

# Natural support for treatment of Auto-inflammatory diseases: A review

Mukta Gupta<sup>a,b\*</sup>, Nahanael D. Tuppa<sup>a</sup>, Naresh Singh Gill<sup>c</sup>

<sup>a</sup>Department of Pharmaceutical Chemistry, Lovely Professional University, Phagwara, Punjab, India

<sup>b</sup>Department of Pharmaceutical Sciences, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, India

<sup>c</sup>Rayat Institute of Pharmacy, Railmajra, SBS Nagar, Punjab, India

\*Corresponding Author E-mail: [mukta.16541@lpu.co.in](mailto:mukta.16541@lpu.co.in)

## Abstract

Auto-inflammatory diseases is a group of clinical manifestation that share common distribution pattern with auto-immune disorders, however differs in symptoms such as recurrent episodes of inflammation. The pathophysiology of auto-inflammatory diseases involves dysfunction of innate immune system. The various examples of auto-inflammatory diseases includes crohn disease, behcet disease, schnitzel syndrome, systemic juvenile idiopathic arthritis, familial Mediterranean fever, TNF receptor associated periodic syndrome, ankylosing spondylitis, stomatitis recurrent aphthous ulcer, psoriatic arthritis, gout, sarcoidosis. Conventional treatment approach of auto-inflammatory diseases involves immunomodulators (cyclosporine, mercaptopurine, methotrexate, azathioprine); corticosteroids ( prednisone, budesonide, methyl prednisone); aminosalicylates (sulfasalazine, mesalamine); biologics (infliximab, certolizumab, adalimumab) and NSAIDS (acetaminophen and ibuprofen) are used. All these drugs are associated with one or more side effects. As per the study conducted by the World Health Organization about 80% of world's population relies on traditional medicine. Various plants have been used traditionally in management of auto-inflammatory diseases. Some of the important natural compounds reported to be used in treatment of auto-inflammatory diseases includes anthraquinone (*Aloe vera*, *Rhamnus cathartica*), curcuminoids (*Curcuma longa*), flavonoids (*Chrysanthemum indicum*, *Colocasia antiquorum*, *Momordica charantia*), volatile oil (*Olchicum autumnale*, *Oenothera biennis*, *Borago officinalis*, *Allium cepa*), polyphenols (*Punica granatum*, *Vitis venifera*). Although a number of herbal medicines are recommended for auto-inflammatory diseases, but further research is required to investigate their safety, efficacy, and potential drug interactions.

**Keywords:** Auto-inflammatory diseases; Herbal products; Natural; Immunity

### **Introduction**

Auto inflammatory diseases can be defined as the inflammatory disorders due to innate immune cells dysfunction which leads to the systemic or organ targeted inflammations. Most of these diseases are genetically caused but clinical data shows that there can be non-genetic causes may also be one factor [1]. The diseases can be identified by various symptoms such as recurrent high fever, diarrhea, nausea, arthritis, joint pains, skin rashes, lesions, inflammations and headache. Examples of auto-inflammatory diseases include schnitzels syndrome, crohn's disease, Behcet's disease and systemic juvenile idiopathic arthritis.

There has been an increasing incidence of auto inflammatory diseases worldwide and is seen in all age groups. However people with age between 20-40 years are mostly commonly affected. Along with the same systemic juvenile idiopathic arthritis is most commonly observed in children of age 6 years onwards.

The exact etiology of auto inflammatory disorder is not clear; however it is assumed that mutations in innate immune system may be one of the causative factors together with other inflammatory mediators. The diseases can be identified by various symptoms such as recurrent high fever, diarrhea, nausea, arthritis, joint pains, skin rashes, lesions, inflammations and headache [2]. Natural products have been used for treatment of various diseases from ancient time. These act as lead compound for identification and development of new drug molecules [3]. These are mainly plant secondary metabolites such as flavonoids, alkaloids, saponins, terpenoids etc [4-5]. Various auto-inflammatory diseases and their treatment with herbal products is listed below.

### **1 . Crohn's disease (CD)**

Inflammatory bowel diseases includes Crohn's disease (CD) and ulcerative colitis which these affect small or large intestine and is the major cause of morbidity. The risk factor for CD involves overproduction of reactive oxygen species and antioxidant capacity. The major target area of CD is colon although other parts can also be affected [1]. Symptoms include fever, abdominal pain, diarrhea, bloating, anal bleeding or fissures and weight loss. CD occurs due to antigenic stimulation which causes abscesses which develop to focal aphthoid ulcers, internal and external fistula and lastly bowel

obstruction due to inflammation. Conventional treatment approach of Crohn's disease include various classes such as immunomodulators (cyclosporine, mercaptopurine, methotrexate, azathioprine); corticosteroids (prednisone, budesonide, methyl prednisone); aminosalicylates (sulfasalazine, mesalamine); biologics such as infliximab, certolizumab, adalimumab and nonsteroidal anti inflammation drugs (acetaminophen and ibuprofen) are used.

Herbal products have also been used for treatment of various inflammatory disorders and also are free from side effects. The herbal plants used for treatment of CD includes Aloe (*Aloe vera*); mastic gum (*Pistacia lentiscus*); wormwood (*Artemisia absinthium*); turmeric (*Curcuma longa*); barley (*Hordeum vulgare*); asparagus (*Asparagus officinalis*) and soya beans (*Glycine max*)[6-9].

## **2. Behcet's disease (BD)**

Behcet's disease occur systemically causing blood vessels inflammation in the entire body. Mostly affected sites are skin, oral and genital areas [10]. The disease can be identified by various symptoms such as genital sores, mouth sores, skin rash, lesions, ocular manifestations, arthritis and fatigue.

Clinical data shows that its pathophysiology is still unknown but it is believed that genetic and immune system irregularities and other triggering factors such as infectious agents may be responsible for this disease [10]. Behçet's disease negatively affects bio psychology and social life of patient therefore reduces the quality of life.

Conventional drugs used are mainly immunosuppressant (cyclosporine, mercaptopurine, methotrexate, azathioprine); anti-inflammatory and steroid agents (prednisone, budesonide, methyl prednisone).The use of colchicine in treatment of BD is well documented and reported. BD can be treated by herbal plants such as colchicine (*Colchicum autumnale*) and liquorice root (*Glycyrrhiza uralensis*)[11-12].

## **3. Schnitzel syndromes**

Schnitzel syndrome is an auto-inflammatory disease which primarily affects extremities and trunk sparing the head, neck, palms and soles [13]. The disease can be identified by various symptoms such as joint pain, bone pain, fatigue, malaise, periodic fever, swollen lymph glands and enlarged spleen and liver. The causative agent involved in pathogenesis of schnitzel syndrome involves the activation of IL-1 which further causes innate immune system dysfunction leading to the disease [13].

Standard therapies that inhibit cytokine IL-1 such as Canakinumab are used. For schnitzel syndrome IL-1 receptor antagonist such as anakinra has shown success in treating schnitzel syndrome. Colchicine (*Colchicum autumnale*) is a herbal plant used for treatment of Schnitzel syndrome [14].

#### **4. Systemic juvenile idiopathic arthritis (SJIA)**

SJIA is an auto-inflammatory disease affecting mostly children of age five and younger than that and mainly targets joints. It is also known as still's disease. The various symptoms of the disease include swollen lymph nodes, rashes, fever, stiffness, swelling and pain at the joints [15]. The treatment of SJIA can be done by using herbal plants such as turmeric (*Curcuma longa*); ginger (*Zingiber officinale*); green tea (*Camellia sinensis*) and cinnamon (*Cinamomum zeylanicum*)[16-19].

#### **5. Familial Mediterranean fever (FMF)**

FMF is a hereditary auto inflammatory disease with two phenotypes that is type 1 and type 2 and affect mainly the female reproductive organs and if it is coupled with arthritis it will affect joints at knees, hips, ankles and elbows [20].

Type 1 FMF can be characterized by fever, inflammation, peritonitis, synovitis, chest and abdominal pains whereas Type 2 can be identified by amyloidosis or may otherwise be asymptomatic. The causative agent is mutation in 781 amino acid proteins [21]. Conventional drugs used are NSAIDS and Immunomodulant. The herbal plant for treatment of FMF is colchicine (*Colchicum autumnale*)[22].

#### **6. TNF receptor associated periodic syndrome (TRAPS)**

TRAPS is an auto inflammatory disease that is hereditary and characterized with long lasting periods of fever. The disease can be identified by various symptoms such as oedema, arthritis, thoracic pain, skin rashes, periodic fever attacks and abdominal pain [23].

It occurs due to mutations in the p55 TNF receptor which further causes the manifestation of the symptoms of the disease. Colchicine (*Colchicum autumnale*) is used for treatment of TRAPS and is potent inhibitor of TNF- $\alpha$  receptor.

#### **7. Ankylosing Spondylitis**

The disorder involves sacroiliac joints, axial skeleton and it is usually more observed in people with age 30 years old and below disguised as chronic back pain [24]. Prevalence

of ankylosing spondylitis in India was found to be at 0.03 percent as per Bone and Joint Decade India 2004 – 2010.

Symptoms include musculoskeletal pain, stiffness and immobility of spine, tenderness in lumbar region to shoulder -neck region and foot and heel pain. The main etiology of ankylosing spondylitis is not clear yet; however it is assumed that people with gene called HLA- B27 are at a high risk of getting it. Also inflammatory mediators such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$  are also causative factors [25-30]. Conventional treatment approach includes the use of immunomodulators, corticosteroids and non-steroidal anti-inflammatory drugs [31]. Natural plants have also been used as treatment from ancient times for treatment of ankylosing spondylitis such as chrysanthemum (*Chrysanthemum indicum*); garlic (*Allium sativum*); turmeric (*Curcuma longa*) and buckthorn (*Rhamnus cathartica*)[32-35].

### **8. Stomatitis recurrent aphthous ulcer (RAU)**

Stomatitis recurrent aphthous ulcer (RAU) is a chronic inflammatory ulcerative disease of oral mucosa and is also known as canker sore. Worldwide the disease is 2-66 percent of the total population.

The etiopathogenesis is still unclear but many causative factors such as stress, malnutrition, trauma, and family history, immunological and psychological factors have been associated with RAU [2]. The symptoms that occur are such as lesions, dysphasia and ulcers on non-keratinized mucosa as edges of tongue, buccal mucosa and the lips. For treatment of RAU various herbal plants have been used which includes myrtle (*Myrtus communis*); safflower (*Carthamus tinctorius*); purslane (*Portulaca oleraceae*); pomegranate (*Punica granatum*); sour cherry (*Vitis venifera*); taro (*Colocasia antiquorum*); catechu (*Acacia catechu*); camphor (*Cinnamomum camphora*); lemon (*Citrus limon*); myrrh (*Commiphora myrrha*); henna (*Lawsonia inermis*) and bayberry (*Myrica pensylvanica*)[36-40].

### **9. Gout**

Gout is a chronic auto inflammatory disease with regular acute flares which cause painful joint inflammation. It is mostly seen in women after menopause and in men with above 40 years of age. Its main etiology is such as disease occurs due to hyperuricemia which leads to the presence of monosodium urate (MSU) crystals in joints

[41], bones, and soft tissues which triggers the release of IL-1 $\beta$  which causes inflammation [42-45].

Symptoms that are observed are severe pain, redness and swelling of joints, chills, fever, lumps in joints, stiffness etc. Conventional treatment of gout includes the use of drugs that reduce uric acid (allopurinol, febuxostat); NSAIDs, and corticosteroids can be used. Various plants are used in the treatment of gout such as bitter melon (*Momordica charantia*); chrysanthemum (*Chrysanthemum indicum*); cinnamon (*Cinnamomum cassia*); sand ginger (*Kaempferia galangal*); wormwood (*Artemisia vulgaris*); noni (*Morinda elliptica*); olive (*Olea europaea*); parsley (*Petroselinum crispum*); blackberry (*Synsepalum dulcificum*); ginger (*Zingiber officinalis*); amla (*Phyllanthus emblica*); elephant garlic (*Allium ampeloprasum*) and wild onion (*Allium cepa*) [46-52].

## **10. Psoriatic arthritis**

The disease is a combination of the auto immune disease psoriasis together with inflammatory arthritis [53]. It occurs in people of age 30 – 50 where it first manifests as psoriasis then arthritis follows or vice versa. The symptoms of psoriatic arthritis are such as fatigue, inflamed toes of fingers, joint pain, stiffness, skin rashes and dents in nails. The main etiology is such as it occurs due to abnormal immune system functions causing inflammation and skin cells overproduction [54]. Folate antagonists such as methotrexate can also be used for its treatment but has toxicity. In treatment of this disease, various herbal plants are used such as evening primrose (*Oenothera biennis*); borage oil (*Borago officinalis*); peony (*Paeonia officinalis*); turmeric (*Curcuma longa*); ginger (*Zingiber officinalis*) and chilli pepper (*Capsicum frutescens*) [55-57].

## **11. Sarcoidosis**

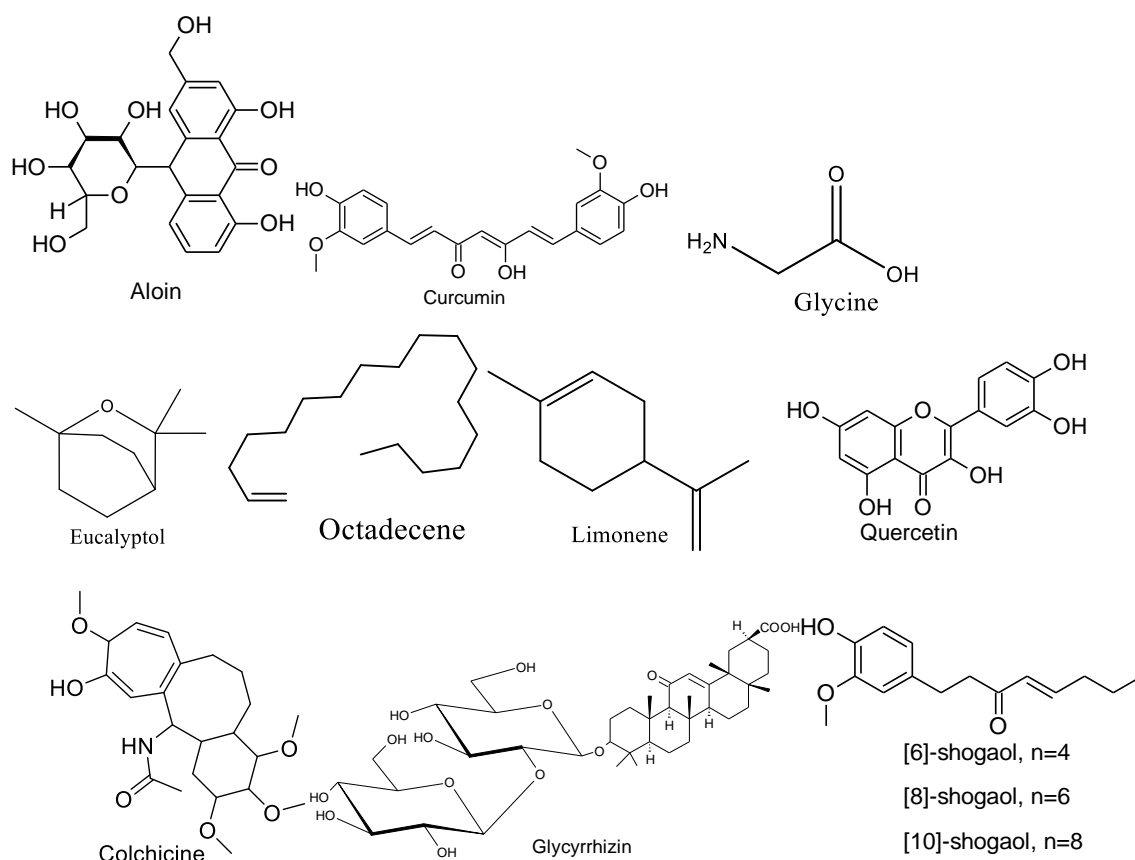
Sarcoidosis is an auto inflammatory disease which is characterized by the growth of tiny collections of inflammatory cells in different parts of the body. The exact etiology of this disease is not clear yet but various mediators such as TNF- $\alpha$ , IL-6 and IL-8 are assumed to be the causative factors [58].

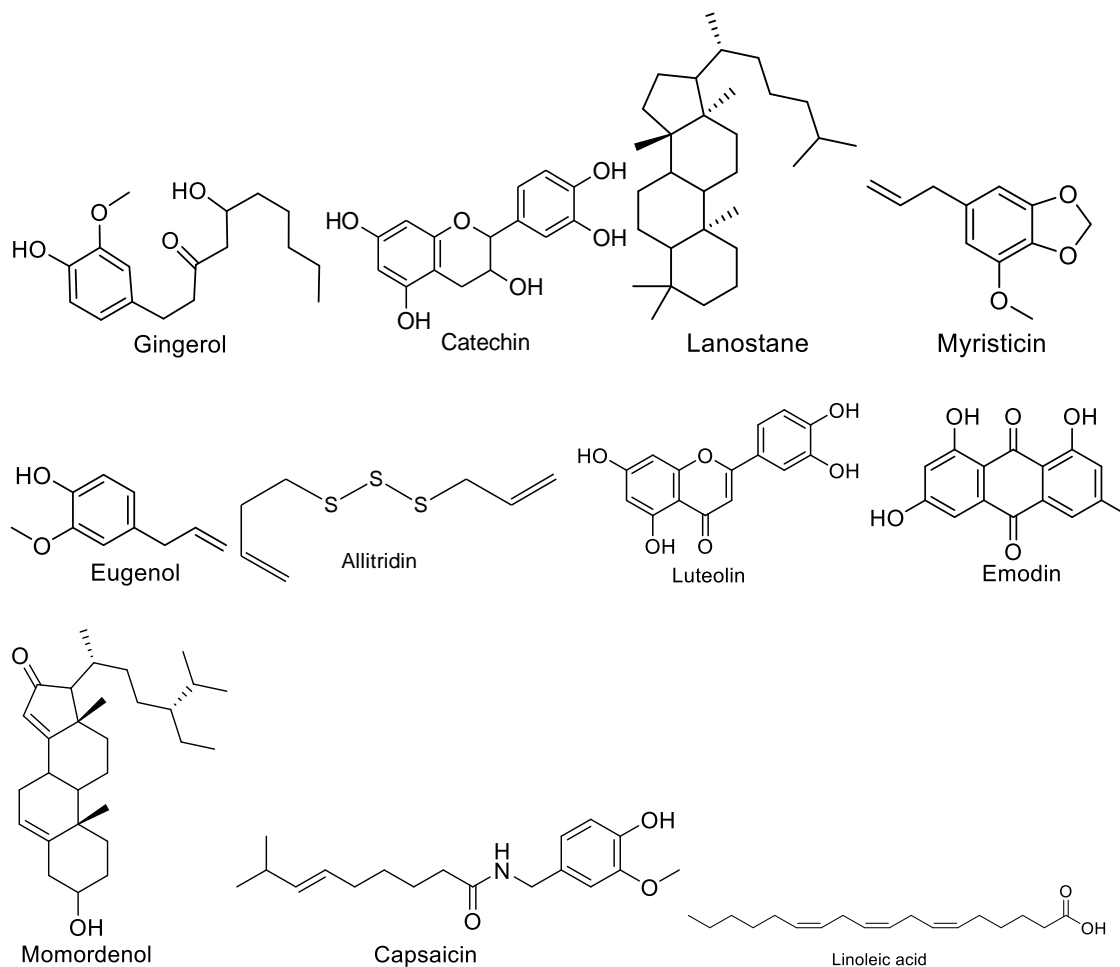
It occurs in lymph's, eyes, skin, lymph nodes and also lungs. Symptoms include skin lesions, plaques, skin lesions, fatigue, wheezing and also weight loss. Various conventional drugs can be used in treatment such as immunomodulators (cyclosporine, mercaptopurine, methotrexate, azathioprine) and steroids (prednisone, budesonide,

methyl prednisone). Herbal treatment therapy of sarcoidosis makes use of reishi mushrooms (*Ganoderma lucidum*); echinacea (*Echinacea purpurea*); devil's claw (*Harpogophytum procumbens*) and meadow (*Filipendula ulmaria*)[59-61]. Plants used for treatment of auto-inflammatory disorders with their molecular targets have been listed in **Table 1**.

The chemical structures of bioactive principles of herbal products used for auto-inflammatory diseases have been represented in **Figure 2**.

**Figure 1:** Chemical structures of bioactive principles of plants used in auto-inflammatory diseases





**Table 1:** Herbal products and their molecular targets

Scientific name	Chemical class	Biological source	Family	Target	Applicat ion	Reference
<i>Aloe vera</i>	Anthraquinone	Aloe vera	Asphadelaceae	NF-KB	CD	3
<i>Pistacia lentiscus</i>	Gum resin	Mastic gum	Pistacio	TNF- $\alpha$	CD	4
<i>Artemisia absinthium</i>	Volatile oils	Wormwood	Astaraceae	Steroid spairing, uric acid	CD, Gout	5,28
<i>Curcuma longa</i>	Curcuminoid	Turmeric	Zingiberaceae	ROS, TNF- $\alpha$ , COX-1, COX-2, NF-KB, 5-LOX	CD, SJIA, AS, Psoriatic arthritis	6,18, 25,34
<i>Hoedeum vulgare</i>	Angiosperm	Barley	Gramineae	IL-2, IL-4	CD	7
<i>Asparagus officinalis</i>	Angiosperm	Asparagus	Asparagaceae	THP-1( $\alpha$ )	CD	8



<i>Glycine max</i>	Glycines	Soyabean	Leguminosae	IL-2, IL-10	CD	9
<i>Colchicum autumnale</i>	Volatile oils	Colchicine	Autumn crocus	Mitosis	BD, SS, FMF, TRAPS	11, 14, 22, 23
<i>Glycyrrhiza uralensis</i>	Saponins	Liquorice root	Fabaceae	COX	BD	15
<i>Zingiber officinale</i> ,	Polyphenols	Ginger	Zingiberaceae	LT, COX 2	SJIA, Gout	19,44
<i>Camellia sinensis</i>	Purine alkaloids	Green tea	Theaceae	EGCG	SJIA	18
<i>Cinamomum zeylanicum</i>	Essential oil	Cinnamon	Lauraceae	ROX, XOD	SJIA, Gout	19,44
<i>Chrysanthemum indicum</i>	Terpenoids and flavonoids	Chrysanthemum	Asteraceae	TNF- $\alpha$ , IL-1 $\beta$ , IL-6, ROS	AS	24
<i>Allium sativum</i>	Allicin	Garlic	Alliaceae	TNF- $\alpha$ , IL-8, HLA-B27 proteins	AS	25
<i>Rhamnus cathartica</i>	Anthraquinones	Rhubarb	Polygonaceae.	Apoptosis	AS	27
<i>Myrtus communis</i>	Monoterpenes	Myrtle	Myrtaceae	ROS, IL-6	RAU	29
<i>Carthamus tinctorius</i>	Fatty acids	Safflower	Asteraceae	IL-10	RAU	30
<i>Portulaca oleraceae</i>	Dicotyledons	Purslane	Portulacaceae	ROS, IL-2	RAU	31
<i>Punica granatum</i>	Polyphenols	Pomegranate flowers	Punicaceae	COX-2, PGE-2	RAU	32
<i>Vitis venifera</i>	Polyphenols	Sour cherry	Rosaceae	LT, COX-2	RAU	33
<i>Colocasia antiquorum</i>	Flavonoids	Taro	Araceae	COX1, COX-2, IL-10	RAU	34
<i>Acacia catechu</i>	Catechin	Catechu	Leguminosae	COX, LOX	RAU	35
<i>Cinnamomum camphora</i>	Monoterpenoids	Camphor	Laurels	ROS, PGE-2	RAU	36
<i>Citrus limon</i>	Citrus fruits	Lemon	Rutaceae	IL-2, IL-6, histamine	RAU	37

<i>Commiphora myrrha</i>	Resins	Myrrh	Burseraceae	IL-1 $\beta$	RAU	38
<i>Lawsonia inermis</i>	Naphthoquinone	Henna	Lythraceae	COX, LOX	RAU	39
<i>Myrica pensylvanica</i>	Myricetin	bayberry	Myricaceae	ROS	RAU	40
<i>Momordica charantia</i>	Flavonioid	Bitter gourd	Curcubitaceae	uric acid	Gout	42
<i>Morinda elliptica</i>	NA	Noni	Rubiaceae	uric acid	Gout	46
<i>Olea europaea</i>	Oleuropein	Olive	Oleaceae	XOD	Gout	47
<i>Petroselinum crispum</i>	Myristicin	Parsley	Apiacea	uric acid	Gout	48
<i>Synsepalum dulcificum</i>	Phenyl propenoids	Berry fruit	Sapotaceae	XOD	Gout	49
<i>Phyllanthus emblica</i>	Punicafolin	Amla	Phyllanthaceae	XOD	Gout	50
<i>Allium ampeloprasum</i>	Onions	Elephant garlic	Liliaceae	uric acid	Gout	51
<i>Allium cepa</i>	Onion	Wild onion	Amaryllidaceae	XOD	Gout	52
<i>Oenothera biennis</i>	Volatile oils	Evening primrose	Onagraceae	PG, IL-1	PA	54
<i>Borago officinalis</i>	Volatile oils	Borage oil	Boraginaceae	IL-2, IL-1 $\beta$	PA	54
<i>Paeonia officinalis</i>	Glycosides	Peony	Paeoniceae	IL-2, IL-6	PA	55
<i>Capsicum frutescens</i>	Alkaloids	Chilli pepper (Capsaicin)	Solanaceae	COX, LOX	PA	57
<i>Ganoderma lucidum</i>	Ganodermataceae	Reishi mushrooms	Sterols, alkaloids	ROS	Sarcoidosis	59
<i>Echinacea purpurea</i>	Daisy family	Echinacea	Phenolic compounds	ROS	Sarcoidosis	58
<i>Harpogophytum procumbens</i>	Pedaliaceae	Devil's claw	Glycosides	COX, LOX	Sarcoidosis	60

<i>Filipendula ulmaria</i>	Rosaceae	Mead wort	Alcoholic compounds	ROS	Sarcoidosis	61
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NF-Kb: Nuclear factor kappa B cells; TNF- $\alpha$ : tumor necrosis factor; ROS: reactive oxygen species; IL: interleukin; COX: cyclooxygenase; LOX: lipooxygenase; EGCG: Epigallocatechine-3-gallate; THP: Tamm Horsfall Protein; HLA- B 27: Human Leukocyte Antigen Subtype 27; XOD: Xanthine Oxidase enzyme; LT: leukotriene, PG: prostaglandin; FMF: familial mediterranean fever; TRAPS: TNF receptor associated periodic syndrome; RAU: recurrent stomatitis aphthous ulcer; SJIA: systemic juvenile idiopathic arthritis; CAPS: cryopyrine associated autoinflammatory syndromes; CD: Crohns disease; BD: Behcets disease; SS: Schnitzel syndrome

### 3. Conclusion

Auto inflammatory diseases are common and the causative factors for the etiology are still not clear. Conventional and nonconventional approaches are available for treatment of auto inflammatory diseases but all are associated with one or more side effects. Herbal products that are used for treatment of various diseases are mainly plants metabolites. The use of herbal products is increasing worldwide due to its safety profile. Various natural products have been used for auto-inflammatory diseases. However, further clinical studies must be conducted to provide its usefulness.

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