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Phytomedicine: A novel alternative for treatment of gout

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Abstract

Gout is a disorder of purine metabolism in which final product that is uric acid gets precipitated in the form of monosodium urate crystal in joints and in the surrounding tissues. These crystals then lead to local immune-mediated inflammatory reaction which involves IL-β, one of the key proteins in the inflammatory cascade. Due to the loss of uricase during the course of evolution in human and higher primate, has made this condition much common. Gout has been a medical problem for centuries and has increased in prevalence across the world. Despite the availability of allopurinol and febuxostat as xanthine oxidase inhibitors for the treatment of gout, some people develop allergic reactions to these drugs. Therefore, focus on research has increased on phytomedicines that act as inhibitors of xanthine oxidase. Thus, uses of medicinal plants to treat gout and related diseases are gaining much importance.

Key words : Gout, uricase, IL-β, xanthine oxidase, phytomedicine

1. Introduction

1.1 Purine metabolism

In humans, uric acid is the final oxidation (breakdown) product of purine metabolism. Uric acid is formed primarily in the liver and excreted by the kidney into the urine. During purine metabolism, guanosine monophosphate (GMP) is split into the base guanine and ribose.

Guanine is deaminated to xanthine. Similarly, adenosine monophosphate (AMP) is deaminated by the enzyme AMP deaminase to inosine monophosphate (IMP) from which the ribose unit is removed by the enzyme xanthine oxidase to form hypoxanthine. Xanthine is oxidized by oxygen and xanthine oxidase with the production of hydrogen peroxide and uric acid (Figure 1).

During early primate evolution, a nonsense codon inserted into its uricase gene and uricase, thus, produced as a truncated, 10 amino acids long, inactive protein fragment in humans and apes (Bomalaski *et al.*, 2002). The biological reason for the loss of uricase activity in humans and certain primates is still not clear. According to one view, this loss has had a distinctly beneficial effect. It has been proved that uric acid is a powerful antioxidant and a scavenger of free radicals. Therefore, these properties of uric acid have contributed to a decreased cancer rate and a lengthened hominoid life span (Friedman *et al.*, 1985).

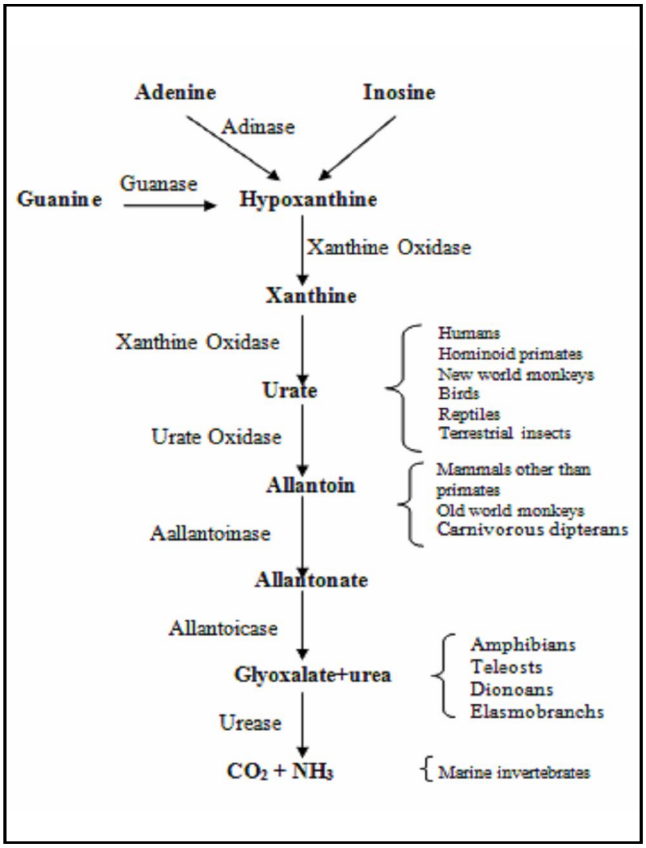

Figure 1: Route of purine degradation in animals (Hayashi *et al.*, 2000)

Due to absence of uricase enzyme in humans, the plasma concentration of uric acid is high (Colloc'h *et al.*, 2006) and an abnormal rise of uric acid can lead to the development of disease known as gout (Figure 2) and hyperuricemia.

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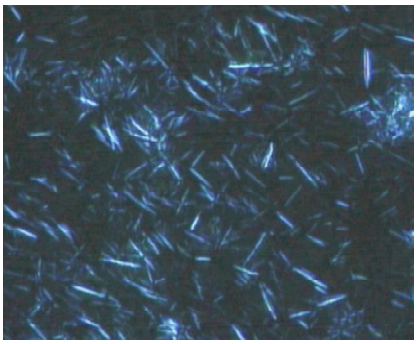

Figure 2: Uric acid crystals

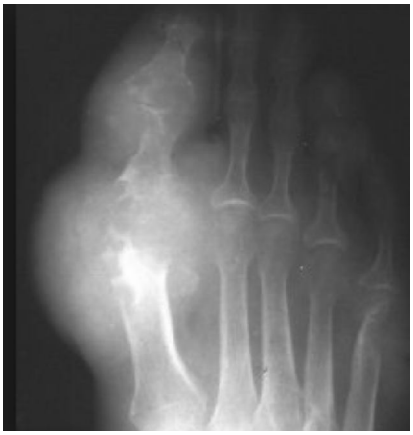

Figure 3: Effect of uric acid

Hyperuricemia has been found to be associated with urate precipitation with the formation of crystals that are involved in gout, tumor lysis syndrome (TLS), chronic kidney disease (CKD), and various cardiovascular diseases (Edwards, 2008; Feig, 2009; Richette and Bardin, 2010). Gout remains among the most common of all inflammatory arthritis, due to lifestyle and dietary factors, such as heavy consumption of beer and liquor as well as diets rich in meats and seafood as important gout risk factors (Saag and Mikul, 2005). The normal serum urate level of uric acid is between 2.18-7.7 mg/dL. In gout, deposition of uric acid crystal takes place in and around the joints (Figure 3). The treatment of hyperuricemia has been performed with drugs that decrease amount of uric acid synthesis by inhibiting xanthine oxidase enzyme.

1.2 Conventional treatment for gout

Therapy for hyperuricemia-associated diseases has been treated by agents that keep plasma urate concentrations from precipitating with the additional benefit of removing existing urate crystals.

Tumor lysis syndrome (TLS) is characterized by the acute onset of hyperuricemia during cancer chemotherapy (Davidson *et al,* 2004; Edwards, 2009; Mughal *et al.*, 2010). Gout, with a prevalence of about 1%, is characterized by the sustained elevation of plasma urate levels (Chohan and Becker, 2009; Richette and Bardin, 2010). Chronic kidney disease is usually associated with hyperuricemia and has a prevalence of about 5% (Kang and Nakagawa, 2005; Sestigiani *et al.*, 2008; Feig, 2009). Currently, available anti-hyperuricemia drugs act on xanthine oxidase, the urate transporter or urate itself. Allopurinol and febuxostat are antihyperuricemia drugs that competitively inhibit xanthine oxidase. Allopurinol has been used as first-line drug for treating gout and TLS, but refractory gout occurs when patients suffer from hypersensitivity or non-responsiveness to allopurinol, intolerance to allopurinol toxicity, or drug-drug interactions with allopurinol (Edwards, 2009; Keenan and Pillinger, 2009; and Mughal *et al.*, 2010). Febuxostat has been reported to be tolerated by most of patients (Terkeltaub, 2010), but its efficacy in treating refractory gout has not been proven. Probenecid is antihyperuricemia drug acting on the renal urate transporter, but it has not been widely used due to toxic effect on kidney and liver (Chohan and Becker, 2009; Richette and Bardin, 2010).

However, for quick reduction of serum uric acid level, uricase enzyme has prominently been used. Uricase (urate oxidase, EC 1.7.3.3.) degrades the poorly soluble uric acid (~11 mg/100 ml H_2O), into the more soluble product allantoin (~147 mg/100 ml H_2O). Urate oxidase has been found in mammalian, plants, and microbial cells. The enzyme may be obtained from several microorganisms of the genus *Micrococcus*, *Brevibacterium*, *Streptomyces*, *Candida*, *Bacillus, Pseudomonas, Arthrobacter*, and *Aspergillus*. We have isolated a novel *Alcaligenes* sp. for the production of uricase for the treatment of hyperurecemia (Figure 4). Uricase from *Alcaligenes* sp. was purified to homogeneity by ammonium sulphate precipitation and DEAE column chromatography. The subunit molecular mass of purified uricase was found to be 30 kDa (Figure 5).

Figure 4: Zone of hydrolysis of uric acid

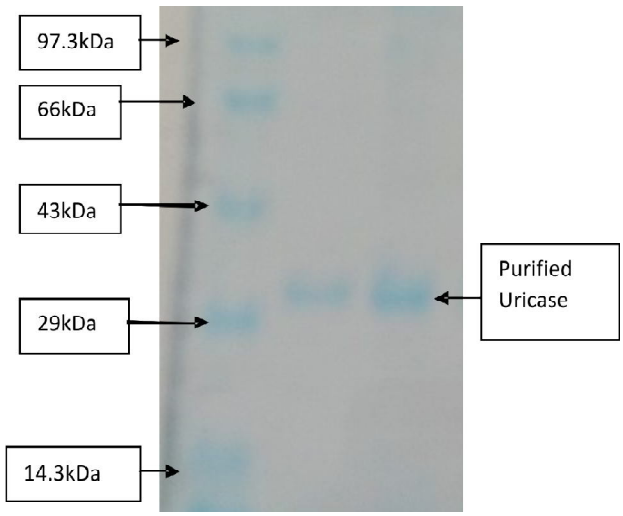

Figure 5: SDS-PAGE of uricase of *Alcaligenes* sp. *by Alcaligenes* sp.

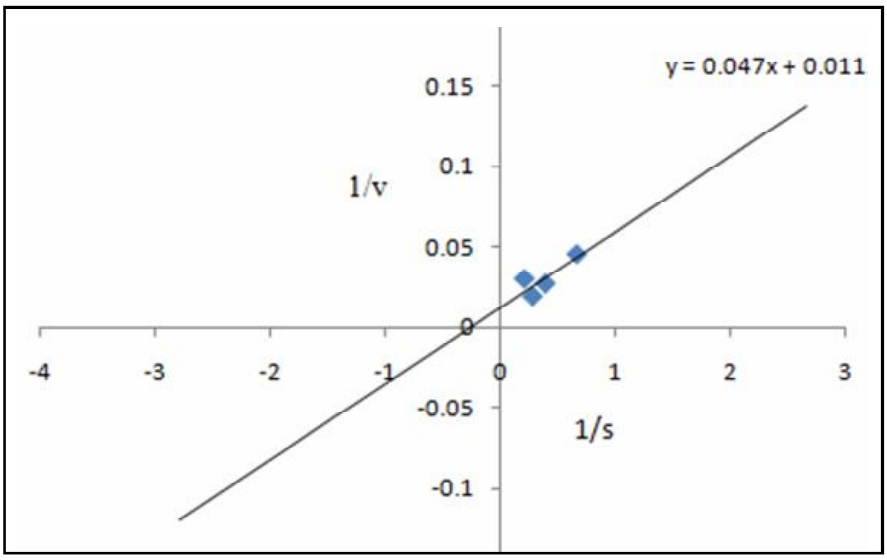

Figure 6: Lineweaver-Burk plot for determining K_m and V_{max} for purified uricase from *Alcaligenes* sp.

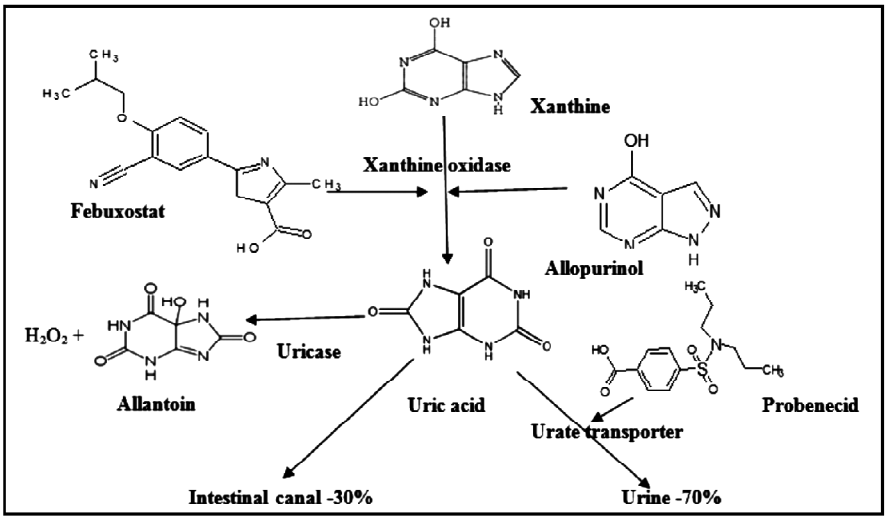

Figure 7: Targets of antihyperuricemia drugs (Yang *et al*., 2012)

The kinetic parameters K_m and V_{max} of the purified uricase from *Alcaligenes* sp. were determined by measuring the uricase activity at different uric acid concentrations (0.01-0.07% w/v). Reaction velocity at varying substrate concentration was determined and a graph was plotted between 1/ [S] vs. 1/ [V]. The K_m and V_{max} values, were calculated from Lineweaver-Burk plot. The K_m and V_{max} of uricase from *Alcaligenes* sp. was found to be approximately 4.27 mM and 90.9 µmol/min/mg, respectively (Figure 6).

Gout prevalence has been increased in direct association with age and the increased longevity of populations in industrialized nations through the disorders associated with age-related diseases such as metabolic syndrome and hypertension (Ar'ev *et al*., 2012). Gout can also cause ocular surface abnormalities, such as tophi deposition, subconjunctival transparent vesicles and vascular changes. These features have provided important clinical significance in early detection of the gout and prevention of eye injury (Lin *et al*., 2013).

The increase in the prevalence of gout worldwide indicates that there is an urgent need for improved efforts to treat the gout. Currently available therapies for gout (Figure 7) have serious adverse side effect on human body. Since, nature contains rich source of medicinal plants and some of them have been reported to inhibit xanthine oxidase (Azmi *et al*., 2012). These medicinal properties of plants can be used as new natural sources of gout medication and a substitute for synthetic xanthine oxidase inhibitors.

1.3 Medicinal plant as alternative to treat gout

Plants contain high amount of antioxidant and biologically active compounds and, thus, acts as target for the searching the new drugs (Gautam *et al*., 2012; Thakur and Azmi, 2013). The treatment of gout involves the use of therapeutic agents such as xanthine oxidase inhibitors (Kong *et al*., 2001; Unno *et al*., 2004). These inhibitor act by blocking the biosynthesis of uric acid from xanthine during purine metabolism in the body (Unno *et al*., 2004). The concentration of uric acid can be regulated by either increasing the excretion of uric acid or reducing the uric acid production to reduce the risk of gout (Umamaheswari *et al*., 2007).

Allopurinol is one of the synthetic xanthine oxidase inhibitor which has been widely used in the therapeutic and clinical management of gout and conditions associated with hyperuricemia as well as related inflammatory diseases (Fields *et al*., 1996; Pacher *et al*., 2006). However, drawback of using allopurinol is that it generates superoxide (Berry and Hare, 2004) and causes allergical reactions in body (Wallach, 1998; Kong *et al*., 2000).

Thus, the use of herbal plants to treat diseases is gaining new interest because of their low allergenicity (Unno *et al*., 2004). Plants are important sources of medicines and in United States, about 25% of pharmaceutical prescriptions contain at least one plant-based ingredient. Based on the traditional knowledge obtained from various sources, roughly 121 pharmaceutical products were formulated during the last century. Phytomedicine obtained from herbal sources are in great demand in the developed world as their ability to cure many diseases. These plant based drugs provide outstanding contribution to modern therapeutics (Pandey *et al.,* 2011). Some of herbal plants and their phytochemicals are worth to be explored as potential xanthine oxidase inhibitor as they are already used as food or food supplements for many years and found safe for human bodies (Abd Aziz *et al*., 2011). The herbs or natural medicines having the potential for inhibiting xanthine oxidase are summarized in Table1 (Kong *et al*., 2000; Umamaheshwari *et al*., 2007).

Polyphenols (Costantino *et al*., 1992), flavonoids (Chang *et al*., 1993; Selloum *et al*., 2001), coumarins (Chang and Chiang, 1995), ellagic acid, valoneic acid dilactone (Unno *et al*., 2004) have been reported to be potent plant-based xanthine oxidase inhibitor.

Table 1: List of herbs that inhibit xanthine oxidase

Plant name	Local name	Percent of xanthine oxidase inhibition (50-100µg/mL)	IC_{50} (µg/mL)	Part of plant used
Angelica dahurica	Angelica root	40-90%	NR	Root
Angelica sinensis	Angelica root head	18-93%	40	Root
Artemisia anomola	Sweet gum fruit	48-89%	33-66	Whole plant
Astragalus membranaceus	Astragalus root	12-64%	85	Root
Carthamus tinctorius	Safflower	23-81%	64	Fruit
Chrysanthemum indicum	Chrysanthemum flower	34-95%	24-91	Flower
Citrus sinensis	Orange	27-51%	98	Fruit shell
Cledodendron trichotomum	Harlequin glory bower	12-86%	65	Leaf
Coccinia grandis	Tondi	40-77%	21-32	Leaf
Cuscuta chinensis	Cuscuta seed	23-55%	53	Seed
Dutura metal	Angel or Devil's trumpet	9.4-62%	77	Leaf
Erythrina indica	Tiger claw	17-79%	70	Bark
Fraxinus rhynchophylla	Flaxinus, Ash	48-96%	28-53	Bark
Glechoma longitube	Glechoma	16-91%	48	Whole plant
Glycyrrhiza uraiensis	Lico rice root	24-49%	NR	Root
Kochia scoparia	Kochia fruit	24-51%	116	Seed
Ligusticum brachylobum	Ligusticum	17-94%	34	Rhizome
Lycopodium clavatum	Lycopodium tuber	13-58%	94	Whole plant
Lycopus europaeus	Gypsywort, Bugleweed	39-93%	26-79	Leaf
Morus alba	White mulberry	18-93%	57	Twig
Piper kadsura	Piper	11-94%	28	Stem
Plantago asiatica	Plantago	26-56%	98-103	Seed, Ariel
Polygonum cuspidatum	Knotweed	12-94%	38	Rhizome
Prunella vulgaris	Selfheal spike	27-63%	86	Whole plant
Rheum palmatum	Rhubarb rhizome	17-57%	101	Rhizome
Salvia mitiorrhiza	Salvia root	27-56%	96	Root
Scutellaria barbata	Scutellaria, Barbal skull cap	31-87%	62	Whole plant
Smilax china	Prickly ivy's, catbriers	18-89%	62	Rhizome
Strychnos nox-vomica	Strychnine tree	38.7-82%	6.8-32	Leaf
Vitex negundo	Chaste tree	6.2-66%	76-88	Leaf

Source: Modified from Kong *et al*., 2000; Umamaheshwari *et al*., 2007

[#] IC50 represents different form of extract (Me-OH; Me-OH-H_2O; H_2O) NR=Not reported

The type of herbal extract used such as methanol (Me-OH), Me-OH-H_2O, or H_2O also have a significant influence on the degree of inhibition of herbal product, has on xanthine oxidase activity. In most of the cases, the herbs prepared as a Me-OH extract has been found to be a greater inhibition of xanthine oxidase as compared to other types of extracts of the same herb (Umamaheshwari *et al*., 2007). Similar effect has been found to be with other herbs or natural medicines that are known to inhibit xanthine oxidase activity from other regions of the world (Kong *et al*., 2000).

However, many studies have reported that herbal medicine has beneficial effect on patients with gout. The herbs which have been used in treatment were chosen either their ability to eliminate uric acid (*Apium graveolens, Urtica* spp, *Taraxacum officinale) or* anti-inflamatory *such as Harpagophytum procumbens, Filipendula ulmaria*, *Salix* spp., *Betula* spp. *Curcuma longa* and *Guaiacum* spp. as reported by Nadia and Barbara, 2013.

2. Indian medicinal plant as antigout agent

2.1 *Gloriosa superba* Linn.

Gloriosa superba Linn. is a well known ethnomedicinal plant which has also been mentioned in Ayurveda (Figure 8a). Phytochemical studies has been reported on *G. superba,* shown the presence of colchicin, b-siltosterol, long chain fatty acids, b and g-lumic colchicines, 2-hydroxy-6-methoxy benzoic, luterlin, N-formyl-de acetyl colchicines and new colchicine glycoside, 3-O-demethylcolchicine-3-O-alpha-D-glucopyranoside. *Gloriosa superba* reproduce by corm and seeds but has very low germination capability which restricts its multiplication. Therefore, biotechnological technique can be very useful in order to increase the efficiency of germination of this important plant. Micropropagation of *Gloriosa superba* can help in meeting the increasing demands for colchicine. Thus, *Gloriosa superba* can acts as potential source of colchicine in India due to availability from both wild and cultivated sources (Hemant *et al.,* 2011). FDA has also approved the use of colchicine is to treat gout. It is one of the active ingredients of antigout tablets marketed by Merck and Co. (Ling and Bochu, 2014).

2.2 *Erythrina indica* Lam.

Erythrina indica Lam. belongs to the family Leguminosae (Figure 8b). This is an important medicinal plant and found in wild deciduous forests throughout India and in Andaman and Nicobar Islands. Bark of *E. indica* has been used medicinally as febrifuge, antibilious and also used to treat dysentery. Bark powder has been traditionally used for rheumatism, itching, fever, asthama and leprosy (Anonymous, 1992). The study has shown that the root bark of *E. indica* has been used for the treatment of trachoma, elephantiasis, and microbial infections (Nkengfacka *et al.,* 2001). Different kinds of phenolic compounds including isoflavones derivatives and various biologically active metabolites have been isolated from the bark of this plant (Azebaze *et al*., 2000; Nkengfacka *et al.,* 2001). There has been numerous reports on the antioxidant and free radical scavenging potential of leaves and barks of *E. indica* (Sakat and Juvekar, 2010) by measuring the increase in absorbance at 295nm associated with uric acid formation. The methanol extract of stem bark of *E. indica* contains higher level of total phenolic content (412.8 mg GAE/g extract) having xanthine oxidase inhibition activity (Kandhasamy *et al*., 2012). Thus, it can be used for treating gout.

2.3 *Citrus aurantium* Linn, *Citrus limetta* W. and A. and *Citrus limon* (Linn) Burm.

Many Indian medicinal plants have been used for the prevention and treatment of gout and related inflammatory disorders. *Citrus limetta*, *Citrus aurantium* and *Citrus limon* (Figure 8 c, d, e) belonging to the family Rutaceae, which is traditionally used by the local people and tribals in India for the treatment of gout, liver disorders, stomachic, brain troubles, *etc*. (Figure 8c,). These medicinal plants possess phytochemical constituents like flavonoids, and a group of polyphenolic compounds, which have been reported to possess xanthine oxidase inhibitory activity. The *in vitro* xanthine oxidase inhibitory activity of the extract of leaves, fruits and peel of *Citrus aurantium, Citrus limettas,* and *Citrus limon* has been determined. These leaf and peel extracts of *C.aurantium, C.limetta* and *C.limon* and the fruit extract of *C.limetta*) has shown xanthine oxidase activity at a concentration of 100¼ g/ml, showing an inhibition greater than 50% (Muthiah, 2012). Since, alternatives with an increased therapeutic activity and less side effects are desired. Thus, the use of the medicinal plants can act as the alternative to chemical drugs such as allopurinol and can be used for treatment of gout.

2.4 *Tephrosia purpurea* (Linn.) Pers.

Tephrosia purpurea (Linn.) Pers. (Fabaceae) is a pantropical, polymorphic, branched, suberect, perennial herb popularly known as *Sarapunkha* in Sanskrit (Figure 8f), Purple Tephrosia in English and *Unali* in Marathi (Kirtikar and Basu, 1975). The plant is used in folk medicine as an antidiabetic, antipyretic, anticancer and antiulcer agent in addition to its usefulness in treatment of diseases related to oxidative stress and free radicals activity (Pavana *et al.*, 2008). Reactive Oxygen Species (ROS) play important role in the initiation and progression of various diseases such as arthrosclerosis, cardiovascular diseases, aging, respiratory diseases, cancer and gout (Esterbauer *et al*., 1991; Ames and Shigenaga, 1992). Root extract of *T. purpurea* has been evaluated as an antioxidant, anti-inflammatory and potent inhibitor of xanthine oxidase which is mainly involved in formation of uric acid, leading to free radical induced damage and gout. The phytochemical analysis revealed presence of significant amount of polyphenols and flavonoids.

T. purpurea root extract posses prominent medicinal properties and can be exploited as natural drug to treat the diseases associated with free radical formation, oxidative stress and xanthine oxidase activity (Nile and Khobragade, 2011).

2.5 *Capparis decidua* Edgew.

Capparis decidua Edgew. is a xerophytic dominating shrub, found in desert region of Rajasthan, showing strong climatic adaptations. It is a densely branched, thorny plant with smaller scanty and caduceus leaves, having pink to red flowers and green berry fruits (Figure 8g). *Capparis dedcidua* is one of the most important floras among 44% of all species of vascular plants which come under'biodiversity hotspots'. Being a desert plant, it possesses diverse chemical constituents, which are of great nutritional and medicinal value and can be used as a potential food supplement (Chauhan *et al*., 1986). It is an important nonconventional food source in India. The name caper is derived from Arabic Caper and relates to *Capparis spinosa* belong to family Capparidaceae. In India, mainly Rajasthan, Uttar Pradesh and Madhya Pradesh, *Capparis decidua* plant has wider diversity where it is commonly

known as 'Kureel' or Kareel in Hindi (Ozacus, 1999). Plant has its wider utility in traditional folk medicine and has been used as ailments to relieve variety of pains or aches such as toothache, cough and asthma heal (Ravi, 2011). Phytochemical studies of *C. decidua* have shown presence of many beneficial compounds, which have shown analgesic, laxative, antihelmintic, antiparasitic and antiprotozoan activity. Root bark powder has been traditionally used to cure rheumatism, dropsy, ulcer, gout, fever, cough, asthma, boils, piles and inflammation (Chakravarty and Venkarasubramaniam, 1932). This plant contains few important secondary metabolites such as quercetin which act as melanogenesis stimulator and also increase tyrosinase protein expression (Lam and Ng, 2009). *Capparis* sp. seeds contain lectin that exhibit potent anti HIV-1 reverse transcriptase inhibition activity and also inhibits proliferation of hepatoma HepG2 and breast cancer MCF-7 cells (Leucha *et al.*, 2009). It has also been reported for having antirheumatic, antidiabitic, antiarthritis and antigout effect (Chakravarty and Venkarasubramaniam, 1932). *C. decidua* has been reported to contain generous quantities of alkaloids, fatty acids, terpenes, vitamins, fibre and oils that show greater medicinal and nutritive value (Sharaf *et al*., 2000). It also contains saccharides, glycosides, flavonoids, volatile oils, sterols and steroids, which showed multiple pharmacological effects such as antigout, odynolysis, antifungus, hepatoprotective effect, hypoglycemic activity, antioxidation, antihyperlipemia, anticoagulated blood, smooth muscle stimulation and antistress reaction (Calis *et al*., 2002).

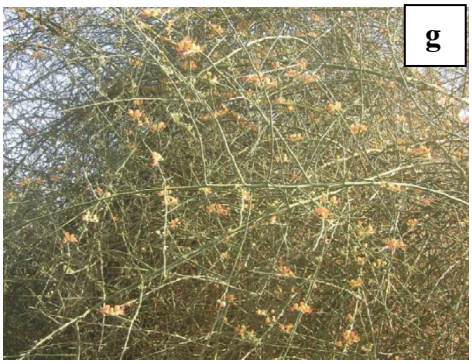

Figure 8: (a) Branch showing flowers of *Gloriosa superb* Linn.
(b) Leaves of *Erythrina indica* Lam. plant
(c) Plant of *C. limetta* W. and A.
(d) Plant of *C. aurantium* Linn.
(e) Plant of *C. limon* (Linn.) Burma.
(f) Stem of *Tephrosia purpurea* (Linn.) Pers showing flowers and leaves
(g) *Capparis decidua* Edgew. plant
(h) Leaves of *Polyalthia longifolia* (Sonn.) Thwaites plant

2.6 *Polyalthia longifolia* (Sonn.) Thwaites

This plant belongs to Annonaceae family, is a lofty evergreen tree, native to India and commonly planted due to its effectiveness in alleviating noise pollution (Figure 8h). The plant has been used in traditional system of medicine for the treatment of fever, skin diseases, diabetes, hypertension and helminthiasis (Kritikar and Basu., 1995). The plant was reported to possess antibacterial, cytotoxic, antiulcer and antifungal activities (Jain *et al.*, 2006; Nair and Chanda 2006a; Nair and Chanda 2006b; Malairajan *et al.*, 2008). The study has reported the *in vitro* xanthine oxidase inhibitory activity of the extracts of the leaves of *Polyalthia longifolia*. The study has shown that the ethanol and chloroform extracts of leaves of *Polyalthia longifolia* exhibit xanthine oxidase inhibitory activity (Andichettiar and Tapan, 2012). In traditional medicine, the plant has been used in various disorders including diabetes. Xanthine oxidase is reported to be involved in the chronic complications, associated with diabetes mellitus. Further, investigations on the active phytoconstituents in the plant and *in vivo* studies are necessary to ascertain the mechanism and usefulness of this plant in preventing gout complications, associated with chronic diabetes.

3. Conclusion

Plant contain mixture of complex compounds having biological properties such as antioxidant, detoxification enzymes, stimulation of the immune system, reduction of platelet aggregation, and modulation of hormone metabolism. The bioactive compounds that have been derived from plants include flavonoids, terpenoids, phenolic acids, and other categories of phytochemicals based on their structure, has been reported for their antigout and anti-hyperuricemic effect. Since, the prevalence of gout has been increased all around the world at steady rate and conventional therapies for gout treatment have been restricted due to their failure to provide long term immunity, high cost and their side effect on human body. Thus, the screening of various herbal plants extract for antigout effect and lesser side effects, can lead to development of novel drug therapy for gout treatment.

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Conflict of interest

We declare that we have no conflict of interest.

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