site thereby preventing the progression of inflammation. The anti-inflammatory action is recorded as being equivalent to ibuprofen which makes it popular for pain management within the OA and back-pain sufferers. It is also claimed to be active also against several types of cancers especially the compound Procumbide which shows anticancer effect[132,133]. It is also used against minor GI complaints[124].

Kaempferol is normally found as glucosides. It is easily absorbed through the wall of small intestine. It has strong anti-cancer role inducing apoptosis, limiting angiogenesis, inhibiting metastasis by lowering the action of MMP – 3[129]. It acts against breast cancers by acting with the estrogen receptor pathway also upregulating p53 which in turn reduces the cell proliferation[135]. It also reduces the growth of pro-myelocytic leukemia. It is seen effective also against the ovarian and lung cancer as well. In ovarian cancer, it prevents growth by inhibiting the action of VEGF whereas in lung cancer it works by upregulating the pro-apoptotic *bax* and *bad* by downregulating anti-apoptotic *bcl-2* and *bcl-x1*. It is noticed that, foods having kaempferol lowers the incidences of prostate, bladder and colon cancers[135,136]. The compound also shows anti-viral and anti-bacterial properties[137]. Its anti-oxidant effect enhances the action of SOD, Catalase and heme-oxygenase. In that way it exerts cardio-protection.

It activates dopamine transporter while regulating the dopamine level in neuronal synapses thereby playing an opposite role of amphetamine and cocaine which blocks the dopamine actions[138]. Like kaempferol it can prevent the growth of ovarian cancer and also reduces the incidences of heart attack and expresses strong anti-inflammatory role[139-141]. Its inhibition of NF–κβ indicates the anti-inflammatory behavior. The adverse effects of luteolin is seen in blocking the progesterone thereby enhancing the possibility of endometrial cancer also causing the gastric hypersecretion.

The compound shows modest blood pressure lowering effect simultaneously provides the laxative action[143,144]. Occasionally it may induce respiratory allergy[144].The combined effects of all the above

ingredients greatly help anti-inflammatory action of this herb.

Meadowsweet (*Fillipendula ulamaria)*: It is perennial native of Europe and offers sweet smell from the flowers. The usable parts are flowers and leaves which are extracted normally with Ethyl Alcohol. The major active components are Salicin, Salicylic acid and Gaultherin. Except salicylic acid others have the β – glucoside linkage. The salicylic acid or its $CH_3$ – or – $COCH_3$ derivatives are known to be the active principle for anti-inflammatory and anti-arthritic actions capable of reducing pain, swelling and inflammation[145]. Each one of them prevents COX preventing the formation of pro-inflammatory mediators like PGs, therefore the oil or extract is used for arthritic conditions to suppress the inflammation and pain. It also produces strong analgesia[146]. The herb can activate AMPK which is indicative to anti-cancer and anti-diabetic actions[147].

The other important ingredients are flavonoids (Rutin, Hyperoside, Spireoside and Kaempferol). They are strong anti-oxidants and possess other medicinal qualities. Because of the glucoside linkage, they are lipophilic by nature.

Rutin acts as a powerful anti-oxidant. It is perhaps stronger than the Quercitin. It combines with $Fe^{+2}$ preventing to react with the $H_2O_2$ to generate the superoxide or free radicals. So it is an anti-inflammatory component. Further it inhibits angiogenesis by preventing the action of VEGF thus acts as a potential anti-cancer agent[148]. It can inhibit the blood clotting but has an adversarial effect on thyroid due to lowering of T3 and T4 level without changing the level of TSH. In addition, it has the ability to cure hemorrhoids, varicosis and microangiopathy. The compounds Hyperoside and Spireoside also bear the almost identical structure like Rutin. Besides sharing of the common features, Hyperoside is an antagonist to the κ – opoid receptor[149,150].

Willow (*Salix family*): It is a native of Europe, Asia and North America. The barks from fresh green branches or leaves are dried and boiled in hot water for sipping as tea. Alcohol extractions are also carried to make the tincture for future use. It is a popular treatment for rheumatism, fever, pain and chills. It has strong analgesic property also offers relief in arthritic pain, swelling and lower back pain[151]. The medicinal components are, phenolic glycosides like, Salicin, salicortin, tremulacin and salireposide whereas the others are tannins, flavonoids and polyphenols (Table 1).

The notable pharmacological actions are directed toward pain, swelling and fever. It is recorded that ~ 120 mg of willow bark extract significantly lowers pain among the OA patients as assessed by the WOMAC pain index. It is noted that phenolic glycosides do not act directly. It works as pro-drugs which are converted by the intestinal or liver enzymes to its active form, the salicylic acid. So the actions are somewhat slower. The herb is effective toward rheumatic fevers, rheumatoid arthritis, pericarditis and Kawasaki disease. It also lowers the risk of heart attack and stroke and inhibits the aggregation of platelets but unlike aspirin its effect is not irreversible. As an additional measure it lowers the incidence of atherosclerotic lesion and inhibits the LDL oxidation. The (-) isomer, Epicatechin is permeable to brain and thus protects from the intracerebral hemorrhage. Being a strong analgesic it provides relief from migraines but at large doses it may cause the GI bleeding. The presence of catechins and tannins causes significant reduction in cancer risk. It is also particularly beneficial to colon cancers due to preventing ability of tumor production[152].

Evening Primrose: The plant blooms in summer displaying bright yellow flowers. Although a native of North America but it is found in many regions of Western Europe also. It is used for both medicinal and culinary purposes. The roots and plants are used for extracting edible oil but it is consumed also as vegetable. Oils (EPO) are often used as medicine. It can control GI problems, coughs, nausea, neuralgia, rheumatism, gout and whooping coughs. As per medicinal use, it is mostly utilized for anti-inflammatory reasons like RA, multiple sclerosis and Sjorgen's syndrome[153]. Often it is employed for the purpose of women's health like in the case of premenstrual syndrome, mastalgia, endometriosis and atopic eczema[154,155]. It is also used for psychiatric causes like schizophrenia, hyperactivity and dementia.

The major constituents of the oil are: 1) cis – Linoleic acid (LA) (~70 %), Cis – γ –Linolenic acid (GLA) (~10 %), Oleic acid, Palmitic acid and Stearic acid which can inhibit both COX – 1 & -2 non-selectively ($IC_{50}$ ~3.9 to 180 μM)[156]. When metabolized, LA is converted to GLA which afterward changes to di-homo-GLA (DGLA). DGLA is the precursor of $PGH_1$ which is processed later to $PGE_1$ and $TXA_1$. They both have the anti-inflammatory properties[157,158]. Additionally, $TXA_1$ offers cardiac protection by preventing the aggregation of platelets[159]. The generation of $PGE_1$ is in essence advantageous to

arthritic conditions and gout[160]. But several human studies indicate that short term use of EPO may not offer much benefits. It is possible that prolong use might raise the level of $PGE_1$ which eventually offers the positive effects toward inflammation created in arthritis.

Juniper/ Juniperus: It is an evergreen shrub and the native of North and Central Europe. The tree produces needles along with deep purple round shaped berries. Either the dried berries or else the alcohol extract of both are used for medicinal purposes. It is commonly used for chronic arthritis, gout, urinary tract infections, cystitis or digestive upsets[161]. But occasionally it produces adverse effects like tachycardia, hypertension and hematuria[162].

The major contents are; volatile oil – monoterpenes (1, 4 – Cineole, Terpin – 4 – ol, Sabinene, Limonene, Myrcene), sesquieterpenes (Caryophylline, Cadinene, Elemene), tannins (Proanthocyanins, Gallotannins), flavonoid Glycosides (Rutin, Isoquercitin, Quercitin). The others are various sugars, resins, diterpene acids, glucuronic acid.

It is commonly used for the treatment of genitourinary and musculoskeletal problems. But it can act as an antiseptic to urinary tract infections and also behave as diuretic. Further it finds uses to prevent the cystitis. Due to its strong anti-inflammatory nature it is useful in treating chronic arthritis, gout or other rheumatic conditions. The extract also can stimulate appetite to help digestion[161].

Nettle/ Urtica: It is a perennial having the incised leaves and produces yellow flowers. The tree is about 1.5 m in height and found both in Asia and Europe. It has sharp hairs that can easily break causing sting and irritation when touched. The extracts of both leaves and roots are used as medicine for hundreds of years. Traditionally, it is used in treating rheumatic arthritis, gout, hay fever, muscle and joint pains[163,164]. But it is used also in treating the benign prostatic hyperplasia and micturition disorders[165]. The alcohol extracts or dried teas are available as herbal medicine. Occasionally it may cause skin rash. Mainly the leaves express the anti-inflammatory property.

The active components are; flavonoids, amines and carboxylic acids produced in the leaves whereas the roots possess sterols and lectins. Among the flavonoids the notables are; Rutin, Isoquercitin, Quercitin and Kaempferol but for amines, they are Histamine, Serotonin, Choline and Acetyl-choline. Regarding sterols, it is mostly the β - Sitosterol and for acids, it is Malic, Formic and Salicylic. The other noticeable components are tannins and glycoproteins. As for lectins, it is mainly the agglutinin. Owing to high chlorophyll content, the extract is often used for food coloring agent (E140)[166,167].

Boswellia/ (*Boswellia scara)* `/Frankicense: As per biblical story, Frankicense resin is one of the precious gifts offered by the Magi to baby Jesus. The trees exist in approximately twenty different species which are found in the Arabian Peninsula, Madagascar and India. If the outer bark is pierced or peeled then the drained sap solidifies to scented crystalline resin often called Frankicense or Olibanum. The resin contains ~8 % volatile oil which is separated by steam distillation. The composition indicates terpenes of different categories and the leftover gum consists of two types of poly-saccharides made of galactose + arabinose or galactose + uronic acid. The oil is used as Ayurvedic medicine for a long time to treat numerous inflammatory ailments like, asthma, arthritis, fever or GI problems[168]. When used as incense it helps relieve mental depression. The medicinal action resides in the oil which is diluted in 95 % ethanol before use. The anti-inflammatory actions are directed toward the mucus and synovial membranes or lining tissues (respiratory tract, gut, urinary and reproductive tract). It also shows anti-bacterial and anti-fungal effect on skin and is effective against acne and retards the aging of skin[169-173]. Regarding spiritual practices, it offers calming effect and help meditate. The medicinal properties solely rely on the terpenes. The terpene composition consists of mono terpenes - 13.1 %), di-terpenes – 42. 5 %, sesquieterpenes – 1 % and some others are in lesser amounts. The mono-terpenes are, α - and β - Pinenes, Sabinene, β – Myrcene, d – Limonene etc. The majority of di-terpenes are Cembrene, iso- Cembrene, and Verticiol etc. The sesquieterpenes are Boswellic acid derivatives, 3 – oxo- Tirucallic acid, α – Copaene, β – Bisabolane and δ – Selinene and others[168].

The most effective ingredient is Boswellic acid and its derivatives. The molecule shows multiple preventive properties. Its anti-inflammatory and anti-arthritic role relies on by preventing the immunomodulatory components. The most distinct is the inhibition of 5 – LOX enzyme[173]. In addition, several other factors are also inhibited, for example, cytokine productions like ILs and TNF – α, blocking the activation of complements and preventing the actions of ROS and NO[169-174]. It is noteworthy that it

can inhibit leucocyte elastase thereby preventing the collagen degradation usually occurred during arthritis or asthma. Further, it also induces apoptosis of various cancer cells (leukemia, brain tumor and colon cancers)[169].

## Conclusion

The arthritis and gout are chronic inflammatory problems arising from the dysfunctional metabolism. Normally, these are irreparable disorder but several of its defective pathways imposing discomfort or sicknesses can be prevented or blocked to a certain extent providing some comfort or relief. Uncontrolled pain created by inflammation is the problems continually faced by the victims, on that perspectives, researches on herbs have gained premium attention despite the recent advancement of large selection of anti-inflammatory medications. Uniquely, majority of them are mimicry of the natural components. In this article, I have chosen ten herbs that are often used for the remission of chronic inflammatory conditions including the arthritis and gout. Advantageously, a single herb possesses multiple medicinal ingredients and many of them are able to control pain and inflammation. The active compounds basically fall into the limited categories of, terpenes, flavonoids, tannins or few other miscellaneous anti-inflammatory agents. They interfere directly or indirectly with various inflammatory mediators. Among the anti-inflammatory agents terpenoids earn major prominence because of its strong ability to modulate the NF–κβ signaling pathways. The other components also possess the capability to lower inflammation or pain. Often many act as anti-oxidants thus captures the ROS or other free radicals to control the inflammatory processes. It is also noticed that some herbs expresses a few fatty acids like, LA, myristic and others which inhibit the COX-1 and COX-2 actions ($IC_{50}$ = 4.0–180 μM) diminishing the production of inflammatory eicosanoids. Thus considering the presence of multiple effective ingredients, lesser side effects and less harshness, it seems logical to use herbs to control the arthritis.

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## References

1 Robson B and Baek O K, *The engines of Hippocrates: From the dawn of medicine to medical and pharmaceutical informatics* (John Wiley & Sons), 2009, 50-55.

2 Supplement and Herb Guide – Arthritis Foundation. www.arthritis.org.

3 How are herbs prepared? Herbal medicine. http://www.unh.edu/health-services/

4 Mitra S P, Arthritis: Classifications, Nature & Cause – A review, *Am J Biopharmacol Biochem Life Sci*. 2013, **2**(3), 1-25.

5 Mitra S P, The biochemical and physiological implications of gout, *Am J Biopharmacol Biochem Life Sci,* 2012, **1**, 1–35.

6 Abbas A K, Lichtman A H and Pillai S, Chemokine and Chemokine Receptors, In *Cellular and Molecular Immunology,* 8th edn, (Elsevier, International Edition Philadelphia, PA), 2012, 39–50.

7 Synergism of essential oils and curcumin, http://www.bcm95.com/Natural-Extracts.html

8 Barzegar A and Mosavi – Movahedi A A , Intracellular ROS protection, efficiency and free radical-scavenging activity of curcumin, *PLOS ONE*. 2011, **6**(10), e26012.

9 Tanabe M, Chen Y D, Saito K and Kano Y, Cholesterol biosynthesis inhibitory component from *Zingiber officianale* roscoe, *Chem Pharm Bull (Tokyo).* 1993, **41**(4), 710–13.

10 Pillinger M H, Capodici C, Rosenthal P, Kheterpal N, Hanft S, Philips M R, *et al.,* Modes of action of aspirin-like drugs: Salicylates inhibit Erk activation and integrin-dependent neutrophil adhesion*, Proc Natl Acad Sci (USA*), 1998, **95**, 14540–45.

11 Maroon J C, Bost J W and Maroon A, Natural anti-inflammatory agents for pain relief, *Surg Neurol Int*, 2010, **1**, 80-86.

12 Lawrence T, The molecular factor NF–κβ pathway in inflammation, *Cold Spring Harb Perspect. Biol,* 2009, **1**, a001651.

13 Ghosh S and Hayden M, New regulators of NF–κβ in inflammation, *Nature Rev (Immunology),* 2008, **8**, 832 – 48.

14 Gilmore T D, Introduction to NF – κβ: player, pathways, perspectives, *Oncogene*, 2006, **25**(51), 6680–84.

15 Vykhovanets E V, Shankar E, Vykhovanets O V, Shukla S and Gupta S, *Prostate*, 2011, **71**(2), 147–56.

16 Camandola S, Leonarduzz G, Musso T, Varesio L, Carini R, Scavazza A, *et al.*, Nuclear factor κβ is activated by arachidonic acid but not by eicosapentanoic acid, *Biochem Biophys Res Comm,* 1996, **229**(2), 643–47.

17 Calder P C, Long chain polyunsaturated fatty acids and inflammation, *Scand J Food Sci Nutri,* 2006, **50**(S2), 54–61.

18 Baynes J W and Dominiczak M H, Medical Biochemistry, 2nd edn, (Elsvier, Mosby), 2005, 555.

19 Karin M, Lawrence T and Nizet V, Innate immunity gone awry: Linking microbial infections to chronic inflammations and cancer, *Cell,* 2006, **124**, 823–35.

20 Akira S, Uematsu S and Takeuchi O, Pathogen recognition of innate immunity, *Cell,* 2006, **124**, 783–01.

21 Huang S, Rutkowasky J M, Snodgrass R G, Kikumi D O, Schneider D A, Newman J W, *et al*., Saturated fatty acids activate TLR – mediated pro-inflammatory signaling pathways, *J Lipid Res,* 2012, **53**, 2002–13.

22 Lee J Y, Plakidas W H, Lee A, Heikkinen P, Chanmugam P, Bray G, *et al*., Differential modulation of Toll – like receptors by fatty acids: Preferential inhibition by n – 3 ploy-unsaturated fatty acids, *J Lipid Res,* 2003, **44**, 479–86.

23 Morgan M J and Liu Z G, Cross talk of reactive oxygen species and NF–κβ signaling, *Cell Res,* 2011, **21**, 103–15.

24 Salar R J and Seasotiya L, Free radical scavenging activity, phenolic contents and phytochemical evaluation of different extracts of stem-bark of *Butea Monosperma (Lam) Kuntze*, *Front Life Sci,* 2011, **5**(3 – 4), 107–16.

25 Sharma P, Jha A B, Dubey R S and Pessarakli M, Reactive oxygen species, oxidative damage and anti-oxidative defense mechanism in plants under stressful conditions, *J Botany,* 2012, **2012,** id 217037.

26 Baeuerle P and Henkel T, Function and activation of NF–κβ in the immune system, *Ann Rev Immunol,* 1994, **12**, 141–79.

27 Nolan G P and Baltimore D, The inhibitory Ankyrin and activator *Rel* proteins, *Curr Opin Genet Dev,* 1992, **2**, 211–20.

28 Baeuerle P A and Baltimore D, In "The physiology of NF–κβ transcription factor*, Molecular Aspects of Cellular Regulation of Gene Transcription*", edited by P. Cohen & J. G. Foulkes, 1991, 409–32.

29 Heras B. de L and Hortalano S, Molecular basis of the anti-inflammatory effects of terpenoids*, Inflamm Allergy – Drug Targets,* 2009, **8**, 28–39.

30 Read M A, Flavonoids: Naturally occurring anti-inflammatory agents, *Amer J Pathology,* 1995, **147**(2), 235–37.

31 Schreck R, Reiber P and Baeurle P A, Reactive oxygen intermediates as apparently widely used messengers in the activation of NF–κβ transcription factor and HIV – 1, *EMBO J,* 1991, **10**, 2247 – 58.

32 Storz G, Tartaglia L A and Ames B N, Transcriptional regulation of oxidative stress – inducible genes: direct activation of by oxidation, *Science,* 1990, **248**, 189–94.

33 Kopp E and Ghosh S, Inhibition of NF–κβ by sodium salicylate and aspirin, *Science,* 1994, **265**, 956–59.

34 Auphan N, Di-Donto J A, Rosette C, Helmberg A and Karin M, Immunosuppression by Gluco-corticoids: inhibition of NF–κβ activity through induction of Iκβ synthesis, *Science,* 1995, **270**, 286–90.

35 Mitchell J A, Saunders M, Barnes P J, Newton R and Belvisis M G, Sodium salicylate inhibits cyclo-oxygenase -2 activity independently of transcription factor (Nuclear factor – κβ) activation: Role of arachidonic acid, *Mol Pharmacol,* 1997, **51**, 907–12.

36 Greenwald R A, Oxygen radicals, inflammation and arthritis: Pathophysiological considerations and implications for treatment, Seminars in *Arth Rheumat,* 1991, **20**(4), 219–40.

37 Sies H, Biochemistry of oxidative stress, *Angew Chem (Int. Ed. Eng),* 1986, **25**, 1058–71.

38 Devasagayam T P A and Kamat J P, Biological significance of singlet Oxygen, *Indian J Exp Biol,* 2002, **40**, 680–92.

39 Sies H and Packer L (Editors), Singlet oxygen, UV – A and Ozone, *Methods in Enzymol,* (Acad. Press, New York*),* 2000, vol 319.

40 Cadenas E, Biochemistry of oxygen toxicity, *Ann Rev Biochem.* 1989, **59**, 79-71.

41 Girotti A W, Lipid hydro-peroxide generation, turnover and effector action in biological systems, *J Lipid Res,* 1998, **39,** 1529-35.

42 Cadenas E and Sies H, Formation of electronically excited states during the oxidation of arachidonic acid by prostaglandin endo-peroxidase synthase, *Meth Enzymol,* 2000, **319**, 67–82.

43 Bates E J, Johnson C C and Lowther D A, Inhibition of proteoglycan synthesis by hydrogen peroxide in cultured bovine articular cartilage, *Biochim Biophys Acta,* 1985, **838**(2), 221–28.

44 Porter L J, *Condensed Tannins*, In *Natural Products of Woody*, Plants – I, edited by J W Rowe (Springer – Verlag: Berlin, Germany), 1989, 651–90.

45 Funatogawa K, Shunji H, Shimomura H, Yoshida T, Hatano T, Ito H, *et al*., Antibactaerial activity of hydrolysable tannins derived from medicinal plants against *Helicobacter pylori*, *Microbiol Immunol*, 2004, **48**(4), 251–56.

46 Chung K T, Wong T Y, Wei C I, Huang Y W and Lin Y, Tannins and human health: A Review, *Crit Rev Food Sci Nutr,* 1998, **38**(6), 421–64.

47 Fukai T, Folz R J, Landmesser U and Harrison D G, Extracellular superoxide dismutase and cardiovascular disease, *Cardiovasc Res,* 2002, **55**(2), 239–49.

48 Zelko I N, Mariani T J and Folz R J, Superoxide dismutase multigene family: A comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2) and EC-SOD (SOD3) gene structures, evolution and expression, *Free Radic Biol Med,* 2002, **33**(3), 337–49.

49 Chelikani P, Fita I and Loewen P C, Diversity of structures and properties among catalases, *Cell Mole Life Sci,* 2004, **61**(2), 192–08.

50 Yang S, Jensen M K, Rimm E B, Willett W and Wu T, Erythrocyte superoxide dismutase, glutathione peroxidase and catalase activities and risk of coronary heart disease in generally healthy women: A prospective study, *Am J Epidemiol,* 2014, **180**(9), 901–08.

51 Hattori H, Imai H, Hanamoto A, Furuhama K and Nakagawa Y, Upregulation of phospholipid hydro-peroxide glutathione peroxidase in rat casein-induced poly-morpho-neutrophils, *Biochem J,* 2005, **389**, 279–87.

52 Khansari N, Shakiba Y and Mahmoudi M, Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer, Recent Pat. Inflamm, *Allergy Drug Discov,* 2009, **3**(1), 73–80.

53 Sahnoun Z, Jamoussi K and Zeghal K M, Free radicals and ant-oxidants: Physiology, Human pathology and therapeutic aspects (Part III), *Therapie*. 1988, **53**(4), 315–39 (French).

54 Mitra S P, Protective role of native bovine serum albumin and alpha-unsaturated fatty acids on catechin oxidation, *Indian J Chem,* 2012, **51B,** 1131–44.

55 Calixto J B, Otuki M F and Santos A R S, Anti-inflammatory compounds of plant origin (Part I): Action on arachidonic acid pathway, nitric oxide and NF – κβ, *Planta Med,* 2003, **69**, 973–83.

56 Levine J D and Reichling D B, Peripheral mechanisms of inflammatory pain, In *Text book of pain* 4th edition, Edited by P D Wall and R Melzack (*London: Churchill Livingstone*), 1999, 59–84.

57 Simonds R E and Foxwell B M, Signaling, inflammation and arthritis: NF- κβ and its relevance to arthritis and inflammation, *Rheumatology (Oxford*), 2008, **47**(5), 584–90.

58 Souza M T S, Almeida J R G S, Araujo A A S, Duarte M C, Gelain D P, Moreira J C F, *et al*., Structure-activity relationship of terpenes with anti-inflammatory profile – A systemic review, *Basic & Clinic Pharmacol Toxicol,* 2014, **115**, 244–56.

59 Foti M C and Ingold K U, Mechanism of inhibition of lipid peroxidation by γ – terpinene, an unusual and potentially

useful hydrocarbon anti-oxidant, *J Agri Food Chem,* 2003, **51**(9), 2758–65.
60 Milde J, Elstner E F and Grassman J, Synergistic inhibition of LDL oxidation by rutin, γ – terpinene and ascorbic acid, *Phytomedicine,* 2004, **11**(2 – 3), 105–13.
61 www.NaturalProductsFoundation.org. (2009), Washington D.C.
62 Humphries J M, Kuliwaba J S, Gibson R J and Fazzalar N L, In situ fatty acid profile of femoral cancellous subchondral bone in osteoarthritic and fragility fractures: Implication for bone remodeling, *Bone,* 2012, **51**, 218–23.
63 Burnett B P, Levy R and Cole B J, Metabolic mechanisms in the pathogenesis of osteoarthritis, *The Knee Surg,* 2006, **19**(3), 191–97.
64 Baker K R, Matthan N R, Lichenstein A H, Niu J, Guermazi I, Roemer A, *et al.*, Association of plasma n-6 and n-3 poly-unsaturated fatty acids with synovitis in the knee: The MOST study, *Osteoarth Cartilage,* 2012, **20**, 382–87.
65 Guardia T, Rotelli A E, Juarez A O and Pelzer L E, Anti-inflammatory properties of plant flavonoids, Effect of rutin quercitin and hesperidin on adjuvant arthritis in rat, II *Framco,* 2001, **56**, 683–87.
66 Mahajan A and Tandon V, Anti-oxidants and rheumatoid arthritis, *J Indian Rheumatol Assoc,* 2004, **12**, 139–42.
67 Malemud C J, Changes in proteoglycans in OA: Biochemistry, Ultrastructure and Bio-synthetic processing, *J Rheumatol,* 1991, **27**, 60–2.
68 Eat K, Nguyan C and Bazin D, Articular cartilage calcification in OA: Insights into crystal induced stress, *Arthritis Rheumatol,* 2011, **63**(1), 10–8.
69 Scrivo R, di-Franco M, Spadaro A and Valesisni G, The immunology of rheumatoid arthritis. *Ann NY Acad Sci,* 2007, **1108**, 312–22.
70 Firestein G S and Zvaifler N J, How important are T–cells in chronic rheumatoid synovitis? II. T cell-dependent mechanisms from beginning to end, *Arthritis Rheumatol,* 2002, **46**, 298–08.
71 Weyand C M and Goronzy J J, Association of rheumatoid arthritis HLA polymorphisms in phenotypic variants of rheumatoid arthritis, *Arthritis Res,* 2000, 2, 212-16.
72 Gregerson P K, Silver J and Winchester R J, The shared epitope hypothesis: An approach to understanding the molecular genetics of susceptibility to rheumatic arthritis, *Arthritis Rheumtol,* 1987, **30**, 1205–13.
73 Auger I and Roudier J, HLA – DR and development of rheumatoid arthritis, *Autoimmunity.* 1997, **26**, 123–28.
74 www.nature-health-and-healing-4u.com
75 www.goutandyou.com.
76 https://www.mskcc.org.
77 Roberts B. Devils' claw as natural remedy for gout. www.streetdirectory.com.
78 Mill S,*The essential book of Herbal Medicine,* 2nd edn, *(*London: Penguin*).* 1991, 677.
79 Bradley P, *British Herbal Compendium*, Bournemouth, *BHMA,* 1992, 239.
80 Chandler F and Osborne F, Burdock, *Can Pharm J,* 1997, **130**(5), 46-49.
81 Leung A and Foster S, *Encyclopedia of common natural ingredient used in Food, Drugs and Cosmetics*, 2nd edn. (John Wiley & Sons, New York), 1996, 649.
82 https://umm.edu/health/medical/altmed/herb/turmeric.
83 Gargari B P, Dehghan P, Aliasgharzadeh A and Jaffar-abadi M A, Effects of high performance inulin supplementation on glycemic control and anti-oxidant status in women with type-2 diabetes, *Diabetes Metab J,* 2013, 37, 140- 48.
84 Arthritis Foundation – How cherries help fight arthritis. www.arthritis.org.
85 Celery seed. https://umm.edu/health/medical/altmed/herb/celeryseed.
86 Takada Y. Bhardwaj A, Potdar P and Aggarwal B B, Non-steroidal anti-inflammatory agents differ in their ability to suppress NF–κβ activation, inhibition of Cox – 2, and Cyclin D1, and abrogation of tumor cell proliferation, *Oncogene,* 2004, **23**, 9247–58.
87 Kato K, Ito H, Kamei K and Iwamoto I, Stimulation of stress-induced expression by curcumin in cultured rat tissues *in vivo*, *Cell Stress Chaperones,* 1998, **3**(3), 152-60.
88 Zhang Y, Naidu S D, Kostov R V, Pheely A, Calabrese V, *Sulfahydryl- reactive phytochemicals as dual activators of transcription-factors NRF – 1*, in *50 Years of Phytochemistry Research,* vol. 43, edited by D R Gang, Washington State (Springer, New York), 2013.
89 Kulkari S K and Dhir A, An overview of curcumin neurological disorders, *Indian J Pharm Sci,* 2010, **72**(2), 149-54.
90 Huang Z, Zhong X M, Li Z Y, Feng C R, Pan A J and Mao Q Q, Curcumin reverses corticosterone-induced depressive-like behavior and decreases in brain BDNF levels in rats, *Neurosci Lett,* 2011, **493**(3), 145–48.
91 Zhang L, Luo J, Zhang M, Yao W, Ma X and Yu S, Effects of curcumin on chronic unpredictable mild stress-induced depressive-like behavior and structural plasticity in the lateral amygdala of rats, *Int J Neuropsychopharmacol,* 2014, **17**, 793-06.
92 Turmeric for health, www.turmericforhealth.com/turmeric-benefits/turmeric-and-gastritis.
93 Otuechevec A, Abarikwu S O, Olateju V I, Animashavu A L and Kale O E, Protective effect of curcumin against the liver toxicity caused by Propanil in rats, *Int Scholarly Res Notices,* 2014, **2014**, id 853697.
94 Shanmugam M K, Rane G, Kanchi M M, Arfuso F, Chinnathambi A, Zayed M E, *et al*., The multifaceted role of curcumin in cancer prevention, *Molecules,* 2015, **20**, 2728-69.
95 Schraufstatter E and Bernt H, Antibacterial actions of curcumin and related compounds, *Nature,* 1949, **164**(4167), 456-60.
96 Wang Y, Lu Z, Wu H and Lu F, Study on the antibiotic activity of microcapsule curcumin against foodborne pathogens, *Int J Food Microbiol,* 2009, **136**(1), 71–74.
97 Ginger overview & information. www.webmd.com
98 Altman R D and Marcussen K C, Effects of ginger extract on knee pain patients with osteoarthritis, *Arthritis Rheum,* 2001, **44**(11), 2531-38.
99 Brown L J and Vargo B D, Ginger's health benefits. www.arthritis.org.
100 Rahmani A H, Shabrmi F M A and Aly S M, Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities, *Int J Physiol Pathophysiol Pharmacol,* 2014, **6**(2), 125-36.
101 Chamani G, Zarei M R, Mehrabani M and Taghiabadi Y, Effect of ginger extract on salivary secretion, *Acta Med Iran,* 2011, **49**(6), 336–40.

102 Alizadeh-Navaei R, Roozbeh F, Saravi M, Pouramir M, Jalai F and Moghadamnia A A, Investigation of the effect of ginger on the lipid levels. A double blind controlled clinical trial, *Saudi Med J.* 2008, **29**(9), 1280–84.

103 Fuhrman B, Rosenblat M, Hayek T, Coleman R and Aviram M, Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E – deficient mice, *J Nutr,* 2000, **130**(5), 1124-31.

104 Verma S K, Singh J K, Khamesra R and Bordia A, Effect of ginger on platelet aggregation in man, *Indian J Med. Res,* 1993, **98**, 240-42.

105 Kiuchi F, Iwakami S, Shibuya M, Hamaoka F and Sankawa U, Inhibition of PG and LT biosynthesis by Gingerols and diarylhepanoids, *Chem Pharm Bull (Tokyo),* 1992, **40**, 387-91.

106 Lumb A B, Mechanism of antiemetic effect of ginger, *Anaestheia,* 1993*,* **48**, 1118-21.

107 Vutyavanich T, Kraisarin T and Rnangsri R, Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial, *Obst Gynecol,* 2001, **97**, 577-82.

108 Ballard R E, McClure J W, Eshbough W H and Wilson K G, A systematic study of selected taxa of *capsicum, Am J Botany,* 1970, **57**(2), 225-33.

109 Kosuge S and Inagaki Y, Studies on the pungent principle of red pepper. Part XI. Determination and contents of the two pungent principles, *Nippon Nogei Kaishi J Agric Chem Soc,* 1962, **36**, 251-56.

110 Story G. M and Crus-Orengo L, in *Feel the burn*, *American Scientist,* 2007, **95**(4), 326-33.

111 Gorman J, in *A perk of our evolution in pain of chilies*, 2010, NY Times. September 20.

112 Rollyson W D, Bioavailability of capsaicin and its implications for drug delivery, *J Control Release,* 2014, **196**, 96-05.

113 Caterina M J, Schumaker M A, Tominaga M, Rosen T A, Levine J D and Julius D, The capsaicin receptor: A heat activated ion channel in the pain pathway, *Nature,* 1997, **389**(6653), 816–24.

114 Haila K M, Lievonen S M and Heinonen M I, Effects of Lutein, Lycopene, Annatto and γ – Tocopherol on auto-oxidation of triglyceride, *J Agric Food Chem,* 1996, **44**(8), 2096-100.

115 Matsufuji H, Nkamura H, Chino M and Takeda M, Anti-oxidant activity of capsanthin and the fatty acid esters in paprika (*Capsicum annuum*), *J Agric Food Chem,* 1998, **46**(9), 3468-72.

116 Gronninger H and Schister R E, Topical capsaicin for neuropathic pain # 225, *J Palliative Med,* 2012, **15**(8), 946-48.

117 Mark D R, Rappaport A, Padia D, Weeks R, Rosun R and Sheftell F, A double blind placebo controlled trial of intra-nasal capsaicin for cluster headache, *Cephalagia*. 1993, **13**(2), 114-16.

118 Laslett L L and Jones G, Capsaicin for Osteoarthritis pain. *Pro Drug Res.* 2014, **68**, 277 – 29.

119 Theriavtt E, Otsuka M and Jessell T, Capsaicin – evoked release of substance P from primary sensory neurons, *Brain Res,* 1979, **170**, 209-13.

120 Anand P and Bley K, Topical capsaicin for pain management: Therapeutic potential of capsaicin and mechanisms of the new high concentration capsaicin 8 % patch, *Brit J Anesthesia,* 2011, **107**(4), 490–02.

121 Limlonwongse L, Chaitauchewong C and Tongyai S, Effect of capsaicin on gastric acid secretion and mucosal blood flow in the rat,*The J. Nutri,*1979, **109**(5), 773-77.

122 Mittlestadt S W, Nelson R A, Daanen J F, King A. J, Kort M E, Kim P Ret al, Capsaicin –induced inhibition of platelet aggregation is not mediated by transient receptor potential Vanilloid Type – 1, *Blood Coagulation & Fibrinolysis.* 2012, **23**(1), 94- 97.

123 Watanabe T, Kawada T, Kurosawa M, Sato A and Iwai K, Adrenal sympathetic efferent nerve and catecholamine secretion caused by capsaicin in rats, *Am J Physiol,* 1988, **255**(1Pt1), E23 – E27.

124 Mncwangi N, Chen W, Vermaak I, Viljoen A M and Gericke N, Devils'Claw: A – Review of the ethnobotany, phytochemistry and biological activity of *Harpagophytum Procumbens*, *J Ethnopharmacol,* 2012, **143**(3), 755-71.

125 Watt J M and Breyer – Brandwijk M G, *The medicinal and poisonous plants of Southern and Eastern Afrika*,2nd edn. (Livingston Press, London), 1962.

126 Eichlero O and Koch C, Uberdie antiphlogistiche, analgetische und spasmolytische wirksamkeit von Harpagosid. Einem glykosid aus der wurzel von *Harpagophytum Procumbens DC*, *Arzeneimitt'el – Forsch,* 1970, **20**, 75-78.

127 Ahmed M E, Afifi M I and Younos I H, *Harpagophytum Procumbens* (Devil's Claw): A possible natural anti-inflammatory agent (An experimental study), *Iran J Pharmacol Therapeu,* 2005, **4**, 54–63.

128 Grant L, McBean D E, Fyfe L and Warnock A M, The inhibition of free radical generation by preparations of *Harpagophytum procumbens in vitro*, *Phytotherapy Res,* 2009, **23**, 104–10.

129 Schulze – Tanzil G, Hansen C and Shakibaei M, Effect of *Harpagophytum procumbent DC* extract on matric metalloproteinases in human chondrocytes *in vitro*, *Arzeneimittel – Forschung,* 2004, **54**, 213- 20.

130 Fiebich B L, Heinrich M, Miller K Q and Krammerer N, Inhibition of TNF – α synthesis in LPS – stimulated human monocytes by *Harpagophytum* extract steilta p69, *Phytomedicine,* 2001, **8**, 28- 30.

131 Jang M H, Lim S, Han S M, Park H J, Shin I, Kim J W, *et al*., *Harphagophytum procumbens* suppresses LPS – stimulated expression of COX – 2 and iNOS in fibroblast cell line I 929, *J Pharmacol Sci,* 2003, **93**, 367-71.

132 Chen R C, Su J H, Yang S M, Li J, Wang T J and Zhou H, Effect of isoverbascoside, a phenyl propanoid glycoside anti-oxidant on proliferation and differentiation of human gastric cancer cells, *Acta Pharmacol,* 2002, **23**, 997-01.

133 Kundu J K, Mossanda K S, Na H K, and Surh Y J, Inhibitory effects of the extracts of *Sutherlandia fruteescess (L) R and Harpagophytum procumbens* DC on phorbol ester induced COX – 2 expression in mouse skin: AP – 1 & CREB as potential upstream target, *Cancer Lett,* 2005, **218**, 21-31.

134 Huang H, Inhibition of estrogen receptor – α expression and function in MCF – 7 cells by kaempferol, *J Cell Physiol,* 2004, **198**, 197-08.

135 Chen A Y and Chen Y C, A review of the dietary flavonoid, kaempferol on human health and cancer prevention, *Food Chem,* 2013, **138**(4), 2099-07.

136 Lu O H, Rankin G O, Liu L, Daddysman M K, Jiang B H and Charlie C, Kaempferol inhibits angiogenesis and VEGF expression

through both HIF dependent and independent pathways in human ovarian cancer cells, *Nutr Cancer,* 2009, **61**(4), 554-63.

137 Tatsimo S J N, Tamokou J D, Havyarimana L, Caspor D, Forgo P F, Hohman J, *et al*., Antibacterial and anti-oxidant activity of kaempferol rhamnoside derivatives from *Bryophyllum pinnatum, BMC Res Notes,* 2012, **5**, 158-64.

138 Zhao G, Qin G W, Wang J, Chu W J and Guo L H, Functional activation of monoamine transporters by luteolin and apigenin isolated from the fruit of *Perilla frutescenes (L), Britt Neurochem Int,* 2010, **56**(1), 168-76.

139 Lin Y, Shi R, Wang X and Shen H M, Luteolin, a flavonoid with potentials for cancer prevention and therapy, *Curr Cancer Drug Targets,* 2008, **8**(7), 634-46.

140 Chen D, Bi A, Dong X, Jiang Y, Rui B, Liu J, *et al.,* Luteolin exhibits anti-inflammatory effects by blocking the activity of heat-shock protein 90 in macrophages, *Biochem Biophys Res Comm,* 2014, **443**(1), 326-32.

141 Nabafi S F, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daqila M, Shalika – Wojniak K et al, Luteolin as an anti-inflammatory and protective agent – A brief review, *Brain Res Bull,* 2015, **119**, 1–11.

142 Onakpoya I J, Spencer E A, Thompson M J and Heneqhan C J, The effect of chlorogenic acid on blood pressure – A systematic review and meta-analysis of randomized clinical trials. *J Hum Hypertens,* 2015, **29**(2), 77- 81.

143 Stacewicz- Sapuntzakis M, Bowen P E, Hussein E A, Damayanti – Wood B I and Farnsworth N R, Chemical composition and potential health effects of prunes- a functional food, *Crit Rev Food Sci Nutr,* 2001, **41**(4), 251-86.

144 Freedman S O, Shulman R, Krupey J and Sehon A H, Antigenic properties of chlorogenic acid, *J Allergy,* 1964, **35**(2), 97-07.

145 Madan R K and Levitt J, In "*A review of toxicity from topical salicylic acid preparations*", *J Am Acad Dermatol,* 2014, **70**(4), 788-92.

146 Anti-inflammatory activity of aspirin – It's all about Salicylic acid, *Am Chem Soc,* www.cas.org/news/insights/science-connections/aspirin.

147 Ai G, Dachineni R, Muley P, Tummala H and Bhat G J, Aspirin and salicylic acid decreases c-Myc expression in cancer cells: a potential role in chemo-prevention, *Tumor Biol,* 2015, **28**, 1-12.

148 Freitas S, Costa S, Azevedo C, Carvalho G, Freira S, Barbosa P, *et al*, Flavonoids inhibit angiogenic cytokine production in human glioma cells, *Phytotherp, Res.* 2011, **25**(6), 916-21.

149 Gonçalves C F, dos Santos M C, Ginabreda M G, Fortunato R S, de Carvalho D P and Ferreira A C, Flavonoid rutin increases thyroid iodide uptake in rats, PloS one, 2013, **8**(9), e73908.

150 Katavic P L, Lamb K, Navarro H and Prisinzano T E, Falvonoids as opoid receptor ligands: Identification and preliminary structure – activity relationship, *J Nat Prod,* 2007, **70**(8), 1278- 82.

151 Mahdi J G, Medicinal potential of willow: A chemical perspective of aspirin discovery, *J Saudi. Chem Soc,* 2010, **14**, 317-22.

152 Willow Bark. www.drugs.com/npp/willow-bark.html.

153 Evening primrose oil for rheumatic arthritis. www.naturalar thritistreatments.net

154 Farzaneh F, Fatehi S, Sohrabi M R and Alizadeh K, The effect of oral Evening Primrose Oil on menopausal hot flashes: a randomized clinical trial, *Arch Gynecol Obstet,* 2013, **288**(5), 1075-79.

155 Morse N L and Clough P M, A meta-analysis of randomized, placebo-controlled clinical trials of Efamol Evening Primrose Oil in atopic eczema, where do we go from here in light of more recent discoveries? *Curr Pharm Biotechnol,* 2006, **7(6**), 503-24.

156 Ringbom T, Huss U, Stenholm A, Flock S, Skattebol L, Perrera P, *et al.*, Cox -1 and Cox -2 inhibitory effects of naturally occurring and modified fatty acids, *J Nat Prod,* 2001, **64**, 745-49.

157 King M W, Introduction to the Eicosanoids, In "*The medical Biochemistry page*" 2013, 1996–2013. http://themedical BiochemistryPage.org/eicosanoids.

158 Chung B Y, Kim J H, Cho S I, Ahu I S, Kim H O, Park C W, *et al*., Dose-dependent effects of Evening Primrose Oil in children and adolescents with atopic dermatitis, *Ann Dermatol,* 2013, **25**(3), 285-91.

159 Vane J, The evolution of non-steroidal anti-inflammatory drugs and their mechanism of actions, *Drugs,* 1987, **33**(1), 18-27.

160 Murakani E M, Yamada H, Ishii O and Igarashi R, Treatment of established collagen induced arthritis with PGE1, *J Rheumatol.* 2000, **27**(10**),** 2389-96.

161 Juniper berries. www.rjwhelan.co.nz/herbs.

162 Juniper – Uses and side effects. http://ezinearticles.com/? Juniperusesandsideeffects.

163 ESCOP. *Urticae Folium / Herba* (Nettle leaf), In *Phytoptherapy, EESCO*, edited by ESCOP Monographs / Fascicule 4. Exeter: ESCOP, 1997, 58-60.

164 Obertreis B, Ruttkowski T, Tencher T, Behnke B and Schmitz H, Ex-vivo in vitro inhibition of LPS stimulated TNF – α and IL-1β secretion in human whole blood by *extractum Urticae Dioicae Foliorum*, *Arzenimittel – Forschung,* 1996, **46**(4)**,** 389-94.

165 Sokeland J, Combined Sabal and Urtica extract compared with Finasteride in men with benign prostatic hyperplasia: Analysis of prostate volume and therapeutic outcome, *Brit J Urol Int,* 2000, **86**(4), 439-42.

166 Chaurasia N and Wichtl M, Flavonglykoside aus *Urtica Dioica*, *Planta Medica.* 1987, **53**, 424 -32.

167 Chaurasia N and Wichtl M, Sterols and steryl-glycosides from *Urtica Dioica, J Nat Prod.* 1987, **50**, 881-85.

168 Mikhaeil B R, Matooq G T, Badria F A and Amer M M A, Chemistry and immunomodulatory activity of frankincense oil, *Z Natfurforsch*. 2003, **58C**, 230- 38.

169 Pnadey R S, Singh B K and Tripathi Y B, Extract of gum resins of *Boswellia Serrata L* inhibits LPS induced NO production in rat macrophages along with hypo-lipidemic property. *Indian J Expt Biol.* 2005, **43**, 509-16.

170 Ammon H P T, Singh T and Safayhi H, Inhibition of LTB4 formation in rat peritoneal neutrophils by ethanolic extract of gum resin exudate of *Boswellia Serrata*. *Planta Med.* 1991, **57**, 203–07.

171 Gupta I, Parihar A, Malhotra P, Singh G B, Ludtke R, Safayhi H et al, Effects of *Boswellia Serrata* gum resin in patients with ulcerative colitis. *Eur J Med Res.* 1997, **2**, 37-43.

172 Safayhi H, Sailer E R and Ammon H P T, Mechanism of 5 – LOX inhibition by Acetyl – 11- keto – Boswellic acid, *Mol Pharmacol.* 1995, **47**, 1212-16.

173 Singh G B and Atal C K, Pharmacology of an extract of *Salai Guggal Ex-Boswellia Serrata*, a new non-steroidal anti-inflammatory agent, *Agents Actions,* 1986, **18**, 407-12.