A Review: Herbal Anti-inflammatory drugs and its medicinal constituents.

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***Abstract*: Diseases associated with inflammatory etiopathology have increased recently. Medicines used to treat such tumors relieve the disease while combating life-threatening consequences. Anti-inflammatory drugs or herbs range from conventional to wild forest plants or herbal plants. It has been studied, evaluated and proven or udertrial for its anti-inflammatory activity. Recent patents on anti-inflammatory and herbal medicine provide insight into the current state and future of this field.**

***Keywords*: Herbal Medicines, NSAID's, Anti-Inflammatory, Medicinal constituents.**

INTRODUCTION:

Immunity is the body's primary defense mechanism against exogenous stimuli such as injury or pathogen infection. Immunity is an important immune system that allows the body to survive during injury [1,2]. Since immunity plays an important role in regeneration, healing, and aggressive processes, it is considered a beneficial pathological process in combating pathogen-induced stresses and toxic conditions [3,4,5]. The inflammatory process involves complex and multicellular reactions and is mainly divided into acute and chronic inflammation [6]. Although immunity protects the body through wound healing and resistance to microbial invasion, chronic inflammation targets critical cells, tissues, and organs leading to the development of various chronic pathologies, including cardiovascular disease, skeletal muscle disorders, and intestinal disease. Diabetes, cancer and neurological diseases accelerate aging [6,7,8]. There are mainly two types of tumors for example.

• Acute inflammation:

This is associated with increased vascular permeability, capillary infiltration and leukocyte emigration.

• Chronic inflammation:

Monoandrogen activation is associated with proliferation (angiogenesis) and fibrosis of immune cells, including macrophages, monocytes, neutrophils, and fibroblasts. Rheumatoid arthritis is a common clinical condition and rheumatoid arthritis (RA) is a chronic autoimmune disease affecting approximately 1% of the population in developed countries [10]. The classic symptoms of an abscess are local redness, swelling, pain, warmth, and loss of function [11]. Nitric oxide (NO), a short-lived free radical gas, ameliorates acute inflammation and has been shown to modulate inflammatory biosynthesis or NO activity in experimental arthritis models [12,13]. NO, L-arginine is not formed by oxidation of the terminal guanidine nitrogen atom by the enzyme nitric oxide synthase (NOS).

Three main isoforms of nitric oxide synthase (NOS) have been identified. There are two constitutive, calcium / cal independent modules, the constitutive NOS isoforms (cNOS). Third, the calcium/cal module in the cytokine-independent NOS (iNOS) isoform is regulated by various inflammatory mediators [14]. Neither increased NOS activity nor NO release has been shown in OSI and chronic inflammation models [15]. Furthermore, the administration of Larginine, a precursor of NO synthesis, increased paw swelling in rheumatoid arthritis [14]. NSAIDs are one of the most widely used drugs in the world. Osteoarthritis, soft tissue injuries and fractures etc. indicated for orthopedic conditions [16]. Ibuprofen and Naproxen etc. NSAIDs like NSAIDs are used in the conditions mentioned above. Another group of drugs are glucocorticoids, such as cortisone and prednisone. However, in addition to their high cost, there are serious side effects and toxicities, including the risk of infection in some patients treated with biological response modifiers such as tumor necrosis factor alpha-blocking agents [17]. Adverse effects of current medications include GI ulcers and bleeding, kidney damage, hypertension, and hyperglycemia. In addition to the above side effects, the biggest weakness of the powerful synthetic drugs available today is their toxicity and subsequent withdrawal

symptoms. Therefore, screening and development of drugs for anti-inflammatory activity is the need of the hour and many efforts are being made to find anti-inflammatory drugs from indigenous medicinal plants [18].
Anti-inflammatory drugs or herbs to traditional wild forest plants or herbal plants. It has been studied, evaluated and proven or under trial for its anti-inflammatory activity. All over the world, such plants grow naturally or are cultivated exclusively for this purpose. Advances in herbs and effective herbs will appear, but a list of commonly used or proven anti-inflammatory herbs and their active ingredients will be useful, and for this purpose [19,20] some herbal remedies are as follows:

1. Oenothera biennis (Evening Primrose):

Borago officinalis (commonly known as Borage and Borraja) is a member of the family Boraginaceae and is native to regions of Europe and northern Africa [21].

This plant is a source of gamma linoleic acid (GLA), containing 25% GLA, by increasing the level of prostaglandin-E (PGE), which causes an increase in cyclic adenosine monophosphate (CAMP); GLA can act as a potent suppressor of TNF-α. The aforementioned mechanism may explain the anti-inflammatory effect of borate oil in rheumatoid arthritis (RA). Regarding this route, it is contraindicated during pregnancy [22].

The antirheumatoid arthritis potential of borage seed oil was evaluated in 2 RCTs as follows: the first study compared borage seed oil 1.4 g daily with placebo in RA patients; At the end of 6 months of treatment, there was an improvement of 36.8% in the treatment group. In the second study, patients received 2.8 g of borage seed oil per day for 6 months; At the end of treatment, amelioration of RA incidence was observed: 64% in the treatment group compared to 21% in the control group [23]. Similarly, the anti-inflammatory effect of boron oil was tested in patients with atopic dermatitis. 12 clinical trials were conducted to evaluate the ameliorative effect of this plant in atopic dermatitis. Of these, 5 showed an anti-inflammatory effect, 2 reported improvement in some patients, and the remaining 5 trials had no control for remission [24].

Medicinal constituents: Flavonoids, phenolic acids and triterpenoids are commonly found in this species [22-24].

Figure 1: Oenothera biennis (Evening Primrose)

2. Curcuma longa:

Curcuma longa (common name Turmeric, Curcuma and Haldi) is a native plant of India. The most important secondary metabolite of C. longa is curcumin, which is responsible for the anti-inflammatory effect of this plant [25,26].

Many clinical trials have been conducted to prove curcumin's anti-inflammatory effects. The results show that curcumin can be effective in improving the inflammation of rheumatoid arthritis (RA) and reducing the clinical manifestations of RA such as joint swelling and morning stiffness compared to phenylbutazone used as a positive control [27]. Additionally, curcumin has previously been tested in patients with uveitis; Complete remission occurred after 2 weeks

[28]. The effectiveness of curcumin in patients with dyspepsia and/or peptic ulcer has been proven by other clinical trials. In this study, after 12 weeks (maximum), subjects experienced remission [29]. Curcumin is useful in the treatment of irritable bowel syndrome (IBS) and acts as an agent to reduce delayed renal function (DGR) after kidney transplant surgery [30]. Curcumin has beneficial effects in the prevention of inflammatory bowel disease (IBD) and in reducing the level of sediment in patients suffering from IBD [31]. It has also been shown to be beneficial in improving ulcerative colitis and psoriasis (by selectively inhibiting phosphorylase kinase) [32].

Medicinal constituents: Turmeric contains three curcuminoids: curcumin (diferuloylmethane; the main component responsible for its vibrant yellow color), demethoxycurcumin, bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zinger protein). and resin [27,30,32].

Figure 2: Curcuma longa

3. Rosmarinus officinalis:

Rosmarinus officinalis (common name Rosemary and Romero) comes from the Mediterranean [33].

An open-label trial evaluated the effects of rosemary extract in patients with osteoarthritis (OA), rheumatoid arthritis (RA), and fibromyalgia over a 4-week period; hs-CRP (an indicator of the presence of inflammation) was significantly reduced in patients who showed an increase in this index; Notably, there was a reduction in inflammation associated with pain scores during treatment, but no remission in fibromyalgia scores [34]. At the molecular level, there is evidence supporting the anti-inflammatory potential of R. officinalis; accordingly, rosmarinic acid can inhibit the activation of the complement system by inhibiting C3b binding; the dose required to produce this effect is very low (34 µM) [35]. In addition, elderberry extract shows gastric protective activity against stomach ulcers, even better than Omeprazole; This advantage is attributed to the activity of pepper in the infiltration of neutrophils and reduced pro-inflammatory mediators: TNF-α and IL-1 [36]. However, in another study in mice, a high dose (500 mg/kg) of rosemary extract reduced testosterone and spermatogenesis leading to infertility [37]. This plant is an important anti-inflammatory agent in wound healing in mice [38]. Carnosic acid in R. officinalis interacts with CYP3A4 and CYP2B6 substrates and thus exhibits toxicity in human hepatocytes with EC50 values similar to Tamoxifen [39].

Medicinal Constituents: The main components of the essential oil are camphor, 1,8-cineole, α-pinene, borneol, camphene, β-pinene and limonene [33-38].

Figure 3: Rosmarinus officinalis

4. Borago officinalis:

Borago officinalis (commonly known as Borage and Borraja) is a member of the Boraginaceae family and is native to regions of Europe and northern Africa [40].

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Medicinal constituents: The chemical constituents of borage leaves and flowers include mucil, tannins, saponins, essential oils, alkaloids (pyrrolizidine), vitamin C, calcium and potassium [41,43].

Figure 4: Borago officinalis

5. Harpagophytum procumbens (Devil's Claw):

H. procumbens (commonly known as Devil's Claw and Garra del Diablo) is a member of the Pedaliaceae family [44].

Among many metabolites, Harpagoside has been proven as an anti-inflammatory component [45]. Devil's claw root extract has been shown to have the potential to inhibit NO, inflammatory cytokines (IL-6, IL-1β, and TNF-α), and PGE2, as well as arachidonic acid metabolism and eicosanoid biosynthesis. -2 inhibition and reduced inflammation [46]. In another preliminary study, devil's claw had no effect on increasing carrageenan edema in the hind paw of rats [47]. An RCT evaluated the effect of Devil's Claw in osteoarthritis. The anti-inflammatory effects of H. procumbens were observed at the end of the treatment period [48]. In contrast, in a pilot study of patients suffering from arthritis (RA and psoriatic arthropathy), researchers did not observe any remission or subjective or objective improvement with 410 mg TDS of liquid extract of H. procumbens after 12 days. week [49]. Gastrointestinal disorders are the main side effects of this plant, so it is contraindicated in patients with gastric or duodenal ulcers, gallstones, and diabetes [50].

Medicinal constituents: The main components of Harpagophyte are iridoid glycosides, phytosterols, aromatic acids and flavonoids [44].

Figure 5: Harpagophytum procumbens (Devil's Claw):

6. Persea americana/Glycine max:

Persea americana (common name Avocado, arbol, and Ruchira) is a fruit native to Central America [51] and belongs to the Lauraceae family. Glycine max (common name soybean and soybean) is a member of the Fabaceae family native to East Asia.

In a prospective, multicenter, 3-month randomized control trial, 153 OA patients were enrolled and treated with avocado/soy anti-aging agent (ASU) in combination with NSAIDs; After 45 days of treatment, the need for NSAIDs decreased, but there was no significant change in the patients' pain score [52]. Three clinical trials in OA patients evaluated the efficacy of ASU. Two of them showed reduced Lequesne function index (LFI), pain and disability; similarly, NSAID requirements greater than 50% were recorded in 71% of patients in the disease group and 36% in the control group, but there was no group change in the joint space (JSW) in the final examination. this was considered as the primary end point and no improvement was reported in clinical trials [53]. In the 3-year follow-up of liver OA patients receiving ASU, there was no improvement in JSW, but 20% prevention of JSW exacerbation [54]. ASU was also administered to 100 patients with linear scleroderma and morphine; This study shows the beneficial effect of ASU in preventing atrophy, deformity, and contracture if treatment with ASU is initiated at an early stage of the disease [55]. Topical and dietary administration of avocado and soybean extracts were evaluated in patients with mild to moderate vulvar lichen sclerosis (VLS). At the end of 24 weeks of the treatment period, the main symptoms and symptoms of the disease are significantly reduced [56].

Medicinal Constituents: Major Medicinal Constituents in Persea America Flavonoids, especially C-glycosyl flavones such as orientin, isoorientin, vitexin, and isovitexin, are the major metabolites reported in Persea seeds [54,55,56].

Figure 6: Persea americana/Glycine max

7. Olea europaea:

Olea europaea (commonly called Olive, Olivera, and Jaitun) is a species of the Oleaceae family [57].

The positive effects of extra virgin olive oil (EVOO) on modulating postprandial plasma lipopolysaccharide, pro-inflammatory cytokines, TXB2 and LTB4, and reducing the risk of coronary heart disease have been demonstrated in healthy subjects and patients with metabolic syndrome [57,58]. Oral olive oil accelerates the wound healing process and shortens the length of hospitalization in patients with second-degree and more severe burns compared to sunflower oil (SFO) [59]. In addition, compared to mice fed with EVOO SFO, the expression of colorectal cancer and anti-tumor cytokine activity in mice with ulcerative colitis was alleviated after consumption of EVOO-enriched diet [60].

Medicinal Constituents: Fruits and seeds. O. europaea fruits contain a significant amount of flavonoids, secoiridoids, secoiridoid glycosides and phenolics such as tyrosol, hydroxytyrosol and their derivatives [57-60].

Figure 7: Olea europaea

8. Zingiber officinale:

Zingiber officinale (commonly known as ginger) is a plant native to Southeast Asia [61].

Oral administration of Z. officinale extract has shown variable and inconsistent effects depending on the amount of consumption. Although single or double administration of compressed ginger extract to mice increased tumor necrosis factor (TNF-α) in peritoneal cells, long-term consumption of the extract increased serum corticosterone levels and decreased anti-inflammatory markers [62]. Z. officinale has also been tested in type 2 diabetes with low-grade inflammation; After 2 months of treatment, serum levels of TNF-α and high sensitivity C-reactive protein (hs-CRP) significantly decreased [61]. In patients with osteoarthritis, zinc is not only effective in improving pain similar to Diclofenac 100 mg, but also has no side effects [63]. clove extract was compared with Ibuprofen and Indomethacin in OA patients; The results showed that Ibuprofen, Indomethacin and ginger extract increased the same level of pain [64,65]. Ginger powder has ameliorative effects in musculoskeletal and arthritis patients by inhibiting cyclooxygenase and lipoxygenase pathways in the synovial fluid [66].

Medicinal constituents: include vanilloid, monoterpenes, sesquiterpenes, diterpenes, flavonoids, amino acids, etc. including [61].

Figure 8: Zingiber officinale (Ginger)

9. Ribes nigrum:

Ribes nigrum (common name is blackcurrant and Casis) oil is a rich source of n-6 polyunsaturated fatty acid (PUFA), γ-linoleic acid, and α-linoleic acid [67].

In one clinical trial which has been fulfilled on RA patients during 6 weeks, researchers have investigated the effect of blackcurrant oil (BCO) on patients; outcomes were as follows: attenuation in morning stiffness in the experimental group and reduction in pro-inflammatory mediators including IL-1β and TNF-α in peripheral blood monocytes [68]. After 24 weeks of treatment period with BC seed oil, disease activity symptoms of RA patients have been reduced. Overall, no significant differences in clinical signs and symptoms have been recorded between the placebo and the case group [69]. Also, BC seed oil has a moderate reinforcement effect on the immune response and inhibitory effect on the PGE2 biosynthesis in 40 healthy volunteers older than 65 years [67]. In another clinical study, 12 healthy subjects have consumed BC oil; attenuating in LTB4 biosynthesis via polymorphonuclear-neutrophil (PMN) and increasing of dihomo-γ-linoleic acid in PMN's phospholipids have been observed [70]. BC skin extract could reduce heat shock protein (HSP70 and HSP90), COX-2, and NF-κB expression in rats which were under diethylnitrosamine (hepatocarcinogen) exposure [71].

Medicinal constituents: Ribes nigrumare are also a good source of vitamins and minerals, including vitamin C, potassium, fiber, and calcium [67].

Figure 9: Ribes nigrum

10. Borago officinalis:

Borago officinalis (commonly known as Borage and Borraja) is a member of the Boraginaceae family and is native to regions of Europe and northern Africa [72].

This plant is a source of gamma linoleic acid (GLA), containing 25% GLA, by increasing the level of prostaglandin-E (PGE), which causes an increase in cyclic adenosine monophosphate (CAMP); GLA can act as a potent suppressor of TNF-α. The aforementioned mechanism may explain the anti-inflammatory effect of borate oil in rheumatoid arthritis (RA). Regarding this route, it is contraindicated during pregnancy [73]. The antirheumatoid arthritis potential of borage seed oil was evaluated in 2 RCTs as follows: the first study compared borage seed oil 1.4 g daily with placebo in RA patients; At the end of 6 months of treatment, there was an improvement of 36.8% in the treatment group. In the second study, patients received 2.8 g of borage seed oil per day for 6 months; showed the rate of amelioration of RA incidence at the end of treatment: 64% in the treatment group compared to 21% in the control group [74]. Similarly, the anti-inflammatory effect of boron oil was tested in patients with atopic dermatitis. 12 clinical trials were conducted to evaluate the ameliorative effect of this plant in atopic dermatitis. Of these, 5 showed an anti-inflammatory effect, 2 reported improvement in some patients, and the remaining 5 trials had no control for remission [75].

Medicinal constituents: The main chemical constituents of borage leaves and flowers include mucil, tannins, saponins, essential oils, alkaloids (pyrrolizidine), vitamin C, calcium and potassium [73,75].

Figure 10: Borago officinalis

11. Vaccinium myrtillus:

Vaccinium myrtillus (commonly known as bilberry and arandano) is a member of the vaccinia family [76].

In a randomized clinical trial of 27 patients with metabolic syndrome who received 400 g of fresh bilberry per day, the results were reported to be: hs-CRP, IL-6, IL-12 and circulating LPS concentrations in the active group [77]. Bilberry induced remission in 63.4% of 13 cases of ulcerative colitis after 6 weeks, with significant reductions in the Mayo score and fecal immunity [78]. After daily administration of one capsule of concentrated bilberry extract (36% w/w anthocyanins), no changes were observed in anti-inflammatory peptide (monocyte chemotactic protein-1) in diabetes [79].

Medicinal constituents: Vaccinium myrtillus contains various phenolic compounds such as flavonols (quercetin, catechin), tannins, ellagitannins and phenolic acids [76].

Figure 11: Vaccinium myrtillus

12. Urtica dioica:

Urtica dioica (common name nettle and Ortigamayor) is a member of the Urticaceae family [80].

In an experimental study, nettle leaves were investigated for their anti-inflammatory effects. Patients with acute arthritis were given Diclofenac 50 mg per day along with Urtica dioica 50 mg oral infusion. This treatment resulted in a significant improvement in CRP levels and some patients complained of diclofenac 200 mg daily; according to these results, U. dioica has an extraordinary synergistic effect when combined with NSAIDs [81]. The primary efficacy of breadcrumbs was evaluated in an RCT in osteoarthritis of the toe; Significant relief in pain, stiffness, and the requirement of anti-inflammatory and analgesic treatment was observed [82]. The combination of breadfruit leaves and rose and bark suppressed IL-1β and COX-2 in chondrocytes. In this in vitro study, the chondroprotective and anti-inflammatory effects of this botanical extract were proven [83]. U. dioica leaf extract has the potential to inhibit the anti-inflammatory transcription factor NF-κB (scientific studies have shown that NF-κB is elevated in the synovial fluid of RA patients) [84]. This extract has anti-inflammatory potential in allergic rhinitis through the following pathways: antagonizing H1 receptors, reducing the production of PGD2 (prostaglandin specific to allergies) and an inhibitory effect on mast cell tryptase [85].

Medicinal constituents: This plant contains many phytochemicals including phenolic compounds, sterols, fatty acids, alkaloids, terpenoids, flavonoids and lignans [80-85].

Figure 12: Urtica dioica

13. Uncaria tomentosa:

U. tomentosa is often called cat's claw and una de gato. It belongs to the Rubiaceae family and is native to the Amazonian and Central American forests [86].

The effectiveness and safety of this plant in improving knee OA was tested in 45 patients divided into 2 groups (placebo and active); active group showed some degree of remission after 4 weeks with inhibition of TNF-α and reduced production of PGE2 [87]. In a 24-week double-blind placebo-controlled trial to evaluate the efficacy of a highly purified

extract of U. tomentosa in RA patients, this extract was given in combination with Sulfasalazine or Hydroxychloroquine; Compared to the placebo group, this herb showed a modest benefit in reducing pain, swelling, and tenderness in the treatment group [88]. U. tomentosa has been reported to induce a remarkable remission in enteritis in mice [89]. Edible cat's claw extract has a protective effect against airway inflammation in mice [90]. The underlying mechanism of cat's claw is TNF-α, IL-1α, 1β, 10 and 17 sequential iNOS and NF-κB regulated. Also, the low inhibitory effect on COX-1 and COX-2 was demonstrated by in vivo assay [86,89]. The bark of this plant showed anti-inflammatory activity similar to that of dexamethasone in animal models, inhibiting about 40% of IL-4 in the absence of dexamethasone [91].

Medicinal components: the main components include spiroindole alkaloid isopteropodine and rhynphophyllin [86,88].

Figure 13: Uncaria tomentosa

14. Elaeagnus angustifolia:

E. angustifolia (common name Oleaster) is a member of the Elaeagnaceae family [92].

The efficacy of oleaster in the treatment of oral cavity (OLP) lesions was evaluated in an RCT with 28 patients. Seventy-five percent and 50-75% of pain and lesion size, respectively, occurred in the working group [92]. Another randomized clinical trial in 90 female knee OA patients reported reductions in TNF-α and matrix metalloprotein-1 (MMP-1) (anti-inflammatory mediators) and IL-10 (an anti-inflammatory cytokine) in the active treatment group. 93]. Oleaster extract showed an anti-inflammatory effect in animal models, but this effect was not significant compared to sodium salicylate [94]. The aqueous extract of this fruit showed anti-inflammatory properties in mice through inhibition of COX-1 and COX-2; evidence shows no correlation between corticosterone levels and anti-inflammatory activity [95].

Medicinal constituents: Mainly contains iron, tin, copper, cadmium, zinc, chromium, nickel and cobalt. [92].

Figure 14: Elaeagnus angustifolia

CONCLUSION: Natural herbs are a safe, effective and better choice as anti-inflammatory agents than synthetic ones. Effective phytoconstituents with comparable mechanisms of action as synthetic molecules. Future research should focus on the molecular mechanisms of the use of these herbal plants in various diseases. Recent patents on anti-inflammatory and herbal medicine provide insight into the current state and future of this field.

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