Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

Original Article

Herbs Alternative to Non-Steroidal Anti-Inflammatory Agents

Nidhi Sodha[1]*, Pillai Kousalya[1], Nadim Chhipa[2], Pragnesh Patani[3]

[1]*Department of Pharmacy, Khyati College of Pharmacy, Palodia, Ahmedabad

[2]Associate Professor, Department of Pharmaceutical Chemistry, Khyati College of Pharmacy, Palodia, Ahmedabad

[3]Principal and Professor, Department of Pharmacology, Khyati college of Pharmacy, Palodia, Ahmedabad

***Corresponding Author:** Nidhi Sodha
*Department of Pharmacy, Khyati College of Pharmacy, Palodia, Ahmedabad,
Email: nidhisodha782003@gmail.com

Abstract
Non-Steroidal Anti-inflammatory drugs (NSAIDs) are commonly prescribed to treat inflammation, pain, and related conditions, but their prolonged use often leads to side effects, including gastrointestinal issues, cardiovascular risks, and renal impairment. Herbal alternatives have gained increasing attention due to their natural anti-inflammatory properties and minimal adverse effects. This review explores several herbs as potential alternatives to NSAIDs, including Turmeric (Curcuma longa), Ginger (Zingiber officinale), Garlic (Allium sativum), Boswellia (Boswellia serrata), Licorice (Glycyrrhiza glabra), Cinnamon (Cinnamomum verum), and Khirni fruit (Manilkara hexandra). These herbs exhibit anti-inflammatory effects by modulating key inflammatory pathways such as COX-2 inhibition, cytokine regulation, and antioxidant activity. Turmeric, rich in curcumin, has been shown to suppress pro-inflammatory cytokines and enzymes. Ginger and garlic are recognized for their dual role in inhibiting COX enzymes and reducing oxidative stress. Boswellia offers potent anti-inflammatory effects by inhibiting 5-lipoxygenase, while licorice has demonstrated both COX and LOX inhibition. Cinnamon's anti-inflammatory benefits are attributed to its polyphenolic compounds, and Khirni fruit has shown promise in reducing inflammation due to its antioxidant properties. These herbs represent a promising alternative to NSAIDs, offering therapeutic benefits with a reduced risk of adverse effects.

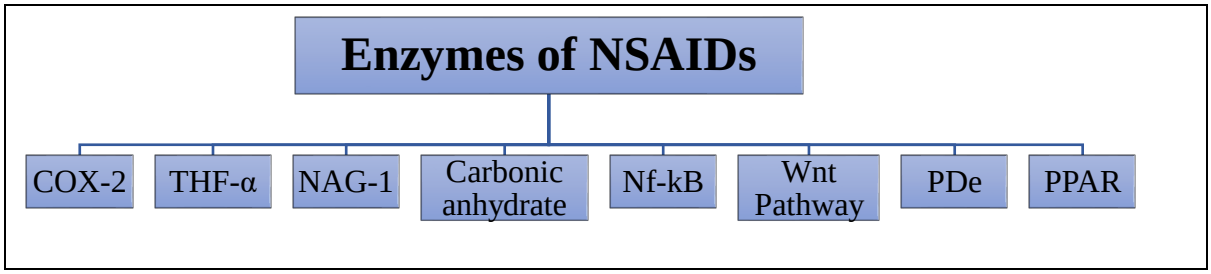
Keywords: Herbal, Anti-Inflammatory, Pain, Side effect, Adverse Drug, NSAID Alternatives including Turmeric, Ginger, Garlic, Boswellia, Licorice, Cinnamon, Khirni fruit, COX inhibition, LOX inhibition, Inflammation, Natural medicine

Introduction
Inflammation
In higher organisms, inflammation is a defence mechanism that evolved in response to harmful insults like microbial infection, tissue injury, and other harmful conditions. It is a necessary immune response from the host that enables the healing of damaged tissue and the removal of harmful stimuli. For hundreds of years, redness, pain, swelling, and heat have been the traditional signs of inflammation. [1]

Non-Steroidal Anti-Inflammatory Agents
The FDA has granted approval for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as analgesics, anti-inflammatory, and antipyretics. [2] Because of these effects, NSAIDs are useful for

treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and some acute trauma cases as opioid-sparing agents. [3,4,5]

Acetylated salicylates (like aspirin), non-acetylated salicylates (like diflunisal and salsa late), propionic acids (like naproxen and ibuprofen), acetic acids (like diclofenac and indomethacin), enolic acids (like meloxicam and piroxicam), anthranilic acids (like meclofenamate and mefenamic acid), naphthyl alanine (nabumetone), and selective COX-2 inhibitors (celecoxib etoricoxib).Also available for use in acute tenosynovitis, ankle sprains, and soft tissue injuries are topical NSAIDs (diclofenac gel). [6,7,8,9]



Mechanism of action Cyclooxygenase (COX)

The inhibition of the enzyme cyclooxygenase (COX) is the main way that NSAIDs work. Arachidonic acid can only be converted into thromboxane, prostaglandins, and prostacyclin by cyclooxygenase. [10] The absence of these eicosanoids is credited with the therapeutic effects of NSAIDs. Prostaglandins are responsible for vasodilation, increase the temperature setpoint in the hypothalamus, and contribute to anti-nociception, while thromboxane are involved in platelet adhesion.[11]

COX-1 and COX-2 are the two cyclooxygenase isoenzymes. The gastrointestinal mucosa lining, kidney function, and platelet aggregation are all aided by COX-1, which is expressed continuously throughout the body. The body does not produce COX-2 by itself; rather, it produces it inducible during an inflammatory response. The majority of nonselective NSAIDs block both COX-1 and COX-2. However, COX-2 selective NSAIDs, such as celecoxib, only target COX-2, resulting in a distinct set of adverse effects. Importantly, COX-2 selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa because COX-1 is the primary mediator for maintaining gastric mucosal integrity and COX-2 is primarily involved in inflammation. [11]

Mechanism of action Tumour Necrosis Factor alpha (TNF-α)

A cytokine known as tumour necrosis factor alpha (TNF-α) has pleiotropic effects on various types of cells It has been shown to play a significant role in regulating inflammatory responses. furthermore, is known to be associated with the pathogenesis of some provocative and immune system illnesses [12]. TNF-α is a 157-amino acid homotrimer protein in terms of structure, primarily produced by natural killer cells, T-lymphocytes, and activated macrophages [13]. It is known to activate a number of different inflammatory molecules, including chemokines and other cytokines TNF-α exists in a solvent and transmembrane structure. The transmembrane TNF-α(tmTNF-α) is the at first blended forerunner structure and is expected to be handled by TNF-α - changing over protein (TACE), a layer bound to be released as soluble TNF-α (sTNF-α) disintegrin metalloproteinase [14].

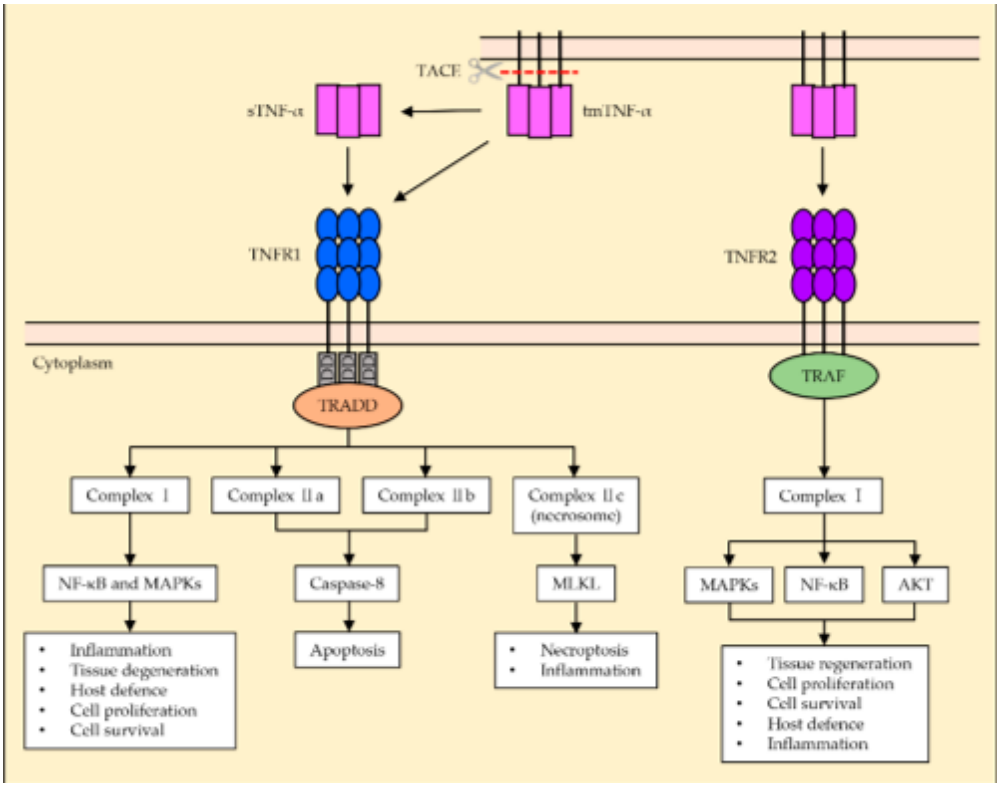


Figure 1. **General tumour necrosis factor alpha (TNF-) signalling pathway of TNFR1 and TNFR2.**

Adverse Effect

NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

1. **Gastric Effect -** The inhibition of COX-1, which prevents the production of prostaglandins that protect the gastric mucosa, is probably to blame for the side effects in the stomach. Patients who have had peptic ulcers in the past are more likely to sustain damage. The use of COX-2 selective NSAIDs, which are COX-1 specific, is a less risky alternative. [15]
2. **Renal effect** - The production of prostaglandins, which are involved in renal hemodynamic, is facilitated by COX-1 and COX-2, which is the cause of renal adverse effects. Inhibition of prostaglandin synthesis does not pose a significant problem in a patient with normal renal function; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the cause of issues when reduced with NSAIDs. Acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/interstitial nephritis are all potential complications.[16]
3. **Cardiovascular effect** - MI, thromboembolic events, and atrial fibrillation are all cardiovascular adverse effects that can be exacerbated by taking NSAIDs. Diclofenac is by all accounts the NSAID with the most noteworthy announced expansion in unfriendly cardiovascular occasions.[17]
4. **Hepatic effect -** Hepatic unfriendly impacts are more uncommon; NSAID-related chance of hepatotoxicity (raised aminotransferase levels) isn't exceptionally normal, and liver-related hospitalization is extremely interesting. Diclofenac has a higher rate of hepatotoxic effects than other NSAIDs.[18]
5. **Hematologic effect -** Due to their antiplatelet activity, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) have a higher risk of hematologic side effects. Patients with a history of GI ulcers, diseases that impair platelet activity (haemophilia, thrombocytopenia, von Willebrand, etc.), and some perioperative cases typically face this antiplatelet effect.[19]
6. **Other effect -** Anaphylactoid reactions that involve the skin and pulmonary systems, such as urticaria, and aspirin-exacerbated respiratory disease are two additional minor side effects. [20,21]

Various Herbs use as Non- Steroidal Anti-Inflammatory Agents

1. Turmeric *(Curcuma longa)* - Turmeric, also known as Curcuma longa, is a perennial herb and is a member of the family Zingiberaceae, or ginger, and cultivated extensively throughout Asia, primarily in China and India. The rhizome, the piece of the plant utilized restoratively, yields a yellow liquid. Dried Curcuma longa is the wellspring of curry powder's primary ingredient is turmeric. trademark yellow tone. It goes by a lot of names, like Curcum in the Middle Easterner area, Indian saffron, Haridra (Sanskrit, Ayurvedic), Jiang Huang (in Chinese, "yellow ginger"), Koyo, or Ukon (Japanese). [22]

Figure 2. Turmeric

It has been shown that curcumin inhibits a variety of different molecules that play a role in inflammation, such as leukotrienes, thromboxane, COX-2, phospholipase, lipoxygenase, collagenase, elastase, hyaluronidase, prostaglandins, nitric oxide, Tumour necrosis factor, MCP-1, interferon-inducible protein, and interleukin-12. [23] C. longa's ability to reduce inflammation may be the source of its anti-inflammatory properties to prevent both inflammatory prostaglandin biosynthesis neutrophil function and arachidonic acid during states of inflammation. Curcuminoids additionally restrain LOX, COX, phospholipases, prostaglandins, leukotrienes, thromboxane, and nitric oxide collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, interferon inducible protein, transforming growth factor (TNF), and interleukin-12. Additionally, they lower prostaglandin. development and repress leukotriene biosynthesis by means of the pathway of lipoxygenase. [24] Studies has demonstrated bisdemethylcurcumin (BDC) has been shown to be more effective as an anti-inflammatory agent. by reducing TNF-induced NF-B activation, making it more effective as an a more effective agent against proliferation and for producing reactive oxygen species (ROS). Hypalon analogues, which needs one sweet-smelling unit in connection to curcumin, likewise displayed improved mitigating and activities that stop proliferation. [25] Curcumin's positive effect (anti- inflammatory compound) appears to be mediated by the in sepsis. suppression of pro-inflammatory cells as a result of upregulation of PPAR- expression of TNF-α and its release from cells [26]

2. Garlic (*Allium sativum*)- Allium sativum L., a member of the Liliaceae family, is the origin of garlic, which is also grown in China, North Africa (Egypt), Europe, and Mexico. It is well-known in Iran, and various parts of this plant have been used for centuries in Iranian and other cultures' folk

remedies. Additionally, it is utilized as a spice and food additive [27,28]. Garlic contains phenolic compounds, saponins, polysaccharides, and organosulfur compounds, among different parts [29]. Anti-inflammatory, antioxidant, and antimicrobial properties of garlic compounds have been linked to protection against cardiovascular disease, cancer, and immune system disorders [30,31,32].

Figure 3. Garlic

It has been demonstrated that garlic extracts have anti-inflammatory properties [33]. Interleukin-6 (IL-6) and monocyte chemotactic protein (MCP-1) gene expression and protein synthesis are decreased and upregulated when LPS-stimulated 3 T3-L1 adipocytes are treated with alliin.[34] Peripheral blood mononuclear cells' expression of IL-4 was unaffected by treatment with garlic extract, but IL-17 expression was reduced. [35] Treatment with garlic greatly reduced liver damage and inflammation brought on by Eimeria papillate infections. [36] Garlic oils primarily exhibit its anti-inflammatory properties by impeding the cytoskeleton's construction and disassembly processes. [37] The ability of garlic oil and its organosulfur components to prevent intestinal damage and systemic inflammation caused by endotoxins, as well as their potential toxicity. [38] It has been demonstrated that a lead compound derived from allicin is a good starting point for the creation of less harmful anti-inflammatory medications. [39]

3. Ginger (*Zingiber officinale*) - Ginger (Zingiber officinale Rosch.) has a place with the family Zingiberaceae. It started in South-East Asia and afterward utilized in numerous nations as a zest and fixing to add flavor to food. [40] There are two broad kinds of fresh ginger: volatiles and non-volatiles. Sesquiterpene and monoterpenoid hydrocarbons, which give ginger its unique flavour and scent, are examples of volatiles. Conversely, non-volatile volatile aromatic compounds consist of zingerone, gingerols, shogaols, and parados.[41]

Figure 4. Ginger

Ginger has gazing potential for treating various illnesses including degenerative issues (joint pain and stiffness), stomach related wellbeing (acid reflux, blockage and ulcer), cardiovascular problems (atherosclerosis and hypertension), spewing, diabetes mellitus, and malignant growth. It additionally has calming and against oxidative properties for controlling the most common way of maturing. Moreover, it has antimicrobial potential also which can help in treating irresistible illnesses. [42,43,44,45]

Prostaglandin biosynthesis inhibitors have a clear correlation with anti-inflammatory and anti-platelet aggregation properties. [46] Gingerol, shogaol, and other primarily related substances in ginger restrain prostaglandin and leukotriene biosynthesis through concealment of 5-lipoxygenase or prostaglandin synthetase. Moreover, they can likewise hinder combination of supportive of incendiary cytokines like IL-1, TNF-α, and IL-8. [47,48] The excessive production of NO, PGE (2), TNF-alpha, and IL-1beta was inhibited by Z. officinale rhizome hexane fraction extract. [49] Ginger rhizome may be useful for the treatment and prevention of allergic diseases due to its potent compounds that prevent allergic reactions. [50] While extracts containing shogaol have no effect on COX-2 expression, gingerols can inhibit COX-2 expression induced by LPS. These results show that important ginger compounds can stop the production of PGE (2). [51]

4. Boswellia (*Boswellia serrata*)- A member of the Burseraceae family, Boswellia serrata oleo-gum-resin that is found in India's dry, hilly regions. It is a large, medium-sized tree with many branches called Indian olibanum, also known as "Dhup"[52] The essential oil of B. serrata contains mono, di, and sesquiterpenes, while the gum portion includes sugar with pentose and hexose that oxidizes and digestive aids. [53] Resin is a pentacyclic triterpenoid in chemistry. nature in which the acids Boswellia (-Boswellia) keto-Boswellia acid, acid, and acetyl-Boswellia acid acetyl-11-keto-boswellic acid), which is the main portion. [54] Utilization of Boswellia serrata (B. serrata) for a wide range of therapeutic uses, including disease, irritation, joint inflammation, asthma, psoriasis, hyperlipidaemia and constipation.[55]

Figure 5. Boswellia

The Boswellia make use of action by preventing 5-LOX products from being made. They also prevent topoisomerase, elastase, and C-3 convertase from operating enzymes. It has been tracked down powerful in the treatment of cancer, ulcerative colitis, asthma, and arthritis. [56,57,58] Vascular cell adhesive molecule 1's TNFα expression is BSE-sensitive. [59] Polyherbal formulation containing Comephorid Mukul, Boswellia serrata, and Strychnic nux vomica, Terminalia arjuna, and Semi carpus

anacardium possesses properties that prevent atherosclerosis and inflammation. [60] modulating P-glycoprotein (P-gp) function, B. serrata extract can be used for treating peritumoral oedema and chronic inflammatory disease. [61]

5. Licorice (*Glycyrrhiza glabra*)- The scientific name for licorice is Glycyrrhiza glabra, and it is a member of the Leguminosae family. One often used plant in ayurveda is G. glabra. It is believed that Iraq is where licorice first appeared.
This plant has therapeutic properties and may be found in parts of Europe and Asia.[62] Licorice contains a variety of substances, including proteins, amino acids, simple sugars, polysaccharides, mineral salts, pectin, starches, sterols, gums, and resins.[63] One of the most valuable plants on the planet, licorice is used in tobacco, cosmetics, the food industry, pharmaceuticals, and many other applications.[64]

Figure 6. Licorice

Licorice's anti-inflammatory properties, demonstrated by its reduction of PGE2, MMPs, TNF, and free radicals, have been substantiated by its traditional use in cough relief, phlegm removal, stimulation of digestive processes, pain relief, and several other applications.[65] DGN products containing licorice significantly reduced RA symptoms. Network metalloproteinases, provocative cytokines, and vascular endothelial development factors were completely directed by licorice handled DGN items in blood and cell supernatants. According to the findings of this study, licorice-processed DGN products regulated the metabolic profile and showed anti-inflammatory effects on CIA rats and LPS-induced RAW264.7 cells through the TLR4/NF-κ/NLRP3 signalling pathway in the treatment of RA. [66]

6. Cinnamon (*Cinnamomum zeylanicum*)- The eternal tree of tropical medicine known as cinnamon (Cinnamomum zeylanicum and Cinnamon cassia) is a member of the Lauraceae family. Cinnamon is quite possibly of the main zest utilized day to day by individuals everywhere. Cinnamaldehyde, cinnamic acid, and cinnamate are just a few of the many derivatives and essential oils found in cinnamon. Cinnamon has been shown to have effects against neurological disorders like Parkinson's and Alzheimer's, in addition to being an antioxidant, anti-inflammatory, antimicrobial, anticancer, lipid-lowering, and cardiovascular disease-lowering compound. [67]

Figure 7. Cinnamon

Gossypin, gnaphalin, hesperidin, Hibi Folin, hypolaetin, oroxindin, and quercetin are examples of flavonoid compounds that have been isolated and have anti-inflammatory properties. [68,69,70,71,72] By inhibiting the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B), 2′-hydroxycinnamaldehyde, which was isolated from the bark of C. cassia, inhibited the production of nitric oxide, this substance may be useful as an anti-inflammatory agent.[73] The ethanolic extract of C. cassia showed significant anti-inflammatory effects by reducing the activation of Src/spleen-tyrosine-kinase- (Src/Syk-) mediated NF-κB. [74,75] By inhibiting the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthesis (iNOS), and nitric oxide (NO) generation in the central nervous system (CNS), a number of chemicals found in C. ramulus shown anti-inflammatory properties. Through this process, C. ramulus may offer a therapeutic benefit for the management of neurodegenerative illnesses caused by inflammation or a means of preventing them.[76] The serum levels of lipopolysaccharide-induced tumour necrosis factor- are decreased when cinnamon aqueous extract is used. [77]

7. Khirni fruit (*Manilkara hexandra)* - The milk tree, or Manilkara hexandra, is an evergreen member of the sapotaceous family with small fruits. containing one or two hard seeds. [78] The plant thrives in the central tropical forests. and western India, in addition to other humid nations. Another name for the tree is "Khirni," 'Raina,' and 'Rayan' in states like Rajasthan, Madhya Pradesh, Maharashtra, and Gujarat. [79,80] The fruits of this plant are rich in protein, sugar, carbohydrates, vitamin A, and minerals like iron, phosphorus, and calcium. [81] The primary cause of these bioactivities is the presence of certain kinds of secondary metabolites, such as saponins, triterpenoids, and flavonoids. Numerous Indian states have reported that different parts of the plant have a wide range of biological properties, including anti-inflammatory, anti-diabetic, antioxidant, anti-ulcer, anti-arthritic, and immunostimatory action. [82]

Figure 8. Khirni Fruit

Both the ethyl acetate and crude methanolic extracts of M. zapota leaves and bark exhibit strong anti-inflammatory properties. [83,84] Significant inhibitory efficacy against the LPS (lipo-poly saccharide)-induced nitric oxide technique was shown by the acetone fraction of M. hexandra seed including the crude saponin combination, suggesting a noteworthy anti-inflammatory activity. [85] A study on the anti-inflammatory properties of M. bidentata resin extract and its separated fractions revealed a reduction in pro-inflammatory cytokines like IL-8 and IL-1β, indicating the potential of bidentata resin extract as an anti-inflammatory and anti-aging agent for the pharmaceutical and cosmetic industries.[86]

Conclusion

In conclusion, herbs offer a promising alternative to non-steroidal anti-inflammatory drugs (NSAIDs) for managing pain and inflammation. Herbs such as Turmeric, Garlic, Ginger, Boswellia, Licorice, Cinnamon and Khirni Fruit have been traditionally used for their anti-inflammatory properties and have shown efficacy in various studies. These natural remedies often have fewer side effects compared to NSAIDs, making them a safer option for long-term use.

However, it is important to approach herbal alternatives with caution. The potency and effectiveness of herbal supplements can vary, and they may interact with other medications. It is essential to consult with a healthcare provider before using herbs as a replacement for NSAIDs, especially for individuals with chronic conditions or those taking other medications. By integrating these herbal options into a comprehensive pain management plan, individuals may achieve relief while minimizing the risks associated with long-term NSAID use.

References

1. Afsar U. AHMED, An overview of inflammation: mechanism and consequences. Front. Bio.6(4):274–281.
2. Phillips WJ, Currier BL. Analgesic pharmacology: II. Specific analgesics. J Am Acad Orthop Surg. 2004 12(4):221-33.
3. Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. Obstet Gynecol. 2006 108(2):428-41.

4. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, Okunogbe A, Han D, Shanman R. Management of Gout: A Systematic Review in Support of an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017 03 166(1):37-51.
5. Oyler DR, Parli SE, Bernard AC, Chang PK, Procter LD, Harned ME. Nonopioid management of acute pain associated with trauma: Focus on pharmacologic options. J Trauma Acute Care Surg. 2015 Sep;79(3):475-83.
6. Zacher J, Altman R, Bellamy N, Brühlmann P, Da Silva J, Huskisson E, Taylor RS. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin. 2008 24(4):925-50.
7. van den Bekerom MPJ, Sjer A, Somford MP, Bulstra GH, Struijs PAA, Kerkhoffs GMMJ. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. Knee Surg Sports Traumatol Arthrosc. 2015 23(8):2390-2399.
8. May JJ, Lovell G, Hopkins WG. Effectiveness of 1% diclofenac gel in the treatment of wrist extensor tenosynovitis in long distance kayakers. J Sci Med Sport. 2007 10(1):59-65.
9. Barkin RL. Topical Nonsteroidal Anti-Inflammatory Drugs: The Importance of Drug, Delivery, and Therapeutic Outcome. Am J Ther. 2015 22(5):388-407.
10. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971 231(25):232-5.
11. Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs. Am J Health Syst Pharm. 2006 63(19):1837-51.
12. Bradley, J.R. TNF-Mediated inflammatory disease. J. Pathol. 2008, 214, 149–160.
13. Horiuchi, T. Mitoma, H. Harashima, S. Tsukamoto, H. Shimoda, T. Transmembrane TNF-alpha: Structure, function and interaction with anti-TNF agents. Rheumatology 2010, 49, 1215–1228.
14. Jiang, Y. Yu, M. Hu, X. Han, L. Yang, K. Ba, H. Zhang, Z. Yin, B. Yang, X.P. Li, Z. et al. STAT1 mediates transmembrane TNF-alpha-induced formation of death-inducing signaling complex and apoptotic signaling via TNFR1. Cell Death Differ. 2017 24, 660–671.
15. Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. Best Pract Res Clin Gastroenterol. 2010 24(2):121-32.
16. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999 106(5B):13S-24S.
17. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013 16(5):821-47.
18. Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Randomized Controlled Trials. Int J Hepatol. 2018 :5253623.
19. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. Am J Med. 1999 106(5B):25S-36S.
20. Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. Clin Rev Allergy Immunol. 2003 24(2):137-48.
21. Szczeklik A. Adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. Ann Allergy. 1987 59(5 Pt 2):113-8.
22. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as ‘‘Curcumin’’: From kitchen to clinic. Biochemical Pharmacology. 2008 75(4):787-809.
23. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). J Altern Complement Med. 2003:161-168.
24. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J Altern Complement Med. 2004 10:1015-8.

25. Ravindran J, Bisdemethylcurcumin and structurally related Hispolon analogues of curcumin exhibit enhanced pro-oxidant, anti-proliferative and anti-inflammatory activities in vitro. Biochem Pharmacol 2010 79:1658-1666.
26. Jacob A, Wu R, Zhou M, Wang P, Mechanism of the Anti- inflammatory effect of Curcumin: PPAR-γ Activation, PPAR Research 2007:89369
27. Singh TU, Kumar D, Tandan SK, Mishra SK. Inhibitory effect of essential oils of Allium sativum and Piper longum on spontaneous muscular activity of liver fluke, Fasciola gigantica. Exp Parasitol. 2009 123:302–308.
28. Eja ME, Asikong BE, Abriba C, Arikpo GE, Anwan EE, Enyi-Idoh KH. A comparative assessinent of the antimicrobial effects of Garlic (Allium sativum) and Antibiotics on diarrheagenic organisms. Southeast Asian J Trop Med Public Health. 2007 38:2.
29. K. A. Szychowski, K. Rybczyńska-Tkaczyk, K. Gaweł-Bęben, M. Świeca, M. Karaś, A. Jakubczyk, M. Matysiak, U. E. Binduga and J. Gmiński, Characterization of Active Compounds of Different Garlic (Allium sativum L.) Cultivars, Pol. J. Food Nutr. Sci., 2018 68 73–81
30. M. Foroutan-Rad, K. H. Tappeh and S. Khademvatan, Antileishmanial and Immunomodulatory Activity of Allium sativum (Garlic): A Review, J. Evidence-Based Complementary Altern. Med. 2017 22, 141–155
31. X. Lu, N. Li, X. Qiao, Z. Qiu and P. Liu. Composition analysis and antioxidant properties of black garlic extract, J. Food Drug Anal. 2017 25, 340–349
32. G. El-Saber Batiha, A. Magdy Beshbishy, L. G. Wasef, Y. H. A. Elewa, A. A. Al-Sagan, M. E. Abd El-Hack, A. E. Taha, Y. M. Abd-Elhakim and H. Prasad Devkota, Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review, Nutrients, 2020 12, 872
33. Ban JO, Lee DH, Kim EJ, Kang JW, Kim MS, Cho MC. et al. Antiobesity effects of a sulfur compound thiacremonone mediated via down-regulation of serum triglyceride and glucose levels and lipid accumulation in the liver of db/db mice. Phytother Res 2012 10: 3729.
34. S. Quintero-Fabián, D. Ortuño-Sahagún, M. Vázquez-Carrera and R. I. López-Roa. Alliin a garlic (Allium sativum) compound, prevents LPS-induced inflammation in 3 T3-L1 adipocytes, Mediators Inflammation, 2013, 381815
35. M. Moutia, F. Seghrouchni, O. Abouelazz, A. Elouaddari, A. Al Jahid, A. Elhou, S. Nadifi, J. Jamal Eddine, N. Habti and A. Badou. Allium sativum L. regulates in vitro IL-17 gene expression in human peripheral blood mononuclear cells, BMC Complementary Altern. Med., 2016 16, 377
36. Dkhil MA, Abdel-Baki AS, Wunderlich F, Sies H, Al-Quraishy S. Anticoccidial and antiinflammatory activity of garlic in murine Eimeria papillata infections. Vet Parasitol. 2011 175:66–72.
37. Shih PC, Kuo CH, Juang JY, Liu CH, Hsu L, Liu CT. Effects of garlic oil on the migration of neutrophil-like cell studied by using a chemotactic gradient Labchip. J Biomed Biotechnol. 2010 31:9059.
38. Chiang YH, Jen LN, Su HY, Lii CK, Sheen LY, Liu CT. Effects of garlic oil and two of its major organosulfur compounds, diallyl disulfide and diallyl trisulfide, on intestinal damage in rats injected with endotoxin. Toxicol Appl Pharmacol. 2006 213:46–54.
39. Krishna A, Yadav A. Lead compound design for TPR/COX dual inhibition. J Mol Model. 2012 18:4397- 4408.
40. Park EJ, Pizzuto JM. Botanicals in cancer chemoprevention. Cancer Metast Rev. 2002; 21:231–55.
41. Jolad SD, Lantz RC, Solyom AM, Chen GJ, Bates RB, Timmermann BN. Fresh organically grown ginger (Zingiber officinale): Composition and effects on LPS-induced PGE2 production. Phytochemistry. 2004, 65:1937–54.
42. Shukla Y, Singh M. Cancer preventive properties of ginger: A brief review. Food Chem Toxicol. 2007, 45:683–90.

43. Jiang H, Xie Z, Koo HJ, McLaughlin SP, Timmermann BN, Gang DR. Metabolic profiling and phylogenetic analysis of medicinal Zingiber species: Tools for authentication of ginger (Zingiber officinale Rosc.) Phytochemistry. 2006,67:232–44.
44. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research. Food Chem Toxicol. 2008, 46:409–20.
45. Nicoll R, Henein MY. Ginger (Zingiber officinale Roscoe). A hot remedy for cardiovascular disease? Int J Cardiol. 2009, 131:408–9.
46. Counch F, Iwakami S, Shibuya M, Hanaoka F and Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull, 1992, 40(2), 387-391.
47. Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorganic Chem. 2001 ,29:156–63.
48. Verma SK, Singh M, Jain P, Bordia A. Protective effect of ginger. Zingiber officinale Rosc on experimental atherosclerosis in rabbits. Indian J Exp Biol. 2004 42:736–8.
49. Jung HW, Yoon CH, Park KM, Han HS, Park YK. Hexane fraction of Zingiberis Rhizoma Crudus extract inhibits the production of nitric oxide and proinflammatory cytokines in LPS-stimulated BV2 microglial cells via the NF kappaB pathway. Food Chem Toxicol. 2009 47:1190–7.
50. Chen BH, Wu PY, Chen KM, Fu TF, Wang HM, Chen CY. Antiallergic potential on RBL-2H3 cells of some phenolic constituents of Zingiber officinale (Ginger) J Nat Prod. 2009 72:950–3.
51. Lantz RC, Chen GJ, Sarihan M, Sólyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine. 2007 14:123–8.
52. Kokate CK, Purohit AP, Gokhale SB. 'Pharmacognosy', Nirali Prakashan, Pune. 2001; 412-413
53. Bhargava GG, Negi JJ, Ghua HRD. Studies on the chemical composition of Salai gum. Indian forestry 1978; 14: 174-181.
54. Pardhy RS, Bhattacharya SC. Boswellic acid, Acetyl-boswellic acid and11-Keto-boswellic acid, four pentacyclic triterpenic acids from the resin of Boswellia serrata Roxb. Indian J. of Chem. 1978; 16B: 176-178.
55. Shao Y, Ho CT, Chin CK, Badmaev V, Ma W, Huang MT. Inhibitory activity of Boswellic acids from Bosweliia serrata against human leukemia HL-60 cells in culture. Planta Medica. 1998; 64: 328-331.
56. S.K. Shrivastava, G.K. Singh and P.K. Basniwal. Boswellic acid an alternative anti-inflammatory therapy. Indian J. Nat. Prod.2003 19: 14.
57. R.R. Kulkarni, P.S. Patki, V.P. Jog, S.G. Gandage and B. Patwardhan. Treatment of osteoarthritis with a herbomineral formulation: A double blind, placebo controlled, cross-over study. J. Ethnopharmacol.1991 33: 91-95.
58. J. Gupta, A. Parihar, P. Malhotra, G.B. Singh, R. Ludtke, H. Safayhi and H.P.T. Ammon. Effects of Boswellia serrata gum resin in patients with ulcerative colitis. Eur. J Med. Res.1997 2: 37-43
59. S. Kov, S. Khanna, H. Shah, C. Rink, C. Philips, H. Preuss, G.V. Subbaraju., G. Trimurtulu, A.V. Krishnaraju, M. Bagchi, D. Bagchi and C.K. Se. Human genome screen to identify the genetic basis of anti-inflammatory effect of Boswellia in microvascular endothelial cells. DNA Cell Biol.2004 24: 244-55.
60. Y.B. Tripathi, M.M. Reddy, R.S. Pandey, J. Subhashini, O.P. Tiwari, B.K. Singh and P. Reddana. Anti-inflammatory properties of BHUx, A polyherbal formulation to prevent atherosclerosis. Inflammation Pharmacol. 2004 12: 131-52.
61. M.D. Kharya and V.K. Dixit. Some observations on salai gum-oleo resin. Indian J. Forestry 1982 4: 322-23.
62. Fiore, C. Eisenhut, M.Ragazzi, E. Zanchin, G. Armanini D. A history of the therapeutic use of liquorice in Europe. J. Ethnopharmacol. 2005, 99, 317–324.

63. Wang, L. Yang, R. Yuan, B. Liu, Y. Liu, C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm. Sin. B 2015 *5*, 310–315.
64. Fenwick, G.R. Lutomski, J. Nieman, C. Liquorice, Glycyrrhiza glabra L.-Composition, uses and analysis. Food Chem. 1990 38, 119–143.
65. Yang, R. Yuan, B.C. Ma, Y.S. Zhou, S.Liu, Y. The anti-inflammatory activity of licorice, a widely used chinese herb. Pharm. Biol. 2017, 55, 5–18.
66. Meng, X. Zhang, X. Su, X. Liu, X. Ren, K. Ning, C.Zhang, Q. Zhang, S. Daphnes Cortex and its licorice-processed products suppress inflammation via the TLR4/NF-κβ/NLRP3 signaling pathway and regulation of the metabolic profile in the treatment of rheumatoid arthritis. J. Ethnopharmacol. 2021, *283*, 114657.
67. P.V.Rao, S.H.Gan ,Cinnamon: A Multifaceted Medicinal Plant, Evid Based Complement Alternat Med. 2014 642942.
68. García Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflammation Research. 2009 58(9):537–552.
69. Kim HP, Son KH, Chang HW, Kang SS. Anti-inflammatory plant flavonoids and cellular action mechanisms. Journal of Pharmacological Sciences. 2004 96(3):229–245.
70. Guardia T, Rotelli AE, Juarez AO, Pelzer LE. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. Farmaco. 2001 56(9):683–687.
71. Stoner G, Wang L S. Obesity, Inflammation and Cancer. Springer; Natural products as anti-inflammatory agents et al.Cell 2010 341–361.
72. Cho N, Lee KY, Huh J, et al. Cognitive-enhancing effects of Rhus verniciflua bark extract and its active flavonoids with neuroprotective and anti-inflammatory activities. Food and Chemical Toxicology. 2013 58:355–361.
73. Lee SH, Lee SY, Son DJ, et al. Inhibitory effect of 2 hydroxycinnamaldehyde on nitric oxide production through inhibition of NF *κ*B activation in RAW 264.7 cells. Biochemical Pharmacology. 2005 69(5):791–799.
74. Yu T, Lee S, Yang WS, et al. The ability of an ethanol extract of Cinnamomum cassia to inhibit Src and spleen tyrosine kinase activity contributes to its anti-inflammatory action. Journal of Ethnopharmacology. 2012 139(2):566–573.
75. Youn HS, Lee JK, Choi YJ, et al. Cinnamaldehyde suppresses toll-like receptor 4 activation mediated through the inhibition of receptor oligomerization. Biochemical Pharmacology. 2008 75(2):494–502.
76. Hwang S H, Choi YG, Jeong M-Y, Hong Y-M, Lee J-H, Lim S. Microarray analysis of gene expression profile by treatment of Cinnamomi ramulus in lipopolysaccharide-stimulated BV-2 cells. Gene. 2009 443(1-2):83–90.
77. Hong J W, Yang GE, Kim YB, Eom SH, Lew J H, Kang H. Anti-inflammatory activity of cinnamon water extract in vivo and in vitro LPS-induced models. BMC Complementary and Alternative Medicine. 2012 12(1, article 237)
78. Vincken JP, Heng L, de Groot A, Gruppen H. Saponins, classification and occurrence in the plant kingdom. Phytochem 2007 68(3):275-297.
79. Malik S, Chaudhury R, Panwar N, Dhariwal O, Choudhary R, Kumar S. Genetic resources of Chironji (Buchanania lanzan Spreng.): A socio-economically important tree species of central Indian tribal population. Genet Resour Crop Evol 2012 59(4):615-623.
80. Malik S, Choudhary R, Kumar S, Dhariwal O, Deswal R, Chaudhury R. Socioeconomic and horticultural potential of Khirni [Manilkara hexandra (Roxb.) Dubard]: a promising underutilized fruit species of India. Genet Resour Crop Evol 2012 59(6):1255-1265.
81. Rhourri-Frih B, Renimel I, Chaimbault P, André P, Herbette G, Lafosse M. Pentacyclic triterpenes from Manilkara bidentata resin. Isolation, identification and biological properties. Fitoterapia. 2013 88:101-108.

82. Hossain H, Jahan F, Howlader SI, Dey SK, Hira A, Sarkar RP., Evaluation of Anti-inflammatory Activity and Total Flavonoids Content of Manilkara zapota (Linn.) Bark. Int.J.Pharm.Phytopharmacol.Res.2012 2:35-39.
83. Konuku K, Karri KC, Gopalakrishnan VK, Hagos Z, Kebede H, Naidu TK, et al. Anti-Inflammatory Activity of Manilkara zapota Leaf Extract. Int J Curr Pharm Res.2017 9(4):130-134.
84. Eskander JY, Haggag EG, El-Gindi MR, Mohamedy MM. A novel saponin from Manilkara hexandra seeds and anti-inflammatory activity. Med Chem Res. 2014 23(2):717-724.
85. Rhourri-Frih B, Renimel I, Chaimbault P, André P, Herbette G, Lafosse M. Pentacyclic triterpenes from Manilkara bidentata resin. Isolation, identification and biological properties. Fitoterapia. 2013 88:101-108