

*Review Article***A Review on Pharmacological Properties of *Colchicum luteum* - A Himalayan Herb****Rayeesa Ali¹, Shayaib Ahmad Kamil¹, Muneeb U Rehman^{2*}, Masood Saleem Mir¹ and Umar Amin¹**

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Abstract

Nature has blessed us with colossal wealth of herbal plants widely distributed all over the world. They act as parcels of human society to combat diseases. As per WHO reports around 80% of world's population relies on herbal medicines for their primary health care. *Colchicum luteum* is a traditional medicinal plant, having some active ingredients used for the treatment of numerous diseases. Various ingredients like colchicine, β -Lumicolchicine, Chlorogenic acid and 3', 4', 5, 7-Tetrahydroxyflavone has been obtained from *Colchicum luteum* during the recent research. Colchicine is the principle active ingredient of *Colchicum luteum*. The plant has potent anti-inflammatory, anti-oxidant, anti-cancer and many other properties. This review is written to put light on pharmacological properties of *Colchicum luteum* and its role alleviating diseases of humans and animals.

Key words: Anticancer, Antigout, *Colchicum luteum*, Herbal Plants**How to cite:** Ali, R., Kamil, S., Rehman, M., Mir, M., & Amin, U. (2018). A Review on Pharmacological Properties of *Colchicum luteum* - A Himalayan Herb. International Journal of Livestock Research, 8(6), 14-23. doi: 10.5455/ijlr.20170712075807**Introduction**

Plants have shown an immense importance in human affairs. The plants which possess therapeutic properties or exert pharmacological effects on body are designated as "Medicinal plants" and they serve as rich source of Alkaloids, Glycosides, volatile oils, tannins and vitamins. As per WHO, about 80% of human population relies on plant based medicine systems (Martin *et al.*, 2013). One of the important medicinal plants is *Colchicum luteum*.

Botanical classification of *Colchicum luteum*-

Kingdom----- Plantae
Division----- magnoliophyta
Class----- magnoliosida
Family ----- Liliaceae
Genus ----- Colchicum
Species----- luteum

Colchicum luteum is known by many names like Yellow colchicum in English, Suranjan shirin or Suranjan talkh in Urdu, Suranjan in Hindi and Virkim-posh in Kashmiri. The plant is a perennial herb found in Himalayas and is widely distributed in China, India, Pakistan and Afghanistan. It has also been reported in hilly areas of Kashmir valley like Bandipora (Lone *et al.*, 2013), Tragbal, Tangmarg and other areas. Yellow flowers of *Colchicum luteum* are earliest to blossom in Kashmir during spring season. Practitioners of traditional medicine have used corms and seeds of the plant for treatment of gout, rheumatism and diseases of liver and spleen (Singh and Aswal, 1994; Kapur and Singh, 1996). Corms are ovoid, oblong and flattened at base with longitudinal groove on one side as shown in Fig.1.



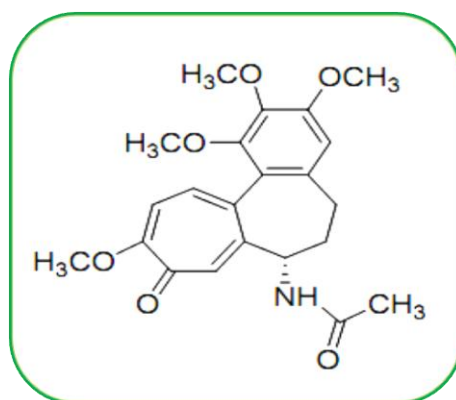
Fig.1: *Colchicum luteum* corms

About 31 different alkaloids have been isolated from *Colchicum luteum* (Capraro and Brossi, 1984). Phytochemical investigation of ethanolic extract obtained from corms of the *Colchicum luteum* Baker (Liliaceae) have shown the presence of Lumicolchicine, Chlorogenic acid, Colchicines, and 3', 4', 5, 7-Tetrahydroxyflavone, on the basis of different modern spectroscopic techniques (Bashir, 2010). However, colchicines were the main alkaloids reported (Ondra *et al.*, 1995). The isolation of colchicines from *Colchicum luteum* for the first time was credited to P.S. Pelletier and J. Caventox in the year 1820 (Kokate *et al.*, 2003; Evans, 2006). Approximately 0.25% and 0.45% colchicine has been reported in corms and seeds respectively as given in Table 1 (Chopra *et al.*, 1986).

Table 1: Percentage of Colchicine in different parts of *Colchicum luteum*

Plant	Parts	Percentage of colchicines
	Seed	0.41- 0.43 %
<i>Colchicum luteum</i>	Corms	0.21- 0.25%
	Flower	0.1- 0.8 %

Chemically colchicine is described as N-[(7S)-1, 2, 3, 10-tetramethoxy-9-oxo-6, 7-dihydro-5H-benzo[a]heptalen-7-yl] acetamide with molecular formula $C_{22}H_{25}NO_6$ and molecular weight is 399.443 g/mol as given in Fig. 2.


Fig.2: Chemically structure of Colchicine is N-[(7S)-1, 2, 3, 10-tetramethoxy-9-oxo-6, 7-dihydro-5H-benzo[a]heptalen-7-yl] acetamide

Pharmacokinetics of colchicines has revealed that the route of administration should be oral but not intravenous due to certain risks associated with intravenous administration (Terkeltaub, 2008). Adverse events associated with intravenous colchicine administration include thrombocytopenia, neutropenia, pancytopenia, acute renal failure and congestive heart failure. Also dose of colchicines should be low. High doses are associated with diarrhea, vomiting and nausea (Colcrys, 2008). Hepatic metabolism of colchicine is altered by inhibitors of CYP3A4 isoenzymes or P-gp inhibitors such as ketoconazole, verapamil, cyclosporine, resulting in colchicine toxicity.

Therapeutic Properties of *Colchicum luteum*

Anti-oxidant Action of *Colchicum luteum*

Promising antioxidant activity offered by the crude ethanolic extract *Colchicum luteum* and its subsequent fractions have been reported (Bashir, 2010). Also, the free radicals are responsible for oxidative damage, characterized by increased lipid peroxidation. However, the inhibition activity of the crude methanolic extract and its fractions against Lipoxxygenase has been reported which might be responsible for its

antioxidant activity (Bashir *et al.*, 2006). The antioxidant potential of *Colchicum luteum* has also been reported by Sevim *et al.*, 2010).



Fig. 3: Therapeutic potential of *Colchicum luteum*

Anti-Fungal Action of *Colchicum luteum*

Mycotoxins like aflatoxins, ochratoxins and others cause damage to proximal convoluted tubule (PCT) of kidney or basement membrane of glomeruli, resulting in kidney dysfunction which ultimately leads to hyperuricemia. Also, long term feeding of yeast has resulted in hyperuricemia in rats (Nikolenko *et al.*, 1989). Hyperuricemia has also been induced in humans by cyclosporine (Lin *et al.*, 1989; West *et al.*, 1987; Gores *et al.*, 1988). Anti-fungal activity of colchicines was documented by Shankla and Sharma, 1969. Brian *et al.*, in 1946 reported a metabolite from fungus "*Penicilium janczewskii*" and named it as "curling factor" on basis of its ability to causes shrinkage and stunting of fungal hyphae. The Curling factor was then subsequently found to be griseofulvin (Brain, 1949). *Colchicum luteum* shares the antifungal mode of action with griseofulvin. It disrupts the mitotic spindle and causes inhibition of fungal mitosis by binding with microtubule associated proteins, which are responsible for movement of chromatids towards poles.

Anti-Cancer Action of *Colchicum luteum*

As we know that the cytoskeleton of cell is composed of microtubules and these microtubules are involved in a number of vital processes like cell division, cell migration and polarization. In-vitro assay have shown binding capacity of *Colchicum luteum* to tubulin, which is main component of microtubule, thereby prevents its polymerization and thus functions as "mitotic poison" (Niel and Scherrmann, 2006).

One of the characteristic features of cancer cells is the increased rate of mitosis and thus they are more vulnerable to colchicine toxicity. Colchicine toxicity however also affects non-target cell (normal cells). Keeping this in view, certain carriers like microspheres, immunoglobulin, erythrocytes, serum-proteins and synthetic polymers, have been used for targeting drug at certain specific sites (Molad, 2002). In-vitro studies on controlled drug delivery modes of *Colchicum luteum* showed very low toxicity (Balasubramanian and Gajendran, 2013).

Anti-Gout Action of *Colchicum luteum*

Gout is an inflammatory metabolic disease characterized by hyperuricemia and deposition of monosodium urate crystals. There are multiple etiological factors associated with gout like high dietary protein (Li *et al.*, 1998), high dietary calcium (Guo *et al.*, 2005), mycotoxins (Pegram and Wyatt, 1981) and others. Uric acid crystallization depends on sodium and urate concentration and when plasma concentration of monosodium urate exceeds 7mg/dl, crystallization takes place (Fiddis *et al.*, 1983). MSU are recognized by body's innate immune system (neutrophils and macrophages) and there occurs signal dependent release of cytokines like interleukin-1 β via NLRP3 inflammasome activation (Ng *et al.*, 2008; Di Giovine *et al.*, 1987). Also, both classical and alternate pathway of complement system gets activated by monosodium urate crystals and results in inflammation (Fields *et al.*, 1983). *Colchicum luteum* exert the anti-gout effect in a number of ways like by causing inhibition of NLRP3 inflammasome activation and suppression of regulatory genes of cell (Misawa *et al.*, 2013; Ding *et al.*, 1990).

Moreover, it results in modulation of adhesion protein expression on endothelial cells; inhibition of IL-1 induced L-selectin expression, cytokine maturation and neutrophil chemotaxis to cytokines (Cronstein *et al.*, 1995; Kuijpers *et al.*, 1994). Also, reduction of uric acid levels has been reported after *Colchicum luteum* administration (Mohammad *et al.*, 2014).

Colchicum luteum as Treatment for Cardiovascular Diseases

Hyperuricemia, which being the major cause of inflammatory metabolic diseases has shown its association with hypertension, coronary diseases and pericarditis (Feig *et al.*, 2008; Gaffo *et al.*, 2009). The possible mechanism of cardiovascular diseases by excess urate is as a result of reduction in Nitric Oxide levels (Cook *et al.*, 2004). Nitric Oxide is a relaxing factor derived from vascular endothelial cells. Increased plasma uric acid levels lead to decrease in plasma concentration of nitrates and nitrates by formation of unstable nitrosated uric acid after reacting with NO. Also there is reduction of VEGF stimulated NO production after direct exposure of vascular endothelial cells to uric acid (Khosla *et al.*, 2005). Moreover, it has been reported that uric acid stimulates MCP-1 production following activation of NF- κ B, MAPKs and cyclooxygenase-2 (Kanellis *et al.*, 2003). Uric acid also mediates activation of

NADPH-oxidase which causes the production of highly reactive superoxide anions by neutrophils and contributes to vascular damage (Martin-Ventura *et al.*, 2012). Non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy were accepted modalities for cardiovascular diseases. However, colchicine which is the main alkaloid present in *Colchicum luteum* also reduces the risk of cardiovascular diseases in many ways. Colchicines cause inhibition of the NADPH-oxidase complex by disruption of microtubule polymerization which results in reduced superoxide production (Chia *et al.*, 2008). Also, results from a study have shown that the administration of colchicines resulted in decrease in C-reactive protein levels in patients with stable coronary artery disease (Nidorf and Thompson, 2007). Further, the colchicine has successfully prevented recurrence of acute pericarditis after failure of conventional treatment with NSAIDs and others.

Anti-Inflammatory and Anti-Arthritic Action of *Colchicum luteum*

Inflammation is a defense mechanism of body which sets up in response to tissue injury, thereby up regulating the healing processes. Damage to cell membranes cause release of inflammatory mediators like prostaglandins, leukotrienes, lysosomal enzymes etc which produce a variety of effects on blood vessels, nerve endings and on cells involved in inflammation (Katzung, 2009). Inflammation also results in granuloma formation with proliferation of macrophages, neutrophils and fibroblast. Rheumatoid arthritis which is an example of inflammatory autoimmune disease condition of joints is characterized by swelling, pain, stiffness and increased cellularity of synovial tissue (Lipsky *et al.*, 2005). As per WHO reports rheumatoid arthritis affects about 0.3-1% of the world's population and females being more susceptible compared to males. By-products of cellular metabolism such as nitrous oxide and superoxide radicals may induce the production of interleukins (IL) and tumor necrosis factor (TNF- α) which contribute to inflammation (Fields *et al.*, 2005). Natural product "Colchicine" obtained from plants of the genus *Colchicum* (*Colchicum luteum* and other species) has been used to treat gouty arthritis for centuries (Roberts *et al.*, 1987). Administration of colchicines in patients with inflammatory diseases has shown increase in levels of anti-inflammatory substances like TGF- β 1 (Darshna *et al.*, 2004; Topal *et al.*, 2006). The anti-inflammatory mechanism of action of colchicines is attributed to diminished number of TNF- α receptor on the surface of macrophages and endothelial cells and prevention of TNF- α -induced activation of macrophages (Ding *et al.*, 1990). Also, the anti-arthritic activity of *Colchicum luteum* because of its modulatory effect on the pro-inflammatory cytokine expression in the synovial of joints and reduction in serum TNF- α level in a dose dependent manner has been reported (Nair *et al.*, 2011; Nair *et al.*, 2013).

***Colchicum luteum* as Treatment for Familial Mediterranean Fever**

Colchicum luteum has been found effective in preventing relapses of systemic inflammatory processes in familial Mediterranean fever (recurrent-polyserositis). FMF is an auto-inflammatory disease which is caused by mutation of a gene located on short arm of chromosome 16 known as “MEFV”, which encodes protein Pyrin. Pyrin regulates the inflammatory cascade and is known to cause suppression of caspase-1 activity (Chae *et al.*, 2008; Sahin *et al.*, 2011). However, inadequate Pyrin production as a consequence of gene mutation results in inflammatory bouts. Also, colchicines have shown to provide protection against oxidative stress in patients with remission of familial Mediterranean fever (FMF). The other possible disease protective modes of colchicines are its effects on pyrin and its interacting proteins (Taskiran *et al.*, 2012), reduction of ASC speck rates in transfected cells and down regulation of MEFV gene expression. Pharmacologic action of colchicine has been potentially explained by its capability to induce reorganization of the actin cytoskeleton and alter expression of the MEFV gene.

Conclusion

People throughout the world prefer natural products over synthetic ones because of fewer side effects associated with them. *Colchicum luteum* is a strong antioxidant with almost insignificant side effects. *Colchicum luteum* targets the basic cytoskeleton of cell that is microtubule; thereby altering different cellular processes like it prevents release of inflammatory mediators and inhibits chemotaxis of inflammatory cells. It also scavenges free radicals. *Colchicum luteum* thus can be effectively used against many diseases like arthritis, hepatitis, cancer and heart failure. Keeping the above properties in view there is future requirement for further evaluation of phytochemical properties of this medicinal plant and its clinical efficacy for treating ailments.

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