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Chemical constituents, cytotoxic activities and traditional uses of *Micromelum minutum* (Rutaceae): a review

Abstract

Micromelum minutum belongs to the family of aromatic deciduous trees and shrubs, Rutaceae. Different types of coumarins together with two alkaloids are found in the plant. Chemical constituents are isolate from different parts of the plant- leaves, stem, stem bark, fruits, seeds and roots. Traditionally, the plant is used for various purposes. Scientific investigations particularly focused on the cytotoxicity of the plant. The reviews compile the botanical description, traditional use, chemical constituents and cytitoxic activities of *Micromelum minutum*.

Keywords: *Micromelum minutum*, Rutaceae, coumarins, alkaloids, botanical description, traditional use, chemical constituents, cytotoxic activities

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Introduction

Rutaceae, the rue family, composed of 160 genera and about 2,070 species of woody shrubs and trees and is distributed in warm temperate and tropical regions.[1] The members of Rutaceae family have been used in perfumery, gastronomy, and traditional medicine and several publications have reported the presence of secondary chemical constituents.[2] Phytochemical survey of this family reveals alkaloids, coumarins, flavonoids, limonoids, and volatile oils[3] and these have been associated to different biological activities, for example, antimicrobial,[4] antidiarrhoeal,[5] anticholinesterasic,[6] antileishmanial,[7] antiprotozoal,[8] larvicidal,[9] and antioxidant activities.[10]

There are seven subfamilies in the Rutaceae family, Aurantioideae is one of them.[11] Clauseneae is one of the two tribes of Aurantioideae subfamily and Micromelum is the only genus of the subtribe Micromelinae. Coumarins, alkaloids, and flavonoids have been isolated from the Micromelum genus.[12] The species of the Micromelum genus are small spineless trees and the species *Micromelum minutum* (synonym: *Micromelum pubescens*) is locally known as "Chemomar", "Cherek-cherek", "Secherek" or "Kematu" in Malayasia,[13,14] The species has revealed a range of physiologically active compounds including anticoagulants, anti-carcinogens and anti-bacterials[15–17] in it. The present review aims to compile up to date documentations of various phytochemical compositions and biological properties of *Micromelum minutum*.

Traditional use

Micromelum minutum is used in ringworm and ague, in the regulation of menstruation and the treatment of fever.[17,18] It also used in traditional Thai medicine for tumor.[19] The leaves are used traditionally as a febrifuge, the stems as a carminative, and the flowers and fruits as an expectorant and a purgative, respectively.[20] The juice from the leaves is used to treat white scum on tongue, bad breath, haemorrhoids and to treat toothache and teething problems in babies. Leaves are also taken as a general tonic and shoots are used as a medicine treating infantile convulsions. The pounded leaves are an ingredient of a poultice used to relieve skin irritation. The leaves are rubbed on the skin to relieve irritations caused by scabies. The leaves or inner bark of the twigs are used in various ways to remedy headache and stomach-ache, to cure coughs and a sore tongue, to arrest profuse menstruation, to treat gonorrhoea, and as a remedy for thrush. Fluid from the bark is used to treat headaches and an infusion of the bark is ingested to cure stomachache.[21] Roots are used as a febrifuge, in decoction or infusions are given for diarrhoea in children, and as a carminative. They are considered to be useful for easing toothache and are also used as a remedy for stomach-ache and headache. Pieces of the root are chewed with betel for coughs. The plant is also used to cure headache.[21]

Phytochemical constituents

Previous phytochemical investigations on the different parts of *Micromelum minutum* have showed the presence of coumarins, triterpenes, alkaloids and phenylpropanoids (Table 1).[13–15, 22–24] An acetone extract of stems of the plant was chromatographed on silica-gel, eluting with hexane-acetone, followed by repeated preparative TLC to afford six new coumarins along with six known ones.[22] Two new monoterpene coumarins, minutin A and minutin B, together with four known coumarins, 8,4″-dihydroxy-3″,4″-dihydrocapnolactone-2',3'-diol; 8-hydroxyisocapnolactone-2',3'-diol; 8-hydroxy-3″,4″-dihydrocapnolactone-2',3'-diol and clauslactone E were purified.[25] *Micromelum minutum* seeds are rich source of coumarins.[14] Lekphrom et al.,[26] isolated a new 7-oxygenated coumarin, 7-demethylmurralonginol isovalerate, and a new natural product, murralonginol, together with seven known 7-oxygenated coumarins, murralonginol isovalerate, murralongin, micromelin, scopoletin, microminutin, murrangatin, and minumicrolin. A new coumarin, with eleven known coumarins, murralonginol isovalerate, osthol, phebalosin, micromelin, murrangatin acetate, osthenon, murrangatin, minumicrolin, murralongin, umbelliferone and murracarpin, was isolated (Table 1).[27]

Table 1 Chemical constituents found in *Micromelum minutum*

Plant part	Compound
Stem	Micromarin-A
	Micromarin-B
	Micromarin-C
	Micromarin-F
	Micromarin-G
	Micromarin-H
	Micromelin
	Murralonginol isovalerate
	Microminutinin
	6-methoxymicrominutinin
	Microminutin
	Murrangatin
	Phebalosin
Stem Bark	Micromelin
	Micropubescin
	Microminutin
	Flindersine
Leaves	3,4-dihydrocapnolactone
	2,3-epoxyisocapnolactone
	8-hydroxyisocapnolactone-2,3-diol
	8-hydroxy-3,4-dihydrocapnolactone-2,3-diol
	8,4-dihydroxy-3,4-dihydrocapnolactone-2,3-diol
	8-methoxycapnolactone
	Stigmasterol
	5(6)-gluten-3-one
	5(6)- gluten-3--ol
	3,11-dihydro-3,5-dimethyl-3-(4-methyl-3-pentenyl)-pyrano[3,2-a]carbazol-9-ol (known as mahanine)
	Minutin A
	Minutin B
	Clauslactone E
Seeds	Micromarin-A
	Micromelin
	Murralonginol isovalerate
	Microminutinin
	6-methoxymicrominutinin
	Micromarin-F
	Micromarin-G
	Microminutin
	Micromarin-H
	Micromarin-C
	Murrangatin
	Micromarin-B
	7-demethylmurralonginol isovalerate
	Murralonginol
	Murralonginol isovalerate
Fruits	Murralongin
	Micromelin
	Scopoletin
	Microminutin
	Murrangatin
	Minumicrolin
	7-methoxy-8-(3-methyl-2-O-isovaleryl-1-oxo-butenyl)-coumarin (named as minutuminolate)
	Murralonginol isovalerate
	Osthol
Roots	Phebalosin
	Micromelin
	Murrangatin acetate
	Osthenon
	Murrangatin
	Minumicrolin
	Murralongin
	Umbelliferone
	Murracarpin

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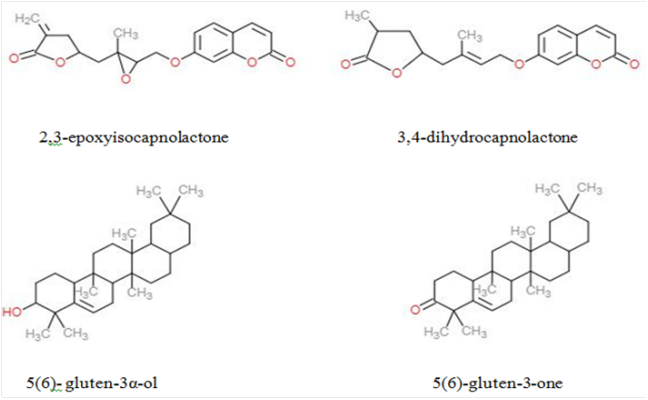
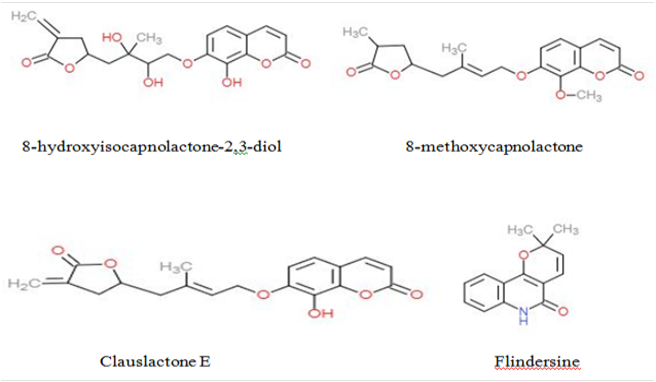


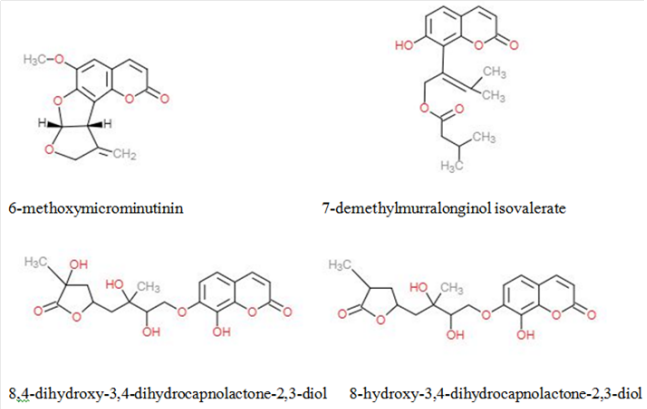
2,3-epoxyisocapnolactone | 3,4-dihydrocapnolactone

5(6)- gluten-3α-ol | 5(6)-gluten-3-one



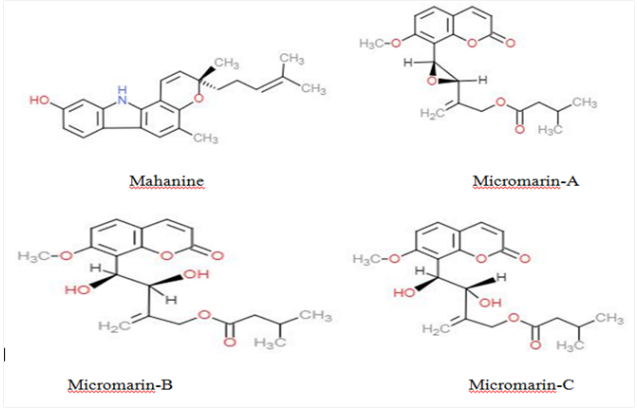
8-hydroxyisocapnolactone-2,3-diol | 8-methoxycapnolactone

Clauslactone E | Flindersine



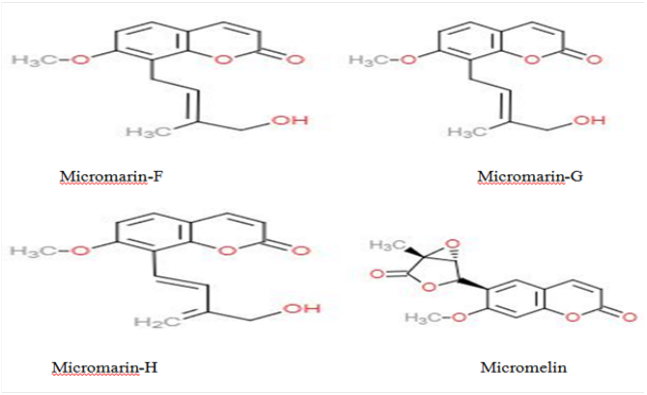
6-methoxymicrominutinin | 7-demethylmurralonginol isovalerate

8,4-dihydroxy-3,4-dihydrocapnolactone-2,3-diol | 8-hydroxy-3,4-dihydrocapnolactone-2,3-diol



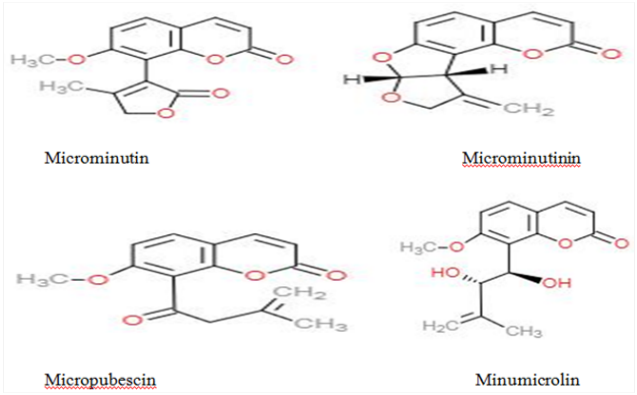
Mahanine | Micromarin-A

Micromarin-B | Micromarin-C



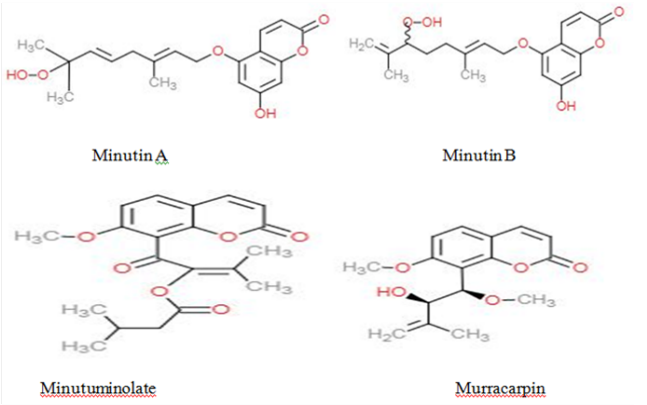
Micromarin-F | Micromarin-G

Micromarin-H | Micromelin



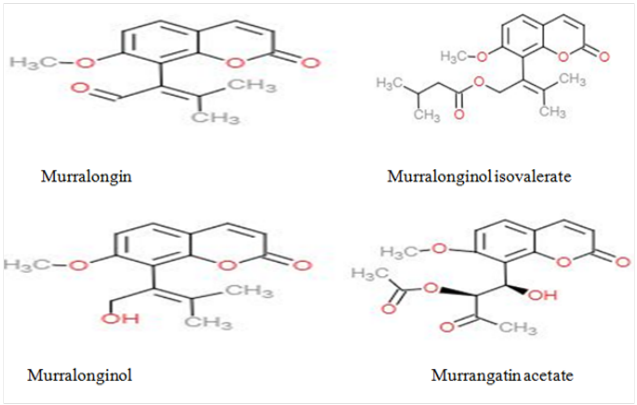
Microminutin | Microminutinin

Micropubescin | Minumicrolin



Minutin A | Minutin B

Minutuminolate | Murracarpin



Murralongin | Murralonginol isovalerate

Murralonginol | Murrangatin acetate

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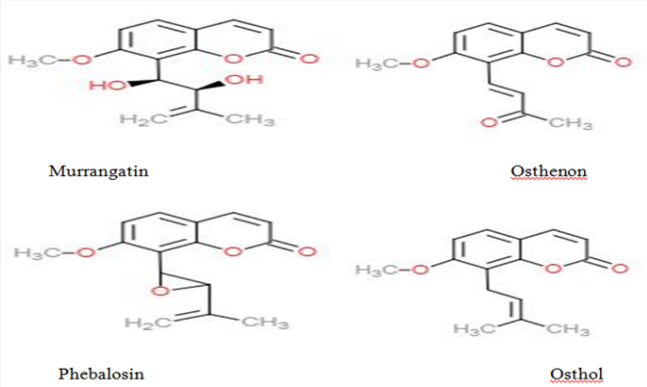

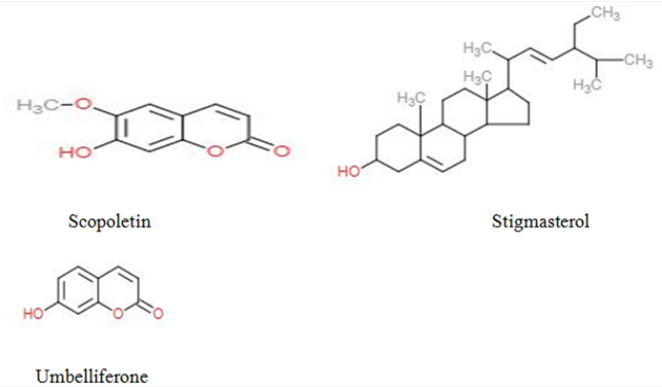

Cytotoxic activities

Micromelum minutum has been mainly investigated for its cytotoxic activities which are compiled in the following passages.

CEM-SS cell line (T-lymphoblastic leukemia cells)

The chloroform extracts of the leaves of *Micromelum minutum* showed strong activity, while the bark extracts had a moderate activity with IC_{50} values of 4.2 and 13.7µg/ml, respectively against a T-lymphoblastic leukemia (CEM-SS) cell line.[28]

Tan et al.,[29] investigated the induction of apoptosis by 2', 3'- epoxyisocapnolactone and 8-hydroxyisocapnolactone-2', 3'-diol which were previously isolated from the leaves of *Micromelum minutum* on CEM-SS cells. The inhibition effect of 2', 3'-epoxyisocapnolactone and 8-hydroxyisocapnolactone-2', 3'-diol at 50% of cell population (IC_{50}) was found to be 4.6µg/ml (13.5µM) and 3µg/ml (7.8µM) on CEM-SS cells, respectively. The induction time for apoptosis by 8-hydroxyisocapnolactone-2', 3'-diol in CEM-SS was earlier than 2', 3'-epoxyisocapnolactone, which was 4 h and 12 h after treatment. This study has effectively demonstrated that 2', 3'-epoxyisocapnolactone and 8-hydroxyisocapnolactone-2', 3'-diol have a good potential as anti-cancer drug.

U937 cell line (myeloid leukemia cells)

Roy et al.,[31] investigated the effect of mahanine, a major constituent of the edible parts of the Thai vegetable *Micromelum minutum*, on the activation of the apoptotic pathway in human leukemia U937 cells. The study declares mahanine inhibits cell growth and induces apoptosis in U937 cells through a mitochondrial dependent pathway. In the study, various end points were used to screen for apoptosis: morphological changes in cells, the relative numbers of viable and apoptotic cells; translocation of membrane bound phosphatidylserine and DNA analysis. It was found that mahanine-induced apoptosis in U937 cells involved activation of caspases, including caspase-3, release of cytochrome *c* into cytosol, loss of mitochondrial membrane permeability, and decreased levels of cellular ATP. As mitochondrial permeability is known to be important in the regulation of cytochrome*c* release, observations in the study indicated that mitochondria were the principal target of mahanine. So more specificallythe study proposed that mahanine causes the mitochondrial membranes to lose their permeability, resulting in caspase-3 activation and apoptosis. Estimated IC_{50} value of mahanine was 8.7µM at 12 h for apoptosis.[31]

KKU-100 cell line (cholangiocarcinoma cells)

Cytotoxic assay against cholangiocarcinoma (KKU-100) cell line was performed employing the colorimetric method as described by Skehan and co-workers.[33] Murralonginol, murralongin, micromelin, scopoletin, microminutin, murrangatin, and minumicrolin isolated from the fruits of *Micromelum minutum* exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 and among these compounds microminutin and murrangatin showed strong cytotoxicity against the cholangiocacinoma (KKU-100) cell line (respective IC_{50} values of 1.7 and 2.9µg/mL).[34] The IC_{50} values of other compounds were 10.0µg/mL (murralonginol), 9.0µg/mL (murralongin), 9.2µg/mL (micromelin), 19.2µg/mL (scopoletin) and 10.2µg/mL (minumicrolin).[34]

HL60 cell line (promyelocytic leukemia cells)

Two of the compounds, 2', 3'-epoxyisocapnolactone and 8-hydroxyisocapnolactone-2', 3'-diol isolated from the chloroform extract of the leaves of *Micromelum minutum* were significantly toxic to HL60 cell lines. The IC_{50} value of 2', 3'-epoxyisocapnolactone against the cancer cell line was 4.2µg/ml and the IC_{50} value of 8-hydroxyisocapnolactone-2', 3'-diol was 2.5µg/ml.[35]

HeLa cell line (cervical cancer cells)

8-hydroxyisocapnolactone-2 ,3 -diol isolated from the chloroform extract of the leaves of *Micromelum minutum* showed strong cytotoxicity towards cervical cancer (HeLa) cell line with the value of IC_{50} was 6.9µg/ml.[35]

HepG2 cell line (liver cancer cells)

8-hydroxyisocapnolactone-2 ,3 -diol isolated from the chloroform extract of the leaves of *Micromelum minutum* showed strong cytotoxicity towards liver cancer (HepG2) cell line with the value of IC_{50} was 5.9µg/ml.[35]

SBC3 and A549 cell lines (lung adenocarcinoma cells)

The cytotoxic activity against lung adenocarcinoma (SBC3 and A549) cell lines was determined by the MTT colorimetric cell viability assay.[36] It showed Clauslactone E, minutin B and 8-hydroxyisocapnolactone-2 ,3 -diol isolated from the leaves of *Micromelum minutum* possess strong cytotoxic activity against the lung adenocarcinoma (SBC3 and A549) cell lines with IC_{50} values of 3.7, 10.4µM for clauslactone E; 9.6, 17.5µM for minutin B; and8.8, 10.1µM for 8-hydroxyisocapnolactone-2 ,3–diol, respectively.[36]

K562 and K562/ADM cell lines (leukaemia cells)

The cytotoxic activity against the leukaemia (K562 and K562/ADM) cell lines was determined by the MTT colorimetric cell viability assay.[43] It showed Clauslactone E, minutin B and 8-hydroxyisocapnolactone-2 ,3 -diol isolated from the leaves of *Micromelum minutum* possess strong cytotoxic activity against the leukaemia (K562 and K562/ADM) cell lines with IC_{50} values of 12.1, and 10.8μM for clauslactone E; 8.7 and 6.7μM for minutin B; 16.9, and 10.1μM for 8-hydroxyisocapnolactone-2 ,3-diol, respectively.[36]

Crown gall tumors

Phebalosin, isoled from the stem bark of *Micromelum minutum* was significantly inhibitory on the development of crown gall tumors on potato discs (~64% and ~70% in two independent determinations).[37]

KB cell line (human epidermoid carcinoma cells)

Murralonginol isolated from the fruits of *Micromelum minutum*, which was the first time isolation of the product from any natural source,[38] was found to be weakly cytotoxic against human epidermoid (KB) cell line with IC_{50} value of 17.8μg/mL. 7-demethylmurralonginol isovalerate and murralonginol isovalerate isolated from the fruits of *Micromelum minutum* were also weakly cytotoxic against the cell line with IC_{50} value of 41.1μg/mL and 30.4μg/mL respectively.[38]

NCI-H187 cell line (human small cell lung cancer cells)

7-demethylmurralonginol isovalerate, murralonginol and murralonginol isovalerate isolated from the fruits of *Micromelum minutum* were weakly cytotoxic against the cell line with the IC_{50} value of 46.5μg/mL, 27.1μg/mL and 49.5μg/mL respectively.[38]

MCF-7 cell line (human breast cancer cells)

7-demethylmurralonginol isovalerate, murralonginol and murralonginol isovalerate isolated from the fruits of *Micromelum minutum* were weakly cytotoxic against the cell line with the IC_{50} value of 24.3μg/mL, 8.2μg/mL and 25.4μg/mL respectively.[38] Cytotoxic assay against human breast cancer (MCF-7) cell line was performed employing the colorimetric method as described by Skehan and co-workers.[39]

Leishmania major

Evaluation of the leishmanicidal activity of the methanol extract of *M. minutum* leaves revealed that the crude extract at 100μg/mL killed 68% of L. major. Among the compounds isolated from the leaves of *Micromelum minutum*, minutin A, minutin B, 8-hydroxyisocapnolactone-2',3'-diol and clauslactone E showed a significant cytotoxic activity against Leishmania major with IC_{50} values of 26.2, 20.2, 12.1, and 9.8μM, respectively (Table 2).[36]

Table 2 Cytotoxic activities of extracts and different constituents of *Micromelum minutum*

Plant extracts or constituents	Cytotoxicity
Chloroform extract of leaves	· Showed strong activity against T-lymphoblastic leukemia (CEM-SS) cell line with IC50 value of 4.2μg/ml.
Methanol extract of leaves	·The crude extract at 100μg/mL killed 68% of Leishmania major.
Chloroform extract of bark	· Had a moderate activity with IC50 value of 13.7μg/ml against T-lymphoblastic leukemia (CEM-SS) cell line.
2',3'-epoxyisocapnolactone	· Showed cytotoxicity against T-lymphoblastic leukemia (CEM-SS) cell line with IC50 value of 4.6μg/ml (13.5μM).
	·Was significantly toxic to HL60 cell lines (promyelocytic leukemia cells) with the IC50 value of 4.2μg/ml.
8-hydroxyisocapnolactone-2',3'-diol	· Showed cytotoxicity against T-lymphoblastic leukemia (CEM-SS) cell line with IC50 value of 3μg/ml (7.8μM).
	·Was significantly toxic to HL60 cell lines (promyelocytic leukemia cells) with the IC50 value of 2.5μg/ml.
	· Showed strong cytotoxicity towards cervical cancer (HeLa) cell line with the value of IC50 was 6.9μg/ml.
	· Showed strong cytotoxicity towards liver cancer (HepG2) cell line with the value of IC50 was 5.9μg/ml.
	· Possesses strong cytotoxic activity against the lung adenocarcinoma (SBC3 and A549) cell lines with IC50 values of 8.8μM and 10.1μM respectively.
	· Possesses strong cytotoxic activity against the leukaemia (K562 and K562/ADM) cell lines with IC50 values of 16.9, and 10.1μM for K562 and K562/ADM cells respectively.
	· Showed a significant cytotoxic activity against Leishmania major with IC50 values of 12.1μM.
Mahanine	· Inhibits cell growth and induces apoptosis in U937 (myeloid leukemia) cells through a mitochondrial dependent pathway. Estimated IC50 value of mahanine was 8.7μM at 12 h for apoptosis.

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Table continued

Plant extracts or constituents	Cytotoxicity
Murralonginol	· Exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of10.0μg/mL. · Found to be weakly cytotoxic against human epidermoid (KB) cell line with IC50 value of 17.8μg/mL. ·Weakly cytotoxic against human small cell lung (NCI-H187) cell line with the IC50 value of 27.1μg/mL. ·Weakly cytotoxic against MCF-7 cell line (human breast cancer cells) with the IC50 value of 8.2μg/mL.
Murralongin	· Exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 9.0μg/mL.
Micromelin	· Exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 9.2μg/mL.
Scopoletin	· Exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 19.2μg/mL.
Microminutin	· Showed strong cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 1.719.2μg/mL.
Murrangatin	· Showed strong cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 2.9μg/mL.
Minumicrolin	· Exhibited cytotoxicity against cholangiocarcinoma cell line, KKU-100 with IC50 value of 10.2μg/mL.
Clauslactone E	· Possesses strong cytotoxic activity against the lung adenocarcinoma (SBC3 and A549) cell lines with IC50 values of 3.7μM and 10.4μM respectively. · Possesses strong cytotoxic activity against the leukaemia (K562 and K562/ADM) cell lines with IC50 values of 12.1, and 10.8μM for K562 and K562/ADM cells respectively. · Showed a significant cytotoxic activity against Leishmania major with IC50 values of 9.8μM.
Minutin B	· Possesses strong cytotoxic activity against the lung adenocarcinoma (SBC3 and A549) cell lines with IC50 values of 9.6μM and 17.5μM respectively. · Possesses strong cytotoxic activity against the leukaemia (K562 and K562/ADM) cell lines with IC50 values of 8.7 and 6.7μM for K562 and K562/ADM cells respectively. · Showed a significant cytotoxic activity against Leishmania major with IC50 values of 20.2μM.
Phebalosin	· Significantly inhibitory on the development of crown gall tumors on potato discs (~64% and ~70% in two independent determinations). · Significantly toxic to brine shrimp (IC50 47ppm, 95% confidence interval 31-69ppm)
7-demethylmurralonginol isovalerate	·Weakly cytotoxic against the human epidermoid (KB) cell line with IC50 value of 41.1μg/mL. ·Weakly cytotoxic against human small cell lung (NCI-H187) cell line with the IC50 value of 46.5μg/mL. ·Weakly cytotoxic against MCF-7 cell line (human breast cancer cells) with the IC50 value of 24.3μg/mL.
Murralonginol isovalerate	·Weakly cytotoxic against the the human epidermoid (KB) cell line with IC50 value of 30.4μg/mL. ·Weakly cytotoxic against human small cell lung (NCI-H187) cell line with the IC50 value of 49.5μg/mL. ·Weakly cytotoxic against MCF-7 cell line (human breast cancer cells) with the IC50 value of 25.4μg/mL.
Minutin A	· Showed a significant cytotoxic activity against Leishmania major with IC50 values of 26.2μM.

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Conclusion

Micromelum minutum has a wide range of use in folk medicine. But most of the scientific studies have been done on the cytotoxicity of the plant because the plant is a rich source of that. This review compiled cytotoxic properties of all types of compounds found and investigated on, not only the coumarins. It also listed the chemical constituents and traditional uses of the plant. These will help researchers in following ways: to develop and design a drug based on cytotoxic properties found here; facilitate researchers who are finding a source for a particular compound and investigate on other properties of the plant constituents that are already found.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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