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Research Article

INDIAN MEDICINAL PLANTS USEFUL IN TREATMENT OF GOUT: A REVIEW FOR CURRENT STATUS AND FUTURE PROSPECTIVE

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ABSTRACT

Objective: The objective of this review is to collect and document information on the Indian medicinal plants with anti-gout potential.

Methods: Bibliographic investigation was carried out by consulting worldwide scientific databases, analyzing Ayurvedic text books and research journals. The search terms were "gout," "uric acid," "hyperuricemia," "xanthine oxidase (XO) inhibitor and uricosuric." Herbal keywords included "herbal medicine," "medicinal plant," "natural products," "phytomedicine" and "phytotherapy."

Result and Conclusion: Medicinal plants have been used to treat various ailments since ancient times; hence, ethnobotanical investigations play an important role in pharmacological studies. In India, traditional medicines are being practiced for the treatment of gout and other rheumatic disorders from ancient time. This review provides a comprehensive summary of 130 Indian plants which have been mentioned in ancient literature or used traditionally for the treatment of gout. Out of these, 41 plants have been reported to possess XO inhibitory activity. Further, isolated phytoconstituents having promising XO inhibitor activity are also included in this review. Although a variety of medicinal plants with anti-gout potential have been found in the literature, there is limited information on evaluation of anti-gout activity of isolated phytoconstituents. The current review contains a detailed discussion of the potential of medicinal plants for treatment of gout.

Keywords: Gout, Xanthine oxidase inhibitor, Uricosuric agents.

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INTRODUCTION

Gout is an inflammatory joint disease, associated with an elevated uric acid level in blood which further leads to the deposition of urate crystals in the joints and kidneys followed by painful inflammation, gouty arthritis, and uric acid nephrolithiasis [1-3]. Xanthine oxidase (XO) is responsible for oxidation of hypoxanthine to xanthine and finally xanthine to uric acid [4,5]. Over activity of this enzyme and increased intake of dietary food rich in nucleic acids (e.g. meat, leguminous seeds) impair renal excretion of uric acid and result in hyperuricemia and gout [6-11].

In India, approximately 0.12-0.19% population is affected by gout, and its prevalence is more in men aged above 50 years [12,13]. The prevalence of gout is less in premenopausal women as estrogen hormone helps in urate clearance [13]. Hyperuricemia is the key predictor for the development of gout. Uric acid level over 6.8 mg/dl leads to the deposition of sodium urate crystals in joints and subcutaneous tissue [14]. This disease occurs in two phase, i.e., acute phase and chronic phase. In acute phase, intermittent attacks occur that resolves spontaneously over a period of 7-10 days. The onset of acute attack is abrupt and the affected joint becomes red, swollen, warm, and tender [7]. If acute attacks are inadequately treated, it can transform to chronic tophaceous gout. Tophi develop in periarticular tissues, cartilaginous helix of ear, and tendon sheaths [15].

Conventional treatment strategies and associated side effects

Treatment of gout is either reducing the production of uric acid (XO inhibitors) or increasing uric acid excretion (uricosuric drugs) [6]. New agents such as uricase analogs and biological cytokine inhibitors have been also used for the treatment of gout [7,8]. Allopurinol, a commonly used XO inhibitor, has various adverse effects such as hypersensitivity syndrome, Stevens Johnson syndrome, renal toxicity, and fatal liver necrosis [9,10]. Gastric and renal adverse effects are common with long-term use of anti-inflammatory agents. Selective COX-2 inhibitors are less toxic than non-selective nonsteroidal anti-inflammatory drugs (NSAID's) but renal side effects are similar to conventional NSAID's. Fatal hypersensitivity syndrome, gastric disturbances and nephrotic damage are associated with the use of urate lowering drugs such as XO inhibitors and uricosuric agents. Nausea, vomiting, severe diarrhea, and kidney damage are common with the use of colchicine. Cytokine inhibitors are highly effective with very few side effects, but these drugs are extremely expensive when compared with traditional treatment [16-18].

Impact of medicinal plants

The use of plant-based drugs for the treatment of various ailments is increasing worldwide as they are considered much safer compared to synthetic drugs [19]. India is a veritable and rich emporium of medicinal and aromatic plants. India has more than 17,500 wild plant species and out of these 4000 species have medicinal value [20]. The market sales and research activities of herbal products are growing steadily [21]. As compared to allopathic drugs, herbal medicines are claimed to be non-toxic, or generally regarded as safe because they are obtained from natural origin and their reported long-term use as folk medicine [22].

In the present review, we have summarized various Indian herbal plants used for management of gout (Table 1). Medicinal plants with reported XO inhibitory activity are also discussed in Table 2. The XO inhibitory activity of isolated phytoconstituents has been carried out by various researchers and their results have been summarized in Table 3.

Plant profiles

The anti-arthritis potential of various plants has been described briefly in the following section. The discussion consists of major families to which most of these plants belong.

Table 1: Indian medicinal plants used in the treatment of gout

Family	Plant name	Common name	Part used	References
Acanthaceae	*Andrographis paniculata*	Bhuin	Roots	[23]
Acanthaceae	*Asteracantha longifolia*	Bhikshu	Roots	[24,25]
Acanthaceae	*Barleria prionitis*	Barleria	Leaves	[25,26]
Acanthaceae	*Ecbolium linneanum*	Blue fox tail nail dye	Whole plant	[27]
Acanthaceae	*Nilgirianthus heyneanus*	Sahachara	Whole plant	[28]
Aizoaceae	*Mollugo cerviana*	Parpata	Roots	[25,29]
Amaranthaceae	*Amaranthus spinosus*	Mokhonkia Phak	Whole plant	[20]
Anacardiaceae	*Pistacia integerrima*	Kakar Singhi	Leaves	[30]
Anacardiaceae	*Semecarpus anacardium*	Marking-nut	Whole plant	[25,31]
Annonaceae	*Polyalthia longifolia*	Devdaru	Stem bark	[23]
Apiaceae	*Adhatoda vasica*	Basak	Leaves	[32]
Apiaceae	*Apium graveolens*	Garden celery	Aerial parts	[33]
Apiaceae	*Coriandrum sativum*	Coriander	Fruit	[9]
Apiaceae	*Petroselinum crispum*	Parsley	Seeds and leaves	[25,34]
Araceae	*Acorus calamus*	Boch	Leaves	[35]
Asparagaceae	*Asparagus racemosus*	Shatavari	Roots	[25]
Asteraceae	*Articum lappa*	Bardana	Roots	[36]
Asteraceae	*Chamomilla recutita*	Pineapple weed	Flowers	[9]
Asteraceae	*Cichorium intybus*	Chicory	Whole plant	[37]
Asteraceae	*Conyza bonariensis*	Flax-leaf fleabane	Whole plant	[38]
Asteraceae	*Elephantopus scaber*	Mejo-jhuti	Leaves	[23]
Asteraceae	*Launaea sarmentosa*	Littoral spine grass	Whole plant	[25]
Bignoniaceae	*Tecoma stans*	Yellow bells	Whole plant	[39]
Brassicaceae	*Brassica oleracea*	Cabbage	Leaves and roots	[40]
Bromeliaceae	*Ananas comosus*	Anaros	Roots	[35]
Caesalpiniaceae	*Caesalpinia bonduc*	Fever nut	Seeds	[25]
Caesalpiniaceae	*Caesalpinia sappan*	Pathimughom	Heartwood	[41]
Caesalpiniaceae	*Cassia fistula*	Cassia stick	Pulp	[25]
Caesalpiniaceae	*Cappris aphylla*	Caper berry	-	[25]
Cannabaceae	*Cannabis sativa*	Bhang	Leaves	[42]
Capparidaceae	*Cappris decidua*	Amargna	Seeds	[43]
Capparidaceae	*Cappris spinosa*	Capeberry	Whole plant	[44]
Caprifoliaceae	*Sambucus nigra*	Elderberry	Fruits	[9]
Celastraceae	*Celastrus paniculatus*	Staff tree	Seeds	[23,25,45]
Compositae	*Blumea balsamifera*	Sambong	Leaves	[46]
Compositae	*Helianthus annus*	Sunflower	Tubers	[25]
Compositae	*Saussurea lappa*	Kuth	Roots	[25]
Costaceae	*Costus speciosus*	Keokand	Roots	[47]
Crassulaceae	*Rhodiola rosea*	Rhodiola	Roots	[48]
Cucurbitaceae	*Citrullus colocynthis*	Kuwabhaturi	Leaves	[39,49]
Cucurbitaceae	*Coccinia grandis*	Ivy Gourd	Leaves	[6]
Cucurbitaceae	*Momordica charantia*	Bitter gourd	Fruits and leaves	[25,50]
Cupressaceae	*Biota orientalis*	Westmont	Leaves	[1]
Cupressaceae	*Juniperus communis*	Juniper	Berries and leaves	[9]
Cruciferae	*Lepidium sativum*	Garden cress	Seeds	[25]
Euphorbiaceae	*Jatropha curcas*	Bhot-era	Roots	[35]
Euphorbiaceae	*Euphorbia antiquorum*	Trinagular spurge	Stem	[51]
Euphorbiaceae	*Tragia involucrata*	Climbing nettle	Roots	[42]
Fabaceae	*Abrus precatorius*	Crab's eye	Leaves and seeds	[25]
Fabaceae	*Crotalaria burhia*	Rattlepod	Leaves	[52]
Fabaceae	*Erythrina stricta*	Ronga modar	Roots	[2]
Fabaceae	*Indigofera tinctora*	Indigo	Whole plant	[53]
Fabaceae	*Phaseolus calcaratus*	Banmungo	Whole plant	[54]
Fabaceae	*Tephrosia purpurea*	Fish Poison	Roots	[55]
Fabaceae	*Trigonella foenumgraecum*	Methi	Seeds	[25]
Flacourtiaceae	*Flacourtica indica*	Governor plum	Bark	[25]
Flacourtiaceae	*Gynocardia odorata*	Challmograa	Seeds	[25]
Guttiferae	*Mesua ferrea*	Iron wood	Stamens	[25]
Hypericaceae	*Hypericum perforatum*	St. Johnswort	Aerial parts	[9]
Iridaceae	*Crocus sativum*	Saffron	Bulbs	[9]
Labiatae	*Ajuga bracteosa*	Khurbanti	Whole plant	[56]
Labiatae	*Rosmarinus officinalis*	Rosemary	Aerial parts	[33]
Lamiaceae	*Mentha canadensis*	Field Mint	Roots	[6,36]
Lauraceae	*Cinnamomum zeylanicum*	Ceylon cinnamon	Whole plant	[33]
Leguminosae	*Adenanthera pavonina*	Coral wood	Whole plant	[25,57]
Leguminosae	*Cassia senna*	Indian senna	Leaves and pods	[58]
Liliaceae	*Gloriosa superba*	Glory lily	Tubers	[59]
Loganiaceae	*Strychnos nux vomica*	Poison nut	Leaves	[6]
Loranthaceae	*Viscum articulatum*	Mandirika jhada	Whole plant	[23]
Lythraceae	*Lagerotroemia speciosa*	Pride of India	Leaves	[3]
Malvaceae	*Abutilon indicum*	Country mallow	Roots	[25]

(Contd...)

Table 1: ***(Continued)***

Family	Plant name	Common name	Part used	References
Malvaceae	*Gossypium herbaceum*	Kopah	Leaves	[35]
Malvaceae	*Hibiscus sabdariffa*	Roselle	Whole plant	[10]
Meliaceae	*Swietenia mahagoni*	Mahogany	Seeds	[60]
Menispermaceae	*Cocculus hirsutus*	Broom creeper	Roots	[61]
Menispermaceae	*Tinospora cordifolia*	Guduchi, Giloy	Whole plant	[62]
Molluginaceae	*Mollugo cerviana*	Threadstem carpetweed	Whole plant	[63]
Moraceae	*Ficus bungalensis*	Borgach	Leaves	[49]
Moraceae	*Ficus carica*	Fig	Whole plant	[33]
Myristicaceae	*Myristica fragrans*	Nutmeg	Nut	[9]
Myrtaceae	*Caryophyllus aromaticus*	Clove	Flower buds	[9]
Oleaceae	*Olea europaea*	Olive	Leaves	[4]
Oleaceae	*Schrebera swietenioides*	Gantha karna	Roots	[35]
Papaveraceae	*Papaver rhoeas*	Corn poppy	Leaves and flowers	[64]
Papilionaceae	*Uraria picta*	Prishniparni	Whole plant	[25]
Periocaceae	*Hemidesmus indicus*	Antamula	Roots	[65]
Piperaceae	*Piper longum*	Long pepper	Fruits	[66,67]
Piperaceae	*Piper nigrum*	Black pepper	Fruits	[42]
Plantaginaceae	*Plantago ovata*	Aspagol	Seeds	[25]
Poaceae	*Coix lachryma- jobi*	Changing	Seeds	[68]
Poaceae	*Cymbopogan citrates*	Lemon grass	Leaves and stalks	[69]
Poaceae	*Imperata cylindrica*	Blady grass	Roots	[70]
Primulaceae	*Primula veris*	Cowslip	Flowers	[9]
Ranunculaceae	*Aconitum falconeri*	Monk's hood	Roots	[71,72]
Ranunculaceae	*Aconitum violaceum*	Mithi	Roots and rhizome	[25]
Ranunculaceae	*Aquilegia fragrans*	Fragrant columbine	Roots	[71]
Ranunculaceae	*Delphinium denudatum*	Larkspur	Roots	[25]
Ranunculaceae	*Nigella sativa*	Fennel flower	Seeds	[73]
Ranunculaceae	*Ranunculus arvensis*	Corn buttercup	Whole plant	[74]
Ranunculaceae	*Thalictrum foliolosum*	Pitarangaa	Whole plant	[75]
Rhamnaceae	*Ziziphus jujuba*	Indian jujbe	Root	[25]
Rubiaceae	*Paederia foetida*	Gandhali	Leaves	[23]
Saliaceae	*Salix alba*	White willow	Whole plant	[23]
Sapindaceae	*Cardiospermum halicacabum*	Small balloon vine	Whole plant	[76]
Sapindaceae	*Dodonaea viscose*	Hopseed	Whole plant	[77,78]
Sapindaceae	*Schleichera oleosa*	Kusum	Seeds	[23]
Scrophulariaceae	*Scoparia dulcis*	Broomweed	Whole plant	[25]
Solanaceae	*Capsicum annum*	Pepper	Fruits	[9]
Solanaceae	*Datura metel*	Angel's trumpet	Leaves	[6]
Solanaceae	*Nicotiana tobacum*	Tobacco	Leaves	[25]
Solanaceae	*Physalis alkekengi*	Strawberry tomato	Leaves and fruits	[79]
Solanaceae	*Physalis minima*	Sunberry	Fruits	[25]
Solanaceae	*Physalis peruviana*	Cape gooseberry	Whole plant	[25]
Solanaceae	*Solanum nigrum*	Black nightshade	Leaves	[80]
Solanaceae	*Withania somnifera*	Ashwagandha	Roots and stem	[81]
Sterculiaceae	*Pterospermum heyneanum*	Barahakani	Flowers and fruits	[23]
Thelypteridaceae	*Christella parasitica*	Bihdhekia	Whole plant	[82]
Umbelliferae	*Daucus carota*	Carrot	Roots	[83]
Uritaceae	*Urtica dioica*	Stinging nettle	Aerial parts	[9]
Violaceae	*Viola odorata*	Wood violet	Aerial parts	[9]
Verbenaceae	*Premna serratifolia*	Headache tree	Whole plant	[25]
Verbenaceae	*Vitex negundu*	Pochatia	Leaves	[6,35]
Vitaceae	*Cissus quadrangularis*	Harjora lata	Stem	[35]
Vitaceae	*Vitis vinifera*	Wine grape	Fruits	[84]
Zingiberaceae	*Curcuma amada*	Amba	Rhizomes	[23]
Zingiberaceae	*Curcuma caesia*	Kola halodhi	Rhizomes	[35]
Zingiberaceae	*Curcuma longa*	Turmeric	Whole plant	[33]
Zingiberaceae	*Kaempferia parviflora*	Krachai dhum	Rhizome	[85]
Zingiberaceae	*Zingiber officinale*	Ginger	Rhizomes	[40]
Zygophyllaceae	*Tribulus terrestris*	Gokharu	Fruits and seeds	[86]

Acanthaceae

A. paniculata, a widely distributed plant in India, is used topically as well as internally for the treatment of gout [90]. In traditional system of medicine, *Asteracantha longifolia* parts are extensively used for various ailments such as rheumatism, inflammation, jaundice, hepatic obstruction, pain, urinary infections, edema, and gout [23,91]. *Barleria prionitis* is distributed throughout the tropical regions of India, Pakistan, Sri Lanka, Philippines, Africa, and Yemen. The extract of the plant is used for massage in toothache, swellings, arthritis, and gout pains [25,92]. *Ecbolium linneanum* is widely distributed along the eastern part of India. It has been used in various ailments such as jaundice, menorrhea, rheumatism, gout, and dysuria [31]. *Nilgirianthus heyneanus* is a traditional Ayurvedic herb, found throughout India. The whole plant is used in nervous system diseases, pruritus, gout, and rheumatoid arthritis [32].

Apiaceae

The paste of fresh leaves of *Adhatoda vasica* is used in dysentery, cough, fever, bronchial congestion, gout, and muscular sprains [37]. The anti-gout potential of *Apium graveolens* has been evaluated on male

Table 2: Medicinal plants with reported XO inhibitory activity

Plant name (Family)	Extract	Part used	XO inhibition (100 µg/ml) (%)	IC_{50}	References
Adenanthera pavonina (Fabaceae)	Methanol	Leaves	47.15	-	[87]
Antigonon leptopus (Polygonaceae)	Methanol	Leaves	59.0	-	[87]
Apium graveolens (Apiaceae)	80% ethanol	Aerial parts	-	>200 µg/ml	[9]
	CH_2Cl_2/methanol			>200 µg/ml	
Articum lappa (Asteraceae)	Methanol	Roots	36.35±2.72	-	[36]
Averrhoa carambola (Oxalidaceae)	Distilled water	Flowers	0.19±2.4	-	[14]
		Leaves	9.34±1.19		
		Ripe fruit peel	1.47±0.3		
	70% methanol	Flowers	2.46±0.6		
		Leaves	20.73±0.7		
		Ripe fruit peel	6.89±2.3		
	Ethanol	Flowers	2.47±0.45		
		Leaves	23.61±0.8		
		Ripe fruit peel	7.11±0.9		
Blumea balsamifera (Compositae)	Methanol	Leaves	-	0.111±0.002 mg/ml	[47]
	Chloroform			0.138±0.004 mg/ml	
	Petroleum ether			0.516±0.003 mg/ml	
Capsicum annum (Solanaceae)	80% ethanol	Fruits	-	>200 µg/ml	[9]
	CH_2Cl_2/methanol			>200 µg/ml	
Carica papaya (Caricaceae)	Distilled water	Leaves	75.68±0.1	-	[11]
		Petioles	0.45±0.4		
		Seeds	18.92±0.5		
		Fruit peel	79.28±0.2		
		Flowers	60.36±0.2		
	70% methanol	Leaves	17.52±1.6		
		Petioles	79.28±0.3		
		Seeds	18.02±0.1		
		Fruit peel	15.31±0.2		
		Flowers	72.52±0.1		
	Ethanol	Leaves	64.41±0.2		
		Petioles	57.91±0.9		
		Seeds	78.38±0.1		
		Fruit peel	8.11±0.1		
		Flowers	19.82±0.1		
Cassia alata (Caesalpiniaceae)	Methanol	Leaves	24.81	-	[87]
Cassia fistula (Cupressaceae)	Methanol	Leaves	61.9	-	[87]
Chammomila recutita (Asteraceae)	20% ethanol	Flowers	-	>200 µg/ml	[9]
	80% ethanol			141.8 µg/ml	
	CH_2Cl_2/methanol			87.6 µg/ml	
Cichorium intybus (Asteraceae)	Methanol	Herb	9.16±1.59	-	[36]
Coccinia grandis (Cucurbitaceae)	Aqueous	Leaves	-	32.25 µg/ml	[6]
	Hydroalcoholic			21.25 µg/ml	
	Methanol			29.75 µg/ml	
Coriandrum sativum (Apiaceae)	20% ethanol	Fruits	-	>200 µg/ml	[9]
	80% ethanol			>200 µg/ml	
	CH_2Cl_2/methanol			>200 µg/ml	
Crocus sativum (Iridaceae)	20% ethanol	Whole plant	-	>200 µg/ml	[9]
	80% ethanol			>200 µg/ml	
	CH_2Cl_2/methanol			>200 µg/ml	
Datura metal (Solanaceae)	Methanol	Leaves	-	76.75 µg/ml	[6]
Daucus corata (Umbelliferae)	CH_2Cl_2/methanol	Roots	-	>200 µg/ml	[9]
Dimocarpus longam (Sapindaceae)	Distilled water	Ripe fruits	3.59±2.1	-	[11]
		Leaves	15.77±1.6		
	70% methanol	Ripe fruits	10.85±0.1		
		Leaves	39.42±0.3		
	Ethanol	Ripe fruits	13.41±1.42		
		Leaves	46.88±1.7		
Dodonaea viscosa (Sapindaceae)	1% v/v ethanol and 0.1% w/v Tween 80	Leaves and branches	-	>200 µg/ml	[77]
Erythrina stricta (Fabaceae)	Pet ether	Roots	-	30.2±2.2 µg/ml	[2]
	Chloroform			21.2±1.6 µg/ml	
	Ethyl acetate			44.9±1.4 µg/ml	
	Residual			100±3.3 µg/ml	
Equisetum arvense (Equistaceae)	Methanol	Roots	33.13±4.00	-	[36]

(Contd...)

Table 2: ***(Continued)***

Plant name (Family)	Extract	Part used	XO inhibition (100 µg/ml) (%)	IC_{50}	References
Hypericum perforatum (Hypericaceae)	20% ethanol	Aerial parts	-	>200 µg/ml	[9]
	80% ethanol			46.7 µg/ml	
	CH_2Cl_2/methanol			55.4 µg/ml	
Juniper communis (Cupressaceae)	20% ethanol	Berries and leaves	-	>200 µg/ml	[9]
	80% ethanol			>200 µg/ml	
	CH_2Cl_2/methanol			>200 µg/ml	
Manikara zapota (Sapotaceae)	Distilled water	Leaves	54.97±0.4	-	[11]
		Peels	12.64±0.7		
		Seeds	2.03±1.5		
	70% methanol	Leaves	73.0.4±2.7		
		Peels	47.33±1.6		
		Seeds	17.19±1.2		
	Ethanol	Leaves	70.81±0.2		
		Peels	41.03±0.1		
		Seeds	11.81±2.4		
Mentha canadensis (Lamiaceae)	Methanolic	Herb	45.24±1.32	-	[36]
Myristica fragrans (Myristicaceae)	20% ethanol	Nut	-	>200 µg/ml	[9]
	CH_2Cl_2/methanol			>200 µg/ml	
Nigella sativa (Ranunculaceae)	Hydroalcoholic	Seeds	-	432.99±11.3 µg/ml	[73]
	Hexane fraction			295.7±12.7 µg/ml	
	Chloroform			355.87±6.71 µg/ml	
	Ethylacetate			313.29±53.4 µg/ml	
	Aqueous			620.11±41.8 µg/ml	
Olea europaea (Oleaceae)	80% ethanol	Leaves	-	42 µg/ml	[4]
Pistacia integerrima (Anacardiaceae)	Aqueous	Leaves		85 µg/ml	[30]
	Chloroform			44 µg/ml	
	Ethylacetate			20 µg/ml	
	n-Butanol			19 µg/ml	
Physalis alkekengi (Solanaceae)		Leaves	55	-	[79]
		Fruits	90		
Primula veris (Primulaceae)	20% ethanol	Flowers	-	63.7 µg/ml	[9]
	80% ethanol			174.7 µg/ml	
	CH_2Cl_2/methanol			132.0 µg/ml	
Rosmarinus officinalis (Labiatae)	20% ethanol	Aerial parts	-	80.9 µg/ml	[9]
	80% ethanol			83.2 µg/ml	
	CH_2Cl_2/methanol			85.1 µg/ml	
Semecarpus anacardium (Anacardiaceae)	Methanol extract	Seeds	-	253±9 µg/ml	[31]
	Hexane fraction			891±12 µg/ml	
	Ethyl acetate			156±5 µg/ml	
	Butanol			493±10 µg/ml	
	Aqueous			378±8 µg/ml	
Strychnos nux vomica (Loganiaceae)	Aqueous	Leaves	-	7.75 µg/ml	[6]
	Hydroalcoholic			32.00 µg/ml	
	Methanol			6.80 µg/ml	
Swietenia mahagoni (Meliaceae)	Methanol	Seeds	47.2±0.005	-	[60]
Tecoma stans (Bignoniaceae)	Methanol	Whole plant	-	41.13±1.33 µg/ml	[39]
	Ethanol			38.97±1.46 µg/ml	
	Aqueous			36.72±1.24 µg/ml	
Tephrosia purpurea (Fabaceae)	Methanol	Roots	99.00±1.2	-	[55]
Urtica dioica (Uritaceae)	20% ethanol	Aerial parts	-	>200 µg/ml	[9]
	80% ethanol			>200 µg/ml	
	CH_2Cl_2/methanol			>200 µg/ml	
Viola odorata (Violaceae)	80% ethanol	Aerial parts	-	>200 µg/ml	[9]
	CH_2Cl_2/methanol			>200 µg/ml	
Vitex negundo (Verbenaceae)	Aqueous	Leaves	-	88.00 µg/ml	[6]
	Hydroalcoholic			76.75 µg/ml	
	Methanol			78.50 µg/ml	

XO: Xanthine oxidase

Sprague Dawley rats and the plant extract caused significant reduction in uric acid levels in both plasma and urine [32]. The XO inhibitory potential of the plant has also been studied using methylene chloride-methanolic and two ethanolic extracts [9]. In the traditional systems of medicine, *Coriandrum sativum* seed extract has been used as stimulants, carminative, antispasmodics, diuretic, and anti-rheumatic. The anti-arthritic activity of the plant was evaluated using various models of arthritis, namely, formaldehyde and CFA-induced arthritis and the dose-dependent decrease in joint swelling was seen in the extract-treated groups [93]. The plant has also been evaluated for XO inhibitory activity [9]. The aqueous extract of *Petroselinum crispum* leaves showed significant reduction in serum uric acid levels of hyperuricemic rats [39].

Table 3: Isolated phytoconstituents and their XO inhibitory potential

Plant name	Isolated constituents	XO inhibition (100 µg/ml)	IC_{50}	Reference
Biota orientalis	Quercetin	17.63%	-	[1]
	Rutin	14.96%		
Blumea balsamifera	Blumeatin		53.21±1.14 µM	[46]
	Tamarixetin		3.16±0.13 µM	
	Rhamnetin		36.09±0.27 µM	
	Luteolin -7-methyl ether		42.19±0.93 µM	
	Luteolin		2.38±0.1 µM	
	Quercetin		2.92±0.03 µM	
	5,7,3',5' -Tetrahydroxyflavanone		32.14±0.91 µM	
	Dihydroquecetin-4' -methyl ether		58.86±0.14 µM	
Caesalpinia sappan	Neosappanone A		29.7 µM	[41]
Cinnamomum cassia	Cinnamaldehyde		7.8±1.1 µg/ml	[88]
	2- Methoxycinnamaldehyde		13.8±1.5 µg/ml	
	2- Hydroxycinnamaldehyde		14.6±2.0 µg/ml	
	Cinnamic acid		26.4±1.2 µg/ml	
	Coniferaldehyde		36.3±1.9 µg/ml	
	Cinnamic alcohol		>50 µg/ml	
	O – Coumarin acid		32.2±2.1 µg/ml	
	Dihydromelilotoside		>50 µg/ml	
	Methydihydromelilotoside		>50 µg/ml	
	Rosavin		>50 µg/ml	
	Cinnacasolide A		>50 µg/ml	
	Cinnacasolide B		>50 µg/ml	
	Cinnacasolide C		>50 µg/ml	
Conyza bonariensis	Syringic acid		500±41 µM	[38]
	Takakin 8 – O glucuronide		170±12 µM	
Lagerstroemia speciosa	Valoneic acid dialactone		2.5 µM	[3]
	Ellagic acid		71.5 µM	
Olea europaea	Oleuropien		53 µM	[4]
	Luteolin-7-O-β-D-glucoside		15 µM	
	Caffeic acid		11.5 µM	
	Luteolin		2.9 µM	
	Apigenin		0.52 µM	
Pistacia integerrima	Quercetin		0.65 µg/ml	[30]
	Kaempferol		1.87 µg/ml	
	Apigenin		35 µg/ml	
	Rutin		61 µg/ml	
Semecarpus anacardium	Tetrahydroamentoflavone		50±3 µg/ml	[31]
Triticum aestivum	6- aminopurine		10.89±0.13 µM	[89]

XO: Xanthine oxidase

Asteraceae

In Ayurvedic medicine, *Articum lappa* has been used for upper respiratory infections, pneumonia, skin problems, canker sores, arthritis, cancer, premenstrual syndrome, seborrhea, urinary tract infections, HIV, renal stone, gout, and rheumatic complaints [94]. The *in vitro* XO inhibitory potential of the plant has also been evaluated [41]. *Chamomilla recutita* is one of the important medicinal herbs found in the Indo-Gangetic plains of India [95]. The XO inhibitory potential of the plant has also been reported [9]. The roots of *Cichorium intybus* are used as antihepatotoxic, antiulcerogenic, anti-inflammatory, appetizer, digestive, stomachic, liver tonic, cholagogue, cardiotonic, depurative, diuretic, emmenagogue, febrifuge, alexteric, and also as tonic. It is useful in gout, hepatomegaly, inflammations, anorexia, dyspepsia, flatulence, colic, burning sensation, allergic conditions of skin, jaundice, splenomegaly, hyperdipsia, skin diseases, leprosy, strangury, amenorrhea, ophthalmia, pharangitis, vomiting, arthralgia, lumbago, asthma, general debility, AIDS, cancer, diabetes, dysmenorrhea, impotence, insomnia, splenitis, and tachycardia [42]. Decoction of leaves has been used in the treatment of jaundice, liver enlargement, gout, and rheumatism [96]. In the Indian system of medicine, *Conyza bonariensis* has been used as pungent, acrid, uterine sedative, and antihelmintic and is useful in the treatment of dysentery, leprosy, erysipelas, blood diseases, leucorrhea, menorrhagia, and toothache [97]. XO inhibitory potential of isolated phytoconstituents syringic acid and takakin 8-*o*- glucuronide has been evaluated *in vitro* [43]. *Elephantopus scaber* is used to cure skin diseases, wounds, jaundice and also used as a snakebite antidote [98]. Leaves of the plant are boiled with *Schleichera oleosa* oil and the paste is applied externally on gout affected body parts [23]. *Launaea sarmentosa* has been traditionally used as a folk remedy in India. It has been used traditionally in the treatment of jaundice, blood disorders, allergy, and gout [25,99].

Caesalpiniaceae

Caesalpinia bonduc, a widely distributed plant all over the world, has been reported to possess various pharmacological activities such as anxiolytic, antinociceptive, antidiarrheal, antidiabetic, adaptogenic, antihelmintic, antiestrogenic, anti-inflammatory, antimalarial, antimicrobial, antifungal, antispasmodic, antioxidant, antiproliferative, antipsoriatic, hepatoprotective, anticonvulsant, and antifilarial [100]. It is also used in the treatment of gout [25]. Neosappanone has been isolated from *C. sappan* and is responsible for XO inhibitory activity, thus useful in management of gout and other joint disorder. [41]. *Cappris aphylla* is used in several medicinal formulations recommended for various ailments such as muscular injury, swelling, jaundice, cardiac diseases, pyorrhea, cholera, dysentery, rheumatism, constipation, stomach disorder, skin diseases, and gout [101]. Conventinally, *Cassia alata* has been used for treatment of ringworm, scabies, ulcers, and other skin diseases such as pruritus, eczema, and itching [102]. The XO inhibitory activity of methanolic extract of *C. alata* leaves has been reported [87]. *Cassia fistula* is native to southern Asia including India [103,104]. In

traditional medicine, it has been used for various ailments such as hematemesis, pruritus, intestinal disorders, leucoderma, diabetes, gout and as antipyretic, analgesic, and laxative [25,104]. The XO inhibitory activity of methanolic extract of *Cassia fistula* leaves has been evaluated *in vitro* [87].

Compositae

Blumea balsamifera is widely distributed throughout Southeast Asia including India [105]. It is used in folk medicine as a stomachic, expectorant, antispasmodic, antipyretic, and diaphoretic. The XO inhibitory activities of extract and isolated flavonoids from the leaves of the plant have been evaluated *in vitro* [46]. Conventionally, *Helianthus annuus* is used in contraception and gout-related complaints [25,106]. *Saussurea lappa* is another herb widely distributed in high altitude areas of India including Kashmir, Lahaul Spiti, and Uttarakhand w[107]. The plant possesses various medicinal values such as antiulcer, anticonvulsant, anticancer, hepatoprotective, antiarthritic, antiviral, and antigout [108].

Cucurbitaceae

The crushed leaves of *Citrullus colocynthis* are used topically for the treatment of gout [40]. In addition to anti-gout property, the plant is also used in nose bleeding, joint pains, skin diseases, rheumatism, and gastrointestinal problems [49]. The XO inhibitory potential of methanolic extract of *Coccinia grandis* has been evaluated *in vitro*. It has also been screened for *in vivo* hypouricemic activity against potassium oxonate-induced hyperuricemia in mice and showed a significant decrease in the serum urate level (3.90±0.07 mg/dl) when compared to hyperuricemic control (11.42±0.14 mg/dl) [6]. Conventionally, *Momordica charantia* has been used in the treatment of diabetes, malaria, jaundice, leprosy, eczema, gout, piles, pneumonia, psoriasis, rheumatism, fever scabies, abdominal pain, and kidney stones. It is also used as abortifacient, antihelmintic, contraceptive, emmenagogue, galactagogue, laxative, and purgative [50].

Euphorbiaceae

Euphorbia antiquorum, Jatropha curcas, and *Tragia involucrata* belong to family Euphorbiaceae and are used in traditional system of medicines for treatment of gout [25,35,109]. Poultice of roots of *J. curcas* is made into paste and applied on the gout affected parts of the body [35]. *T. involucrata* is also used in the treatment of bronchitis, asthma, venereal disease, skin infections, and diabetes [109].

Fabaceae

In Indian traditional system of medicine, the seeds of *Abrus precatorius* have been used for the treatment of ophthalmic infections, diabetes, allergy, and kidney damage. The plant also exhibited antioxidant, antihepatitis, antimicrobial, diuretic, aphrodisiac, purgative, antifertility and anti-gout activities [29,110]. The bark and leaves of *Adenanthera pavonina* have been used as astringent, vulnerary, anthelmintic, and aphrodisiac. The bark is also used in colonorrhea, ulcers, pharyngopathy, gout, and rheumatism [57,111]. *Crotalaria burhia,* another plant belonging to same family, is used in the treatment of eczema, gout, hydrophobia, and swellings [52]. The leaves of *Erythrina stricta* are applied topically to treat joint pains. Bark powder is used in rheumatism, itching, epilepsy, and asthma [2]. Roots are made into paste and applied to gout affected parts of body [35]. The XO inhibitory potential of different fractions of *E. stricta* has been evaluated *in vitro* [2]. In addition to these, *Indigofera tinctoria, Tephrosia purpurea,* and *Trigonella foenumgraecum* also find application in traditional system of medicines for treatment of gout [53,55,112].

Malvaceae

Conventionally, *Abutilon indicum* has been used as a remedy for treatment of jaundice, piles, ulcer, leprosy, and gout [25,113]. Leaves of *Gossypium herbaceum* are used as emollient, mucilaginous, hematinic, and diuretic. It is also used in gastric irritation, diarrhea, dysentery, dysuria, otalgia, and rheumatoid arthritis [114]. Poultice of leaves is mixed with its seed oil and is applied topically in gout and rheumatism due to its anti-inflammatory action [35]. The effects of *Hibiscus sabdariffa* has been investigated on oxonic acid-induced hyperuricemia in rats. The extract effectively inhibited hyperuricemia by increasing uricase activity and by decreasing serum uric acid levels. The XO activity was not affected by the extract [10].

Ranunculaceae

Conventionally, the roots of *Aconitum falconeri* have been used in paralysis, sciatica, gout, fever, rheumatism, and diarrhea [71]. *Aconitum violaceum,* a widely distributed plant in central Himalaya, is used to cure various ailments such as cough, asthma, inflammation, and heart-related problems [115,116]. The roots of *Aquilegia fragrans* have been traditionally used in cystitis, gout, eczema, psoriasis, and diabetes [71]. *Delphinium denudatum* is widely distributed in the Himalaya region from Pakistan to Kashmir and northwest India. The roots of the plant are used for the treatment of toothache, rheumatism, syphilis, snake bite, aconite poisoning, epilepsy, and gout [25,117]. In traditional system of medicine, the seeds of *Nigella sativa* have been used as bitter, aromatic, appetizer, stimulant, diuretic, galactagogue, anthelmintic, acrid, thermogenic, carminative, purgative, and aphrodisiac. It is also used in cough, ascites, jaundice, fever, paralysis, conjunctivitis, piles, skin disease, anorexia, flatulence, abdominal disorders, diarrhea, dysentery, and hemorrhage [118]. The XO inhibitory activity of the *N. sativa* extract and different fractions of extract was evaluated *in vitro* [73]. *Ranunculus arvensis* and *Thalictrum foliolosum* are also used to treat gout and other joint disorders [119,120].

Solanaceae

Capsicum annum is used as carminative, appetizer, and stomachic. Externally, it is used as a counter irritant in the treatment of rheumatism, lumbago, and neuralgia [121]. The XO inhibitory potential of *C. annum* has been evaluated *in vitro* using methylene chloride-methanolic and ethanolic extracts [9]. *Datura metel* is one of the most useful medicinal plant having antiseptic, narcotic, sedative, antiasthmatic, and antiulcer properties [122]. The *in vitro* XO inhibitory potential of *D. metel* leaves has been investigated using aqueous, hydroalcoholic and methanolic extracts [6]. Conventionally, *Nicotiana tobacum* has been used to treat skin diseases, local infections, bronchitis, asthma, and inflammation. An ointment made by simmering the leaves in lard has been employed in curing old ulcers and painful tumors [123]. *Physalis alkekengi* is used in the treatment of wide range of diseases including gout, inflammation, rheumatism, and kidney stones [124]. The *in vitro* XO inhibitory activity of the plant revealed that 0.3 mg/ml of extract exhibited inhibitory effect on XO activity [79]. Fruits of Physalis minima are used in the treatment of gout [25]. In traditional system of medicines, *Solanum nigrum* has been used as hepatoprotective, laxative, aphrodisiac, tonic, and diuretic. It is also used in liver cirrhosis, cancer, and gout [80]. *Withania somnifera*, a popular Indian medicinal plant, has been used in the Ayurvedic and indigenous medicinal system for over 3000 years [125]. It is traditionally used in treatment of rheumatism, gout, hypertension, nervine, and skin diseases [81].

Zingiberaceae

Curcuma amada, Curcuma caesia, and *Curcuma longa* are various species of curcuma which find applications in treatment of gout in traditional medicinal system [33,35]. The anti-gout activity of *C. longa* was evaluated on male Sprague Dawley rats and the plant extract caused significant reduction in uric acid levels in both plasma and urine [33]. The decoction of *Kaempferia parviflora* powder with alcohol has been reported to cure allergy, asthma, impotence, gout, diarrhea, dysentery, peptic ulcer, and diabetes [85]. *Zingiber officinale* is cultivated commercially in India, China, Southeast Asia, West Indies, Mexico, and other parts of the world [126]. Its rhizomes are used as hepatoprotective, aphrodisiac, antigout, sudorific, antipyretic, antiscurbutic, and food condiment [40].

DISCUSSION AND CONCLUSION

Gout is a major problem worldwide and significant advances in the treatment of gout have been made in past few decades. However, the

current available treatment options are not completely satisfactory and associated with many side effects. In addition, due to economic problem, even today modern medical health care is out of reach of most of the population of developing countries like India. To eliminate this problem, a safe, non-toxic, and cost-effective drug is required. In this paper, we have collected the data mentioned in literature on the medicinal plants used in the treatment of gout. These plants exhibit anti-gout effect by different mechanisms, such as XO inhibition, uricosuric activity, anti-inflammatory activity, and antioxidant activity. In addition, plant extracts and isolated constituents which showed promising XO inhibition are also considered and most of the isolated constituents are found to be phenolic glycosides and flavonoids. Different flavonoids such as quercetin, apigenin, rutin, genistein, and astilbin also have been reported to possess XO inhibitory and uricosuric activities [127,128].

Future prospective

This review provides a comprehensive summary of medicinal plants described in ancient literature for the treatment of gout. Of these, traditional medicinal plants, only few have scientific validation. Many crude extracts have been used for the treatment of gout but their phytochemical constituent should be screened for anti-gout activity. Further, the preclinical and clinical studies of these active constituents should be performed to explore the safe drugs. Beside this, combination therapy can also be used to develop more effective agents in the treatment of gout due to their synergistic effect.

Although herbal drugs are claimed to be non-toxic or generally regarded as safe but safety concerns arises due to intrinsic toxicity, adulteration, contamination, heavy metals content, herb-drug interactions, misidentification, or poor quality control. Hence, the safety profile of these medicinal plants should be carefully assessed. The careful assessment of mechanisms and toxicity studies of herbal drugs may lead to development of safe and effective agents for management of gout which can be developed into suitable formulations.

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