

## Review Article

# Strategy on Remedial Use of Colchicine and Its Derivatives: A Review

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- Colchicine derivative
- Microbial transformation
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## Abstract

Colchicine is one of the oldest medications still in use today and is commonly used for the treatment of gout and familial Mediterranean fever. Its anti-inflammatory properties have raised the question of its utility in managing several cardiovascular diseases, including postoperative atrial fibrillation and pericarditis. Colchicine is commonly produced by plants like *Colchicum autumnale* and *Gloriosa superba*. It is originally used to treat rheumatic complaints, especially gout, and still finds its uses for these purposes today despite dosing issues concerning its toxicity. It is also prescribed for its cathartic and emetic effects. Initially oral colchicine has not been approved as a drug by U.S. Food and Drug Administration (FDA). But now FDA approved colchicine as a drug for some disorders.

The present review is mainly focused on the chemistry of colchicines and its derivatives. Microbial transformation techniques have been highlighted on the production of efficient, direct and green biotransformation of thiocolchicine into thiocolchicoside, performed by a specific strain of *Bacillus* sp. The same process, with minor modifications, can be used to convert the by-product 3-O-demethyl-thiocolchicine into thiocolchicoside. In addition, it has been described the upcoming demand of colchicines derivatives for curing various cancer and chronic pain.

## ABBREVIATIONS

FDA: Food and Drug Administration; SAR: Structure-Activity Relationship; P-gp: P-glycoprotein; FMF: Familial Mediterranean Fever; COPE: Colchicine for Acute Pericarditis; HPLC: High Performance Liquid Chromatography; SFE: Supercritical Fluid Extraction; LBP: Low Back Pain

## INTRODUCTION

The colchicine has been on the market since before the existence of Food and Drug Administration (FDA). In 2006, the FDA has given approval as therapeutic herbal drug to prevent gout attacks in adults. In 2015, URL Pharma, Inc., a pharmaceutical company owned by Takeda Pharmaceuticals in Japan (but based in Philadelphia), seized the opportunity and launched Colcrys®, the first branded colchicines [1]. In 2009, Mutual Pharmaceutical Company, Inc. Received letter of approval for manufacturing from FDA.

Although colchicine's medicinal properties have been recognized for centuries, the drug was first approved in 2009, under the United States Food and Drug Administration (FDA) unapproved drugs initiative [2]. FDA approval brought changes in colchicine dosing regimens, and a greater emphasis on safety in the

context of co-morbidities and drug-drug interactions. The plant source of colchicine, the autumn crocus (*Colchicum autumnale*), was described for treatment of rheumatism and swelling in the Ebers Papyrus (circa 1500 BC), an Egyptian medical papyrus [3]. It has been used in medicinal application dating back to the times of ancient Greece, initially as a purgative agent and later as treatment for gout. Colchicum extract was first described by Padanius Dioscorides, a Greek surgeon in the Roman Army in the first century BC as a treatment for gout in De Materia Medica [4].

Use of the bulb-like corms of *Colchicum* to treat gout probably dates to around 550 AD, as the "hermodactyl" recommended by Alexander of Tralles. *Colchicum* corms were used by the Persian physician Avicenna, and were recommended by Ambroise Pare in the 16<sup>th</sup> century, and appeared in the *London Pharmacopoeia* of 1618 [5]. *Colchicum* plants were brought to North America by Benjamin Franklin, United States Ambassador to France who suffered from gout himself [6]. Colchicine alkaloid was first isolated in 1820 by the two French chemists P.S. Pelletier and J. Caventou [7], and they regarded it as veratrine. In 1833, P.L. Geiger purified an active ingredient, which he named colchicines [8]. The determination of colchicine's structure required decades, although in 1945, Michael Dewar made an important contribution when he suggested that, among the

molecule's three rings, two were seven-member rings [9]. Its pain-relieving and anti-inflammatory effects for gout were linked to its ability to bind with tubulin.

However, Dewar did not prove the structure of colchicine; he merely suggested that it contained two seven-membered rings. Colchicine's structure was determined by X-ray crystallography in 1952 [10]. Its total synthesis was first accomplished in 1959 [11].

## CHEMISTRY OF COLCHICINE

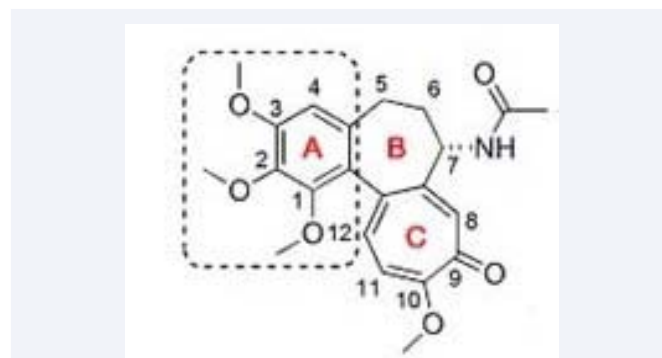
The exact mechanism of action by which colchicine exerts its effect has not been clearly understood. However, it has been established that Colchicine binds to tubulin, thereby interfering with the polymerization of tubulin, interrupting microtubule dynamics, and disrupting mitosis. This leads to an inhibition of migration of leukocytes and other inflammatory cells, thereby reducing the inflammatory response to deposited uratecrystal. Colchicine may also interrupt the cycle of monosodium urate crystal deposition in joint tissues, thereby also preventing the resultant inflammatory response. Overall, colchicine decreases leukocyte chemotaxis/migration and phagocytosis to inflamed areas, and inhibits the formation and release of a chemotactic glycoprotein that is produced during phagocytosis of urate crystals.

The chemical name for colchicine is (S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzol [a] heptalen-7-yl) acetamide, is a pale yellow powder soluble in water in 1:25 dilution. The structural formula is represented below:

Structurally, colchicine consists of a trimethoxyphenyl ring (A-ring), a saturated seven-membered ring containing an acetamido group (B-ring), and a tropolone ring (C-ring) (Figure 1). The A- and C-rings of colchicine are key structural features required for its high binding to tubulin and biological activity [12-16]. Any modification in the C-1, C-2 and C10 of A-ring of colchicine causes a complete loss of binding, whereas demethylation of C-3 position has no role in tubulin binding. Modifications to both the B- and C-rings are possible. In addition, both a minimal size and a nitrogen atom at C-7 of the B-ring are required for P-glycoprotein (P-gp) recognition and transport [22] (Figure 1). Therefore, many studies have focused on structural modifications of C-7 of the B-ring to discover colchicine analogues with improved potency and less toxicity or analogues that overcome drug resistance. Colchicine consists of pale yellow scales or powder; it darkens on exposure to light due to photoisomerization and formation of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -lumicolchicines [17,18]. Colchicine is soluble in water, freely soluble in alcohol and in chloroform, and slightly soluble in ether [19]. The optimum storage temperature for colchicines is  $-15^{\circ}$  to  $-25^{\circ}\text{C}$ , in dark-colored bottles.

## APPLICATION OF COLCHICINE AND ITS DERIVATIVES

Colchicine was originally derived from a plant, sometimes called the "Autumn crocus", and was found to be effective for lowering levels of uric acid in the blood. The combination of probenecid with the brand name CoBenemid (initially approved in 1961) was deemed to be effective for the treatment of chronic gouty arthritis when complicated by frequent recurrent, acute attack of gout in 1973 [20].



**Figure 1** (1). Methyl group at C-1, C-2 and C-10 position are essential for tubulin binding. (2). Demethylation at C-3 position has no role in tubulin binding as 'A' (3). 3-demethylation proved less toxic and more potent molecule used for anti-cancer.

It has been used as an antiparasitic agent in ethnoveterinary use [21]. Colchicine is also used in the treatment of Behcet's syndrome and some forms of psoriasis [22-24]. The corms of *C. luteum* have aphrodisiac, carminative and laxative property. They are used in India to treat gout, rheumatism and also diseases of the liver and spleen. When grown from seed its plant can take 4 - 5 years to flower. All parts of *C. luteum*, but especially the bulb, are poisonous causing vomiting, violent purging, serious inflammation of the stomach and bowels, and death.

The corm contains an alkaloid demecolcine (colchamine) in addition to colchicine that is best known as an orally-administered drug in the treatment of chronic myeloid leukaemia. Colchicine is also used to treat familial Mediterranean fever (FMF; an inborn condition that causes episodes of fever, pain, and swelling of the stomach area, lungs, and joints) in adults and children 4 years of age and older. Colchicine is not a pain reliever and cannot be used to treat pain that is not caused by gout or FMF. Colchicine is in a class of medications called anti-gout agents. It works by stopping the natural processes that cause swelling and other symptoms of gout and FMF.

Colchicine has been used for centuries to treat and prevent gouty attacks [25], and more recently has been recommended to treat and prevent serositis in patients with familial Mediterranean fever and recurrent pericarditis [26,27]. Preliminary data from nonrandomized trials have also supported the use of colchicine for the treatment and prevention of acute pericarditis [28]. In a single-center, open-label, randomized trial, called the Colchicine for Acute Pericarditis (COPE) study, the addition of colchicine to conventional therapy with either aspirin or glucocorticoids halved the recurrence rate after an initial attack of acute pericarditis [29].

In atherosclerotic vascular disease, an artery wall thickens as a result of the accumulation of calcium and fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries specifically due to atheromatous plaques. Disruption of the plaques may lead to acute coronary syndrome (including ischemic chest pain, acute myocardial infarction, unstable angina); cardiac arrest; and/or stroke such as non-cardio-embolic ischemic stroke [30].

Coronary disease and coronary heart disease is a form of atherosclerotic vascular disease caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and reduces blood flow to the heart. Stable coronary diseases are those that occur predictably in intensity, character or frequency at known levels of exertion or other stimuli. Unstable coronary diseases are those that change in intensity, character or frequency. There have been also published reports that show the benefit of using colchicine in treating major recurrent aphthous stomatitis and preventing further recurrences of ulcers [31,32].

## SOURCES OF COLCHICINE

*Colchicum luteum* and the seeds of *Iphigenia sp.* contain colchicine to the extent of about 0.25% and 0.9% respectively [33]. These plants are not available in sufficient quantities to warrant any commercial utilization. *Colchicum autumnale*, commonly known as autumn crocus, wild saffron and naked lady [34]. It is also known as "Meadow saffron". It is known as "naked lady" due to the fact that flowers emerge from the ground long after the leaves have died back. It is present in most parts of the temperate areas of Europe, Asia and America [35].

The dried corms of *Colchicum luteum* contain around 0.25% of colchicine and the seed contain about 0.4% of colchicine. The systematic study on genus *Iphigenia* was carried out in search for new commercial source for colchicine. Studies on *Iphigenia indica* (L.) by A. Gray had revealed that its seeds contain as much as 0.51% colchicine. A number of *Iphigenia* species occur around Puna (Kaul et al., 1964). Their seeds were collected in the month of August (1970) and after thorough drying at room temp. (25°C) were analysed for colchicine content [36]. Since there is considerable confusion about the correct identity and taxonomic status of the various species of *Iphigenia sp* growing in India as presented in the literature, few important characteristics of 4 species were studied [37].

Six variety of *Gloriosa* are available in tropical and subtropical countries. *Gloriosa superba*, *Gloriosa rothchildiana*, *Gloriosa planti*, *Gloriosa lutea*, *Gloriosa casuariana* and *Gloriosa vuchuria*. The amount of colchicine in six different species of *Gloriosa*, viz., has been determined using HPLC method. Of the six different species, *Gloriosa planti* exhibited the highest level of colchicines, followed by *Gloriosa lutea*, *Gloriosa casuariana* and *Gloriosa superba* [36-40].

A mixture of alkaloids consisting mainly of colchicine has been isolated from dried tubers of *G. superba* [41]. Hence, *G. superba* acts as substitute plant of tropics to *Colchicum autumnale* for the alkaloid colchicine. Colchicine levels in *Gloriosa superba* corms have been reported to the level of around 0.9% (DM) [42]. It grows in Africa, India and south eastern Asia [200]. Earlier studies revealed that colchicine levels are the highest during the initial growth of plant, and these levels decline during maturation in *Gloriosa superba* [43]. *Gloriosa* is a genus of five or six species in the plant family colchicaceae, from tropical Africa, India and Southeastern Asia.

## COLCHICINE AND ITS DERIVATIVES EXTRACTION PROCESS

All parts of the plant *Gloriosa superba* contains colchicine. Its

content in tuber and seeds varies from 0.15 to 0.3% and 0.7 to 0.9% respectively

The aromatic amino acids like Phenylalanine, Tyrosine and tryptophan which are derived from the sikhimate pathway are required as building blocks for production of the secondary metabolite Colchicine [44]. Colchicine is one of the seven Upanishads in the Indian medicine, which cure many ailments like Gout, Familial Mediterranean

Fever but may prove fatal on misuse as it is a semi poisonous drug. It also has antibacterial and antimicrobial activity [45]. Various solvent are used for quantification in the various extractions (Dichloromethane, Methanol, acetonitrile: water: phosphoric acid (70:30:0.1, v/v/v) and Hot water extraction) of stem, leaf, tuber, pod and flower of *Gloriosa superba*. Among the various extracts dichloromethane gave maximum and the sonication method gave the minimum extraction of colchicines.

Various compounds have been isolated from the plant parts mainly tubers and seeds, viz colchicine, colchicoside (its semi-synthetic derivative- thicolchicoside), superbine, gloriosine, lumicolchicine, 3-demethyl-N-deformyl-N-deacetylcolchicine, 3-demethylcolchicine, N-formyl deacetylcolchicine (Figure 2). The plant material *Gloriosa superba* (leaves, stem, tubers and pods) selected for extraction of colchicine alkaloid was collected and dried till 10% of moisture content.

## SOLVENT EXTRACTION

Powdered plant material (mainly seeds) is subjected to extract twice (w/v) with petroleum ether with frequent shaking for 1 h for 10- 12 hours till to make sure that all colchicines removed from powdered seeds. The solid residues left after filtration is air dried and, is again extracted with dichloromethane at room temperature for 1 hour with frequent shaking. Then 10% solution of ammonia is added to the mixture with vigorous shaking for 10 min; the mixture is left undisturbed for 30 min and then filtered. The residue is washed twice with dichloromethane and then combined with the filtrate. The organic phase was vaporated to dryness and then dissolved in 70% ethanol to yield the test

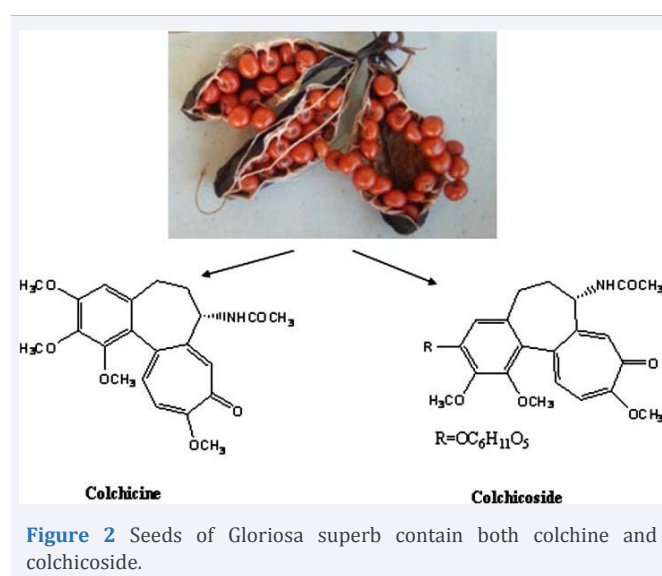


Figure 2 Seeds of *Gloriosa superba* contain both colchicine and colchicoside.

sample [46]. By chemical means colchicines is converted to thiocolchicine and subsequently it is converted to powered form (Figure 3 &4).

### FREEZE DRYING EXTRACTION

Freeze dried material is extracted using methanol in a cold room (10°) overnight and the homogenate is centrifuged at 1252 × g for 5 min. The methanolic extract is evaporated to dryness and then the residues redissolved in water. The aqueous extract is then centrifuged at 7826 × g for 5 min. The supernatant is first partitioned twice against petroleum ether and then discarded, and then once in diethyl ether discarding the supernatant each time. The residue is washed five times with equal volumes of chloroform, which is retained and evaporated to dryness. The chloroform residue is redissolved in 95% HPLC grade methanol and then filtered through a 0.2µm millipore filter to yield the test sample [47].

### Sonication method

Plant material is collected and then mixed with a mixture of acetonitrile: water: phosphoric acid (70:30:0.1, v/v/v). The mixture is sonicated for 5 min and shaken for 10 min and then centrifuged for 5 min. The extract is diluted with 95% HPLC graded methanol, and then filtered through a 0.2µm millipore filter to yield the test sample.

### Hot water extraction

Plant material is collected and then washed thoroughly in tap

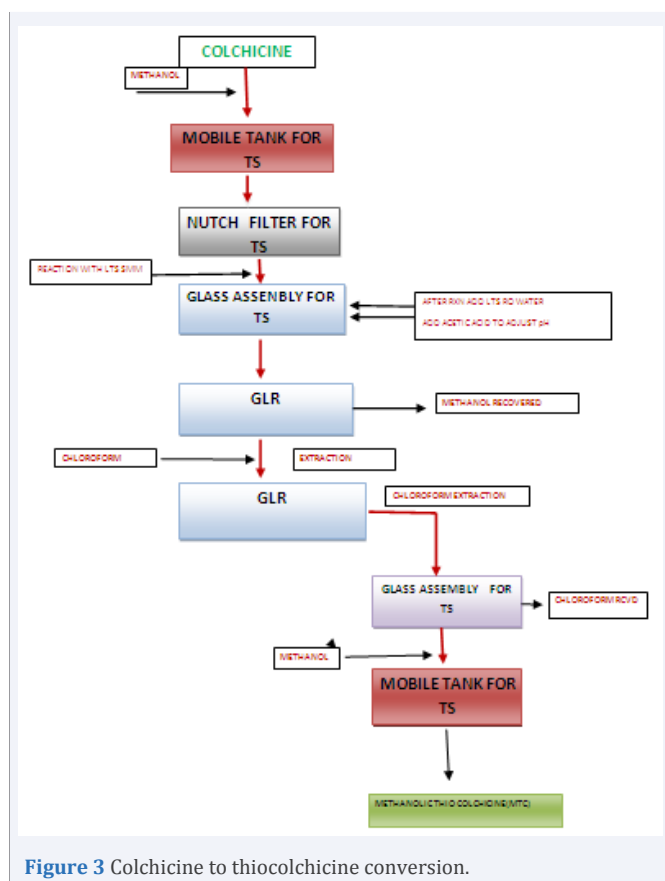


Figure 3 Colchicine to thiocolchicine conversion.

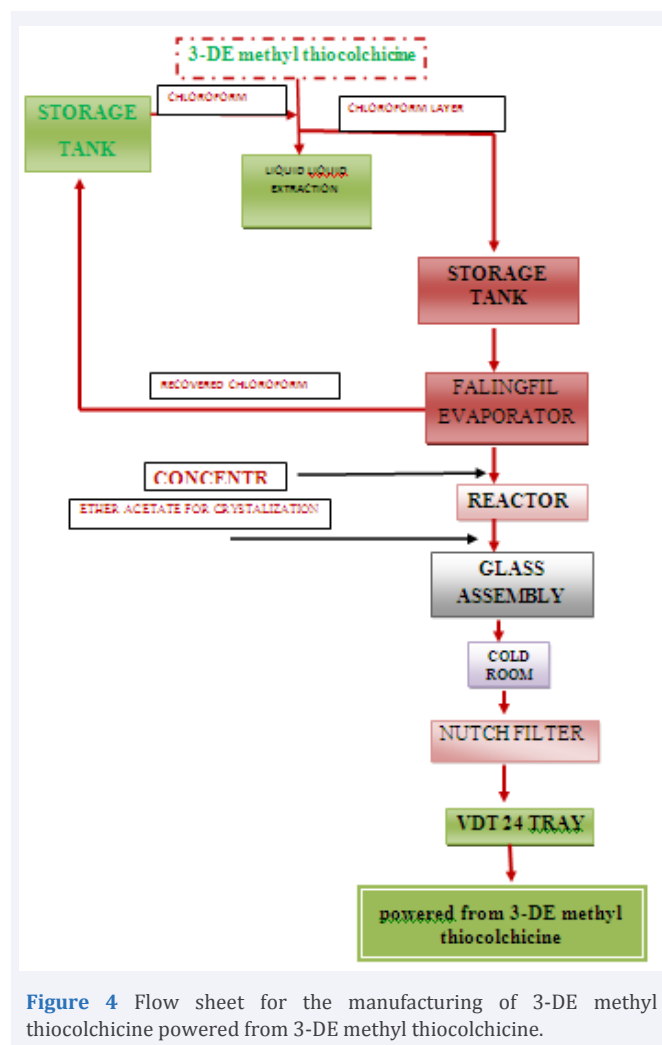


Figure 4 Flow sheet for the manufacturing of 3-DE methyl thiocolchicine powered from 3-DE methyl thiocolchicine.

water. The plant material is soaked in water and subjected to rotary vacuum extractor with pressure at 15 psi and temperature at 121°C, then the extract is filtered using filter paper then the sample diluted with 95% HPLC graded methanol, then filtered through a 0.2µm millipore filter to yield the test sample.

### High performance liquid chromatography (HPLC)

Identification of colchicine is carried out by comparing the retention time of the sample with that of the standard obtained from Sigma, USA. A Luna C18250 × 4.60 mm column is used as stationary phase. The mobile phase used is 25% HPLC grade methanol with a flow rate of 0.2 ml/min. 100µl of sample is injected and the peaks are detected at specific wavelength.

### Supercritical fluid extraction

This technology is best suited for the extraction of natural products. As there is an increasing concern for safe, eco-friendly and pollution free manufacturing processes, SCFE technology provides a ready and total solution to these challenges. Its superiority over the conventional technologies of extraction, especially for natural products in the food and pharmaceutical industry is well recognized.

Supercritical fluid extraction (SFE) is a promising extraction process. The principle of the process is utilizing a supercritical fluid whose physicochemical properties are between those of a liquid and a gas [48]. Supercritical fluids have better transport properties than liquids because that depends on its density which is tuneable by changing pressure and temperature [49]. SFE is an environmentally benign process compared to conventional industrial solvent Extractions i.e. do not require the use of organic solvents. The resulting products are completely free from toxic residues in high purity and selectivity which are important for pharmaceutical industries. Many supercritical fluids can be easily removed from the extract products by depressurization to the atmospheric pressure, depressurizing products free of solvent. One of the most frequently used supercritical fluids is CO<sub>2</sub>; it has low critical conditions (T<sub>c</sub>= 31.12oC, and P<sub>c</sub>= 73.7 Bar) [50,51], is available in high purity, and is safe and cheap .It is good for solubilising non-polar compounds such as hydrocarbons and can dissolve some medium polar compounds, e.g.. alcohols, esters, aldehydes, and ketones [52,53]. The solubilizing properties of neat supercritical CO<sub>2</sub> are comparable to hexane and benzene. It can be used at low temperature for extracting thermally labile or easily oxidized compounds. Another advantage of CO<sub>2</sub> is that it is SCFE is a two-step process which uses carbon dioxide (CO<sub>2</sub>) for extraction, above its critical temperature (31°C) and critical pressure (74 bar). The feed, generally in powder form, is charged into the extractor. Supercritical CO<sub>2</sub> is fed to the extractor through a high pressure liquid CO<sub>2</sub> pump. The extract laden CO<sub>2</sub> is sent to a separator via a pressure reduction valve. At reduced temperature and pressure conditions, the extract precipitates out in the separator. The extract free CO<sub>2</sub> stream, leaving the separator is then recycled to the CO<sub>2</sub> tank.

Several operating parameters need to be taken in consideration for developing a successful SFE process. First, the compound (s) of interest must be sufficiently soluble in the supercritical fluids. The considered operating parameters include the type of sample , method of sample preparation , type of fluid , choice of modifiers , method of fluid feeding, and condition of extraction including pressure, temperature, flow rate, and extraction time . Other factors are water content, and particle size of the matrix [54-57].

### Regio-specific Microbial Transformation

Derivatives of colchicine i.e., 3-demethylcolchicine, colchicoside, thiocolchicocide with improved therapeutic properties for anti-inflammatory and anti-tumor drugs [58-60] will have good commercial demand as these compounds were used clinically for the treatment of certain forms of leukemia and solid tumors [61], Demethylated colchicine at C-3 position of the ring-A showed about 35-fold less toxicity as compared to parent molecule and equal to anti-tumor activity to that of thiocolchicine [62]. 3-demethylcolchicine and its glucosides, however, are only minor constituents in the colchicine producing plants [61]. In order to commercialize these compounds, efforts have been made to find alternative routes for production of 3-demethylated colchicine and thiocolchicine. It has been noticed that chemical demethylation not only results for demethylation of the methoxy group at C-3 of the aromatic ring of colchicine but also leads to formation of a mixture of 1-,2-,3- and 10- mono, di, and tri-, demethyl derivatives. The chemical conversion of colchicine

into 2-, 3-, demethyl colchicine is about 40-50 % [63] and not viable for commercial production. Production of 3-demethyl thiocolchicine from colchicines /thiocolchicine by microbial transformation process is depicted in Figure 5 (from authors R & D). In this process *Bacillus sp* is used as biocatalyst.

By microbial transform technology only the methyl group at C-3 position is removed and in that place a carbohydrate group which added by glycosylation process. The newly derived compound by glycosylation process is known as colchicoside.

Bellet P. et al., 1959 [64], using different strains of *Streptomyces* and of other species of Bacteria and Fungi, tried to transform colchicine and its derivatives into the corresponding 3-demethylated derivatives. Hufford CD. et al.[ 65], using *Streptomyces griseus* and/or *Streptomyces spectabilis* also studied the demethylation process of colchicine. Izawa M, et al. 1981 [66], studied the enzyme activity from microorganisms like *Streptomyces*, *Bacillus*, etc. to understand the process of regio-specific demethylation, characterized by low conversion yields and productivity. Poulev et al. 1995 [67], have obtained the specific biotransformation of colchicine using bacterial microorganisms, but still achieve poor yields and productivity. Bombardelli et al., 2000 and 2002 [68]. Again demonstrated the process of demethylation followed by glycosylation by using the following strains of *Bacillus megaterium*. Exclusively: DSM 90, 509, 322,333,1667,1670,1671.

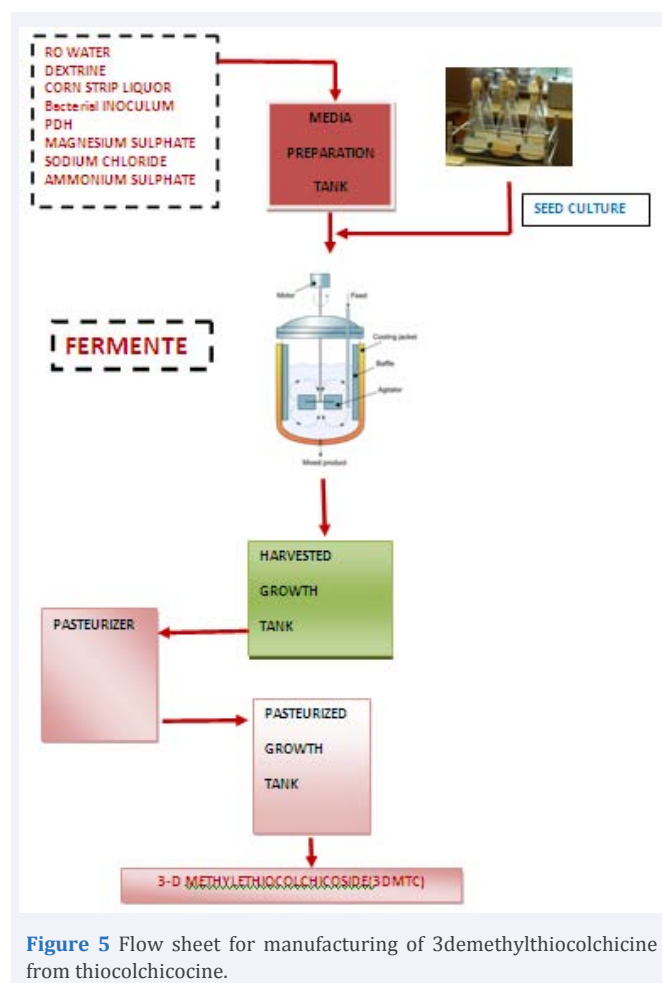


Figure 5 Flow sheet for manufacturing of 3demethylthiocolchicine from thiocolchicine.

Behera et al. 2008 [69], demonstrated the process of demethylation of colchicine at higher level compare to the earlier reports, by using a different strain of *Bacillus sp1* (ACBT03). This novel mutant of *Bacillus sp*, was isolated in its wild-form from soil sample of an industry area, where *Gloriosa superba* L. is processed for colchicine production. This newly isolated mutant has potential for demethylation of colchicine and its derivatives. The *Bacillus sp* is posses CYP3A4 enzyme responsible [70-72], for demethylation process at specific site [73-77]. This demethylation process was followed by glycosylation, due to the glycosyl transferase activity expressed by *Bacillus megaterium* [78].

In 2002, Alchem International Ltd, India was commercialized the process of Regio-specific Microbial Transformation of colchicines to 3-demethylated colchicines through fermentation technology by using *Bacillus sp* as biocatalyst. The newly discovered *Bacillus spp* is having high potential for colchicine tolerance up to 10gm/L and can be used for biotransformation of colchicine and thiocolchicine to its respective glycosylated derivatives. At about 11 to 13 PCV and in the middle phase of exponential it converts colchicine/thiocolchicine to colchicoside and thiocolchicoside. The biotransformation process efficiency is more than 50%. The above said process can be well commercialized through scale up process at fermenter level.

## MARKETING COLCHICOSIDE FORMULATED DRUGS

Most commonly used muscle relaxants are central nervous system depressants. Although these groups of drugs usually help to reduce spasticity, but decrease in muscle tone elsewhere, may lead to a decrease in the mobility of the patient. Also the development of sedation, is found to be a major limiting factor in the use of muscle relaxants for the treatment of Acute Low Back Pain (LBP), as they can affect daily activities and decrease working capabilities [79,80].

Hence, these limiting factors in the use of muscle relaxants raised a need for an ideal muscle relaxant devoid of effects on psychomotor performance, free of sedation and higher tolerability. These two salts block cyclooxygenase which is required for prostaglandins biosynthesis.

Thiocolchicoside (Muscoril, Myoril, Neoflex) is a muscle relaxant with anti-inflammatory and analgesic effect. It acts as a competitive GABA receptor antagonist and also glycine receptor antagonist with similar potency and nicotinic acetylcholine receptors to a much lesser extent [81,82].

As stated earlier thiocolchicoside is a semi-synthetic derivative of colchicine, a natural glycoside of *Superba gloriosa*. It's *in-vitro* profile shows affinity for the inhibitory glycine and GABA A receptors and therefore the compound is endowed with glycinomimetic activity and is being used in rheumatology and orthopaedic field for its myorelaxant property [83,84]. It has been reported that thiocolchicoside produces muscle relaxation without any sedative side effects. It is indicated for the adjunctive treatment of muscle spasm in acute low back pain (LBP).

Thiocolchicoside is yellow crystalline powder. It is soluble in water, slightly soluble in ethanol and insoluble in chloroform.

It is a glycosulfurated analogue of colchicine and is a well known centrally acting muscle relaxant used in the treatment of musculoskeletal disorders. Chemically it is N-[(7S)-3-(β-D-Glucopyranosyloxy) -1,2-dimethoxy-10-(methylsulfanyl) - 9 - oxo - 5, 6,7,9 tetrahydrobenzo [a] heptalen-7-yl] acetamide. Suitable formulation of colchicoside and aceclofenac /diclofenac has been in market by top pharmaceutical manufacture (Table 1).

## FUTURE PROSPECTIVE OF COLCHICINES

Cancer is the leading cause of death in U.S. and many developed countries. According to the World Health Organization Fact Sheet 2005, 7.6 million people died of cancer worldwide, and more than 70% of those deaths were reported in low and middle income countries. The number of global cancer deaths is projected to increase 45% from 2007 to 2030 [85,86].

Several different approaches have been implemented for prevention, early detection, diagnosis and treatment of various types of cancers. In terms of treatment, there are a number of effective chemotherapeutic drugs in the market, with diverse mechanisms of action that target various stages of cancerous cells, with the main objective of stopping cell proliferation. Compounds that inhibit cell proliferation and exert cytotoxic activity by perturbing microtubule dynamics have been explored with some success.

Colchicine is a very cheap alkaloid agent that has been used in medicine for a long time [87-90]. Colchicine is a microtubule destabilizer that has very strong binding capacity to tubulin to perturb the assembly dynamics of microtubules [91-93]. Colchicine also can increase cellular free tubulin to limit mitochondrial metabolism in cancer cells through inhibition of the voltage-dependent anion channels of the mitochondrial membrane.

**Table 1:** List of pharmaceuticals manufacturers marketing thiocolchicoside and nonsteroidal anti-inflammatory drugs.

Brand Name	Composition	Company
BAFLEX cap	Thiocolchicoside 4mg	INTAS
BAFLEXcap	Thiocolchicoside 8mg	INTAS
BAFLEX inj	Thiocolchicoside 4mg	INTAS
LUPIFLEX tab	Thiocolchicoside 4mg	LUPIN
LUPIFLEX tab	Thiocolchicoside 8mg	LUPIN
MOBIWAK cap	Thiocolchicoside 4mg	WOCKHARDT
MOBIWAK cap	Thiocolchicoside 8mg	WOCKHARDT
MOBIWAK inj	Thiocolchicoside 4mg	WOCKHARDT
MOBIWAK PLUS cap	Thiocolchicoside 8mg, diclofenac potassium 50mg	WOCKHARDT
MYORIL cap	Thiocolchicoside 4mg	SANOFIAVENTIS
MYORIL cap	Thiocolchicoside 8mg	SANOFIAVENTIS
MYORIL inj	Thiocolchicoside 4mg	SANOFIAVENTIS
MYOSIDE cap	Thiocolchicoside 4mg	TORRENT
MYOSIDE cap	Thiocolchicoside 8mg	TORRENT
PERISET inj	Thiocolchicoside 4mg	IPCA
RELMUS cap	Thiocolchicoside 4mg	NOVARTIS
RELMUS cap	Thiocolchicoside 8mg	NOVARTIS

Unfortunately, a major limitation in the use of anti-mitotic drugs in cancer chemotherapy is their severe side effects. However, it has been confirmed that colchicines derivatives are better option for microtubule polymerization inhibitor, develops multi-drug resistance in tumor cells due to its P-gp substrate and induction activity, which in turn leads to its rapid efflux from tumor cells. This auto-induction of the efflux of colchicine derivatives with less toxicity remains a major challenge to medicinal chemists.

In order to overcome with the high toxicity nature of colchicines lot of trials are in progress to bring alternation in structural moiety of colchicines. Such modified colchicines derivatives are colchicoside, thiocolchicoside, 3-demethylate colchicines, 3-demethylate thio-colchicines, and 3-demethylate thiocolchicoside.

Deacetamidothiocolchicine derivatives have also been evaluated for their antitumor activity against various human tumor cell lines, some of which express the multidrug resistance (MDR) phenotype, for their impact on the cell cycle and their binding to tubulin. Colchicine and thiocolchicine were used as reference compounds. Thiocolchicine was the most active agent on MDR-negative cells in terms of growth inhibition.

In conclusion, there is now an increasing appreciation of transport processes as determinants of drug disposition. Among the various transporters expressed in organs, such as the liver, intestine, and brain, the efflux transporter P-gp has been noted to be an especially important modulator of drug absorption and excretion. Moreover, inhibition of P-gp has been associated with a number of clinically significant drug-drug interactions. In this connection derivatives of colchicines would be more effective as compared to other anticancer drugs in terms of less side effects, and under low budgetary provision for cancer suffering patient with monetary depression.

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