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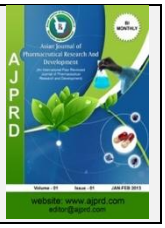

Open Access **Research Article**

# Review of the Potential of Kamandrah (*Croton Tiglium L.*) As A Medicinal Plant

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## A B S T R A C T

Herbal plants are widely used to cure various diseases. Research from the Euphorbiaceae family shows activity against cancer and tumors. Croton is a member of the Euphorbiaceae family which has wide uses in the field of medicine. The Croton genus consists of various species including *Croton lechleri, Croton palanostigma, Croton dracoides*, and *Croton tiglium* with various useful secondary metabolite contents. The plant Croton tiglium L is a medicinal plant originating from China, South Asia, and India. The seeds, leaves, bark and roots of *C.tiglium* can relieve various diseases, including: antifungal, anti-inflammatory, anticonvulsant, wound healing, antitumor activity. The main compound content of *Croton tiglium* is alkaloids, flavonoids and diterpenes. The literature review aims to explore *C tiglium* plants based on morphological characteristics, therapeutic uses, pharmacological actions and activities and plant compound content.

The research method used was to collect and analyze the selected literature electronically with the keywords "*Croton tiglium L", "Chemical constituent", "isolation", "Pharmacological action", and "Therapeutic use*". Selected literature included international and national journals that had been published on several sites, such as NCBI, Elsevier, and Pubmed, and others. Selected literature in the form of journals consisting evidence and information on chemical content and pharmacological activity.

**Keywords:** "*Croton tiglium L", "Chemical constituent", "isolation", "Pharmacological action", and "Therapeutic use*".

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## INTRODUCTION

### Kamandrah (*Croton tiglium L.*)

The kamandrah plant (*Croton tiglium L.*) is a plant that comes from the Euphorbiaceae family. Kamandrah is a medicinal plant that is widely found in Indonesia. All parts of the plant have a spicy taste (a characteristic trait) which causes inflammation of the mouth, throat, and lips, especially the seeds [9]. The *Croton tiglium* plant is easy to grow in tropical areas, where within six months to one year it can flower and bear fruit. Its spreading is relatively fast, starting from tropical Asia to India, New Guinea and Java, then to northern Indonesia and China.

### Benefits of *Croton tiglium L.*

Kamandrah plants are useful as antifungal[8], anti-inflammatory[11], anticonvulsant[16], wound healing[22], antitumor[25], bioinsecticide[26], HIV[24], neuroprotective[5], antinociceptive[18], antioxidant[20]

### Methods

### Inclusion and Exclusion Criteria.

1. This stage was conducted to decide whether the data found was appropriate to use in research or not. Studies are eligible to be selected if the following criteria are met:
2. Journals consisting pharmacological activities.
3. The data were international and national journals that had been published on several sites, such as NCBI, Elsevier, and Pubmed, etc.
4. Journal consisting morphological characteristics, compound content, therapeutic use, activity, and pharmacological action on the Croton tiglium L plant.

5. The exclusion criteria in this study were journals consisting of morphological characteristics, compound content, use of extracts, activity, and pharmacological action but not the species Croton tiglium L.

**Search Keywords**

The literature search in this review article was carried out electronically with the keywords "Croton tiglium L", "Chemical constituent", "isolation", "Pharmacological action", and "Therapeutic use".

**Data Analysis**

At this stage, the data that had been collected will be analyzed to show that national and international journals consist of morphological characteristics, compound content, therapeutic use, activity, and pharmacological action using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method.

## RESULT AND DISCUSSION

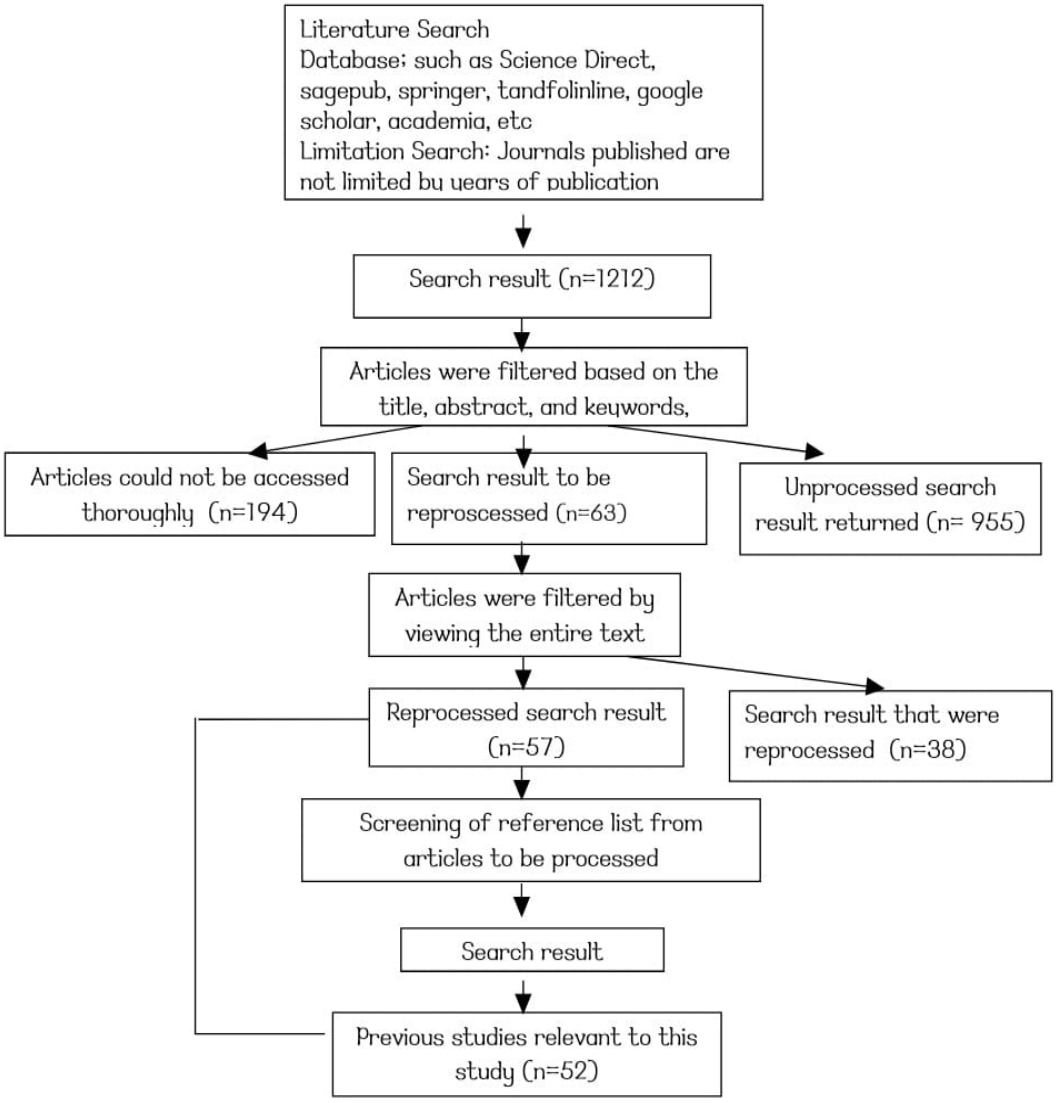


**Figure 1:** Analysis Stage Schematic with PRISMA

The search results based on the target site, namely https://sciencedirect.com using the keywords "Croton tiglium, compound content, therapeutic use and pharmacological action" obtained 19 research journal articles. The site https:// journal.sagepub.com gets 2 results journal articles based on keywords. https://link.springer.com/ as many as 3 journals, Google Scholar as many as 23 journals. The site

https://www.tandfonline.com/ has 5 journals. The following scheme obtained from the PRISMA method can be seen in Figure 1.

**Table 1:** Chemical contents of Croton tiglium plants

| Number | Part of the Plant | Content Extraction | Extraction/Isolation Method |
|---|---|---|---|
| 1 | herbaceous | -Berberine. Isoguanisin<br>-crotonoside | -Capillary elektroforesis<br>etyl eter extract[15] |
| 2 | seed | -12-O-Acetylphorbol-13-decanoate and 12-O-decanoylphorbol-13-(2-Methylbutyrate) [27]<br><br>- Diterpen, ester (tigliane and ingenane) [39]<br><br>-4-deoxy-4b-phorbol diesters (1–4) named as 12-O-tiglylphorbol-4-deoxy-4b-phorbol-13-acetate (1), 12-O-tiglylphorbol-4-deoxy-4b-phorbol-13-hexadecanoate (2), 13-O-acetyl-phorbol-4-deoxy-4b-phorbol-20-oleate (3) and 13-O-acetylphorbol-4-deoxy-4b-phorbol-20-linoleate (4)<br><br>-lectin [1]<br><br>-saponin, alkaloid, phenolic, tannin, triterpenoid, karbohidrat [32]<br><br>-Phorbol ester [18]<br><br>-Isoguanin [13]<br><br>-12-O-tetradecanoylphorbol-13-1setat (TPA &DCT)<br><br>- Oleic acid, hexadecanoid<br><br>-phorbol-12Otetradecanoyl-13-acetate<br>-Isoguanosine,12-O-Acetylphorbol-13-tigliate, 13-O-Acetylphorbol-20-linoleate<br><br>-phorbol ester<br><br>- Carbohydrates (glycosides), flavonoids, steroids (triterpenes), alkaloids, proteins<br><br>-12-O-Tiglylphorbol-13-acetate (11), 12-O-(2-methyl)-butyrylphorbol-13-aetate (12), and 12-O-tiglylphorbol-13-isobutyrate<br><br>-phenolic, flavonoid, steroid, triterpenoid, terpenoid, phorbol ester dan kumarin<br><br>-Isoproterenol [14] | -metanol extract<br><br>-LC MS MS<br><br>-1D, 2D-NMR and HR- ESI–MS spectroscopic [33]<br><br>-filtration gel chromatography<br><br>-etanol extract<br><br>-HPLC, HPTLC<br><br>-isolate<br><br>- ethanol extract, spectrophotometry<br><br>-etanol extract dan reflux [19]<br><br>-GCMS<br><br>-methanol extract, isolate<br><br>-HPLC<br><br>-water dry extract<br><br>-acetone extract<br><br>-HPLC [5]<br>-Refluks, ekstrak etanol |
| 3 | Leaf | -Tiglianes Diterpenoids<br><br>-Crotonol A, B [30]<br><br>-nonsesquiterpenoid [3]<br><br>- Oleic acid, hexadecanoid<br><br>- tigliane-typediterpenoids [36] | -Ekstrak etanol, isolate<br><br>-Ekstrak etanol dan purifikasi<br><br>-ekstrak etanol dilanjutkan purifikasi<br><br>-ekstrak etanol dan refluk |
| 4 | Fruit | -glycerides<br>of saturated fatty acids, phorbol-12, 13-diesters, phorbol-13, 20-diesters, and phorbol-12, 13, 20-triesters<br><br>-tigliane-typediterpenoids<br>-isoproterenol<br>-fatty acid<br><br>-planitin ,glycerids of crotonic and tiglic acids ,the glucoside crotonoside and alkaloids. | -isolate[10]<br><br>-refluks , etanol extract<br>-isolate<br><br>-serbuk [23] |
| 5 | Branch | phorbol ester, diterpenoid | Etanol extract, isolate [33] |
| 6 | Stem | Oleic acid, hexadecanoid | Etanol extract. Refluk |

**Table 2:** Benefits of active compounds in *Croton tiglium* plants

| Number | Benefit | Chemical Compounds |
|---|---|---|
| 1 | Anti-tumor | -phorbol-12Otetradecanoyl-13-acetate 4<br>- tigliane-type diterpenoids 34<br>- Diterpen, ester (tigliane and ingenane [29]<br><br>-4-deoxy-4b-phorbol diesters (1–4) named as 12-O-tiglylphorbol-4-deoxy-4b-phorbol-13-acetate (1), 12-O-tiglylphorbol-4-deoxy-4b-phorbol-13-hexadecanoate (2), 13-O-acetyl-phorbol-4-deoxy-4b-phorbol-20-oleate (3) and 13-O-acetylphorbol-4-deoxy-4b-phorbol-20-linoleate (4) 35<br><br>-isoguanin [13]<br>-crotonoside [31]<br>-12-O-Tetradecanoylphorbol-13-acetate (TPA)<br><br>-12-O-Tiglylphorbol-13-acetate (11), 12-O-(2-methyl)-butyrylphorbol-13-aetate (12), and 12-O-tiglylphorbol-13-isobutyrate [33] |
| 2 | Anti-HIV | -12-O-Acetylphorbol-13-decanoate and 12-O-decanoylphorbol-13-(2-methylbutyrate) [7,21] |
| 3 | Anti-TBC | Tiglianes Diterpenoids [35] |
| 4 | GI disorders, laxative [26, 30] | -glycerides of saturated fatty acids, phorbol-12, 13-diesters, phorbol-13, 20-diesters, and phorbol-12, 13, 20-triesters [10,12] |
| 5 | Anti-inflammatory | -phorbol [30]<br>-ester with the 20-aldehyde group |
| 6 | Hemolytic dan agglutinatioan activity | Lectin [1] |
| 7 | Anti-cancer<br>Cervical-cancer | -Crotonol A,B [30]<br>-Nonsesquiterpenoid [3]<br>-saponins, alkaloids, phenolic compounds,tannins, triterpenoids, and carbohydrates [32]<br>-Isoguanosine, 12-O-Acetylphorbol-13-tigliate, 13-O-Acetylphorbol-20-linoleate |
| 8 | Anthelmintic | flavonoids, alkaloids, saponins, tannins, glycosides [2] |
| 9 | Anti-dermatophytic | Oleic acid and hexadecanoic acid [17] |
| 10 | Relaxing-activity | Phorbol ester [18] |
| 11<br><br>12.<br>13. | Anti-bacteri dan anti-fungal [28]<br><br>Anti-Convulsant<br>Anti-diabetic | flavonoids, alkaloid, saponins, tannin, glycosides<br><br>-<br> |

## Mechanism of action of chemical ingredients in *Croton tiglium*

### Anti-HIV

The compounds that have anti-HIV activity in kamandrah plants are 12-Acetylphorbol-13-decanoate and 12-O-decanoylphorbol-13-(2-methylbutyrate). The compound was able to inhibit HIV-induced cytopathic effects (CPE) in MT-4 cells and to activate protein kinase C (PKC). 12-O-Acetylphorbol-13-decanoate and 12-O-decanoylphorbol-13-(2-methylbutyrate) effectively inhibited the cytopathic effect of HIV-1 [inhibitory concentration (IC100) values 7.6 ng/ml and 7.81 mg/ ml, and the minimum cytotoxic concentration (CC0) values were 62.5 and 31.3 mg/ml respectively (Sahar, et al., 1999). In research (Matsuya, et al., 2005) it was reported that 12-O-(methoxymethyl) phorbol 13-decanoate showed strong inhibitory activity against HIV-1 infection in MT-4 cells (EC50: 1.3 ng/mL) and relatively low cytotoxicity (CC50:8.3 mg/mL)

### Anti-TB

The diterpene ester compound tigliane, tetracyclic diterpenoid carbon, and its analogues found in kamandrah leaves, have antitubercular activity with MIC values of 19.5, 20.9, 20.5, and 13.4 Mm 35 respectively.

### Gastrointestinal

The ethanol extract of kamandrah has the activity as a laxative using the intestinal transit method in the treatment group with a dose of 0.06 mL/30 g. (72.5%) had a difference with the negative control (48.4%) and positive control (50.6%) which showed a weak laxative effect at a dose of 0.75 mL/30 g bw. This shows that the ethanol extract of C. tiglium seeds at a dose of 0.06 mL/30 g is effective as a laxative. The results of treatment tests with doses of 0.06, 0.04, 0.026 and 0.07 mL/28 g body weight showed a mouse population response of 100, 60, 40 and 40% respectively. The results of Thompson and Weil's analysis show that ED50 is 0.027 mL or equal to 639.5 g/kg BW. LD50 is 0.0707, equivalent to 1674.5 mg/kg BW. The results of calculating the safe limit for the extract are LD50/ED50 = 0.0707/0.027 = 2.7 26

According to research30 Croton tiglium low doses increase gastrointestinal motility and fecal pellet production, while high doses have an inhibitory effect

### Anti-inflammatory

Phorbol ester from kamandrah leaves showed strong cytotoxicity against K562, A549, DU145, H1975, MCF-7, U937, SGC-7901, HL60, Hela, and MOLT-4 cells,

with IC50 values ranging from 1.0 to 43 μM, additionally showed inhibition of COX-1 and COX-2, with IC50 values of 0.14 and 8.5 μM 30

### Hemolytic Activity

Partial inhibition of lysis of rabbit erythrocytes pretreated with several galactose-specific lectins suggests the involvement of galactose residues in rabbit red blood cells. While trypsinization increased the agglutinability of rabbit RBCs without affecting the rate of lysis, Activity suggests different pathways of hemagglutination and hemolysis following lectin binding to carbohydrate receptors. Variations in the level of lysis and agglutination of erythrocytes from each rabbit indicate the possibility that the lectin works specifically on blood in rabbits 1

### Anthelmintic

Concentrations of C. tiglium seed extract (100, 125, and 150 mg/ml) caused much higher mortality than other concentrations, while ivermectin caused nematode death within 6 hours. The lower concentration (25 mg/ml) was significantly more lethal than the negative control (RPMI-1640 medium) at 2, 4 and 6 hours of exposure. Each concentration damaged the cuticle and muscle of H. contortus. . This study shows that all concentrations of C. tiglium seed methanol extract produce anthelmintic activity 2

### Anti-dermatophytic

Croton tiglium ethanol stem extract had the greatest inhibitory activity against T. mentagrophytes and E. floccosum with MICs of 0.16 mg/mL and had lower activity against T. rubrum (MIC: 0.31 mg/mL). Oleic acid and hexadecanoic acid were found to be the main constituents in the stem extract which showed strong anti-dermatophyte activity 17

### Relaxing activity

Phorbol ester is the main active compound in C. tiglium and is known as an activator of protein kinase C (PKC). PKC activation mediates various signaling pathways that are important for the formation, regulation, and maintenance of the digestive tract. Phorbol esters can induce rapid and sustained contractions in smooth muscle cells isolated from guinea pig intestines and phorbol contractions are related to Ca 2+ 18

### Antibacterial and antifungal

Croton tiglium Linn is a good source of antimicrobial protein. A 50 kDa protein was purified from plants and showed potent broad-spectrum antimicrobial activity28

### Anti-cancer and anti-tumor

A phorbol ester derivative isolated from acetone extract of Croton tiglium seeds with inhibitory activity on human tumor cells HL-60 and lung carcinoma A549. 12- O -Tiglylphorbol-13-acetate,12- O -(2-methyl)-butyrylphorbol-13-aetate, and 12- O -tiglylph

## CONCLUSIONS

Kamndrah plants (Croton tiglium L) contain chemical compounds that can be obtained by various extraction and isolation methods from all parts of the plant (herbs, seeds, leaves, fruit, twigs, and stems) and have potential as medicinal plants for HIV, TB, Gastrointestinal, anti-inflammatory, hemolytic, anti-inflammatory, anti-dermatophytic, relaxant activity, anti-bacterial, anti-fungal, anti-cancer, and tumor.

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Mechanism of action of chemical ingredients in Croton tiglium

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