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Review Article

A Comprehensive Review on Medicinally Important Plant, *Croton tiglium* L.

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A b s t r a c t

Croton tiglium L. is a traditional medicinal plant grown in tropical and subtropical zone. The extract of seeds is generally used as medicine as they are rich in secondary metabolites, such as, alkaloids, flavonoids, terpenoids and saponins. Plant is used in the treatment of various ailments in developing countries such as wound healing, constipation, a purgative, traditional dyspepsia, dysenteria, diarrhea and also as analgesic, antimicrobial, insecticidal and anti-inflammatory. The aqueous extract also exhibits antitumor and anti-HIV activity but at the same time the plat contains tumor enhancing principle-phorbol ester. Besides the popular use of this plant in folk medicine, the plant contains some toxic substances which have toxic effect on human health. In this review the complete update on the plant has been enlightened to bring out the hidden medicinal values of the plant.

K e y w o r d s

Croton tiglium

Croton oil

Phorbol ester

Purgative

Introduction

World health organization (WHO) estimates that around 80% of the world population of developing countries relies on traditional plant medicines for primary healthcare needs, of which a major proportion correspond to plant extracts or their active principles (Sampson et al., 2000). It is now believed that consuming natural medicine is relatively safer than consuming synthetic drugs and this resulted in high demand of natural medicines in the world. *Croton* (Euphorbiaceae) is one of the largest genera of flowering plants, established by Linnaeus in 1737, with between 1200 and 1300 species. *Croton tiglium* is an Asian evergreen shrub or tree distributed from India to New Guinea and Java, China, Indonesia and Philippine islands, cultivated to limited extend in Southern California as an ornamental and curious plant (Duke, 1983). Among *Croton* species, only *C. tiglium*, is indigenous to India and cultivated and widely distributed in North-Eastern part of India. It is also known as *Chengkian* (Malay), Ba Dou (China), *Cheraken* (Javanese), Croton-oil plant, Croton seed, *Jamalgota* (Hindi), *Jayapala* (Sanskrit, Singhalese), *Jaypal* (Bengali), *Kemalakiyan* (Sundanese), *Krotonöl* (German), *Nepala* (Telugu), *Nervalam* (Malayalam, Tamil), Physic plant, *Purgierbaum* (German), Purging croton, Purging nut, *Salood* (Thai), Tiglium, Tiglium seed, and *Túba* (Filipino/Tagalog).

Plant description

It is a small, evergreen shrub or tree, 15-20 feet in height; trunk rather crooked, with smooth bark; branches slender, smooth, terete; bark pale whitish-brown, marked with scars of fallen leaves and young shoots sprinkled with stellate hairs. Leaves are alternate, on stalks nearly half as long as the blade; blade about 4.5 inches long by 2 inches wide when full grown, thin, glabrous, ovate, attenuate at the apex, faintly and rather distantly serrate, pale bright green, vein prominent beneath, petiole breaking up immediately on entering the leaf into five veins, the two lateral faint, the two intermediate well marked, giving with the midrib a triple nerved aspect to the leaf; on either side of base of the blade and connected with the petiole is a prominent sessile gland; stipules are minute, filiform, deciduous; the young leaves and buds are with scattered stellate hairs.

Flowers are in lax, terminal, erect, racemes, unisexual; the male at the upper part of the raceme, the female less numerous at the lower part; pedicels longer than the flowers; bracts minute. Male flower; calyx five spreading, broadly triangular, blunt sepals, with valvate aestivation, petals five, inserted on the flat receptacle, alternate with and reflexed between the sepals, oblong linear, blunt, set with rather long white hairs above, glabrous beneath, pale green; a persistent roundish yellow gland stands within each sepal, alternating with the petals; stamens 14-20 as long as the petals, one opposite each petal and sepal, the remainder irregularly dispersed over the receptacle, which is covered with short white hairs, anthers are small broad, innate, cells semilunar. Female flower; calyx deeply five-partite, divisions ovate, acute, spreading or reflexed, set with few or more stellate hairs and with a small rounded prominence in the angle between each, glands 5, blunt, prominent, opposite the sepal as in the male flower; petals round; ovary sessile thickly covered with stellate hairs, 3-celled, with a single pendulous ovule in each; style 3, deeply bifid; fruit about the size of a hazel nut, slightly inflated, pale, smooth, brownish-yellow, capsular, 3-celled, with a single large seed in each cell; dehiscing septicidally into 3 cocci, and afterwards loculicidally. Seeds nearly 0.5 inch long by about 2/5^{ths} wide, ovoid, rounded on the back, marked on the ventral surface by a fine raised raphe; Testa thin, brittle, light brown, black within; Embryo with large foliaceous cotyledons, laying in the centre of the oily endosperm (Bentley and Trimen,1980).

Phytochemical analysis

Croton tiglium L., a well-known traditional medicinal plant have been studied extensively. It has been reported that *C. tiglium* seeds include 30-50% oil, 10% proteins and small amount of albumin (Kim et al., 1993). It yields about 50-60% of an acrid fixed oil **(**Prajapati et al., 2003). This plant is rich in secondary metabolites including alkaloids and terpenoids (Rizk, 1987), the latter including irritant co-carcinogenic phorbol esters (Phillipson, 1995). Phytochemical analysis of seeds confirmed that seeds containing various secondary metabolites, such as, alkaloids, flavonoids and saponins and Gas Chromatography (GC) analysis of hexane soluble extract of seeds identified about eight fatty acids such as linoleic acid, oleic acid, myristic acid etc. (Saputera et al., 2006). Among *Croton* species, only *C. tiglium*, native and cultivated in India, has been extensively studied as a source of phorbol derivatives, having been shown to contain tigliane phorbol esters. TPA (12-O-tetradecanoylphorbol-13-acetate) is an irritant and inflammatory and Others phorbol esters obtained from *C. tiglium* seeds are 13-O-acetylphorbol-20-linoleate, 13-O-ttigloylphorbol-20-linoleate, 12-O-acetylphorbol-13-tigliate, 12-O-decanoylphorbol-13-(2-methylbutirate), and 12-O-acetlyphorbol-13-decanoate (EI-Mekkawy et al., 1999), 12-O-tetradecanoylphorbol-13-acetate and 12-O-(2-methylbutiroyl)-phorbol-13-dodecanoate (EI-Mekkawy et al., 2000). Bu et al. (2011) isolated two new compounds badounoids A (1) and B (2), together with 13 known non-sesquiterpenes from leaves of *C. tiglium* and their structures were established by means of spectroscopic methods. Isoguanosine (naturally occurring nucleoside analog of guanosine) was isolated from *C. tiglium* (Cherbuliez and Bemhard, 1932). This compound possess various biological activities such as incorporating into mammalian nucleic acid (Lowry and Brown,1952), stimulating the accumulation of cyclic AMP in the brain (Huang et al., 1972), and inhibiting IMP (Vasu and David,1985), pyrophosphorylase and glutamic acid dehydrogenase. From leaves of *C. tiglum* pyrazine derivative crotonine was isolated and its structure was elucidated as 2-(furan-2-yl)-5-(2,3,4-trihydroxy-butyl)-1,4-diazine by spectroscopic analysis (Wu et al., 2007).

Traditional use

Croton seeds were familiar medicinally in India before 450 BC. Chinese had written records in the second century B.C. for using *C. tiglium* to treat gastrointestinal

disorders, intestinal inflammation, rheumatism, headache, peptic ulcer and visceral pain (Qiu, 1996; Wang et al., 2008; Morimura, 2003; Tsai et al., 2004).The seeds of *C. tiglium* have been used as traditional medicine for many applications such as wound healing, constipation, a purgative and traditional dyspepsia and dysenteria. The essential oil of *C. tiglium* has been reported to have purgative, analgesic, antimicrobial, insecticidal and inflammatory properties (Qiu, 1996; Wang et al., 2008). The leaves of *C. tiglium* have been used to treat diarrhea, linea, pain and hurts. The croton seed and oil has been used as Ayurvedic medicine in minute doses against dropsy, constipation, cold, cough, asthma and fevers. Usually most compounds useful for medicinal purposes are secondary metabolites (De Padua et al., 1999; Jamaran, 1995). *C. tiglium* is still utilized in homoeopathy and in combination with some sort of acupuncture (as a constituent of Baunscheidt oil).

Established scientific use

Till date different activities of *C. tiglium* have been established by various laboratories of the world. So far diterpenoids, alkaloids, flavonoids and steroids have been characterized from the seeds, they were found to have antitumor, anti-inflammatory, analgesic and lipid lowering effects (Wu et al., 2007).

Antitumor activity

Phorbol esters present in *C. tiglium* are well known potent tumor promoting agent but it should be mentioned that there are many phorbol esters that exhibit profound beneficial biological effects without causing tumorigenesis. Han et al. (1998) reported the effect of TPA (12-O-tetradecanoylphorbol-13-acetate) in patient with myelocytic leukemia and marked decrease in bone marrow myeloblasts as well as temporary remission of disease symptoms were observed when TPA was administered alone or in combination with Vit D3 and AraC. Recently Kim et al. (1993 and 1994) have shown a strong antitumor activity of aqueous extract of *C. tiglium* and the active component of aqueous extract was presumed to be isoguanosine. According to literature survey, the antitumor activity of isoguanosine has not been confirmed. Skipper et al. (1959) tested isoguanosine against leukemia L1210 in mice but reported that it had a negligible antitumor activity. But according to Kim et al. (1993) isoguanosine has considerable activity against various cell lines both *in vitro* and *in vivo* tests especially against solid tumor and ascitic tumor.

Tumor enhancing activity

Van Durren et al. (1966) and Van Durren and Sivak (1968) reported that croton oil contains tumor enhancing principle and reported that tumor enhancing agent is phorbol esters. The mode of action of phorbol esters on cellular and intracellular membranes was established by Van Durren and Sivak (1968). TPA (12-O-tetradecanoyl phorbol-13-acetate) is an irritant and inflammatory agent that has been extensively used as a tumor promoter on the skin of mice (Glaser et al., 1988).

Anti-HIV activity

Since the discovery of HIV scientists have tried to develop anti HIV agents from natural sources and from the experiments of Kawahata et al. (1995) it was apparent that the MeOH and water extracts of the seeds of *C. tiglium* significantly inhibited the infectivity and HIV-1-induced cytopathic effect (CPE) on MT-4 cells. *C. tiglium* seeds contain anti-HIV-1 phorbolesters, 12-O-acetlyphorbol-13-decanoate and 12-O-decadienoyl-phorbol-13-(2-methylbutyrate) that inhibit the cytopathic effect of HIV-1 on MT-4 cells; TPA (12-O-tetradecanoylphorbol-13-acetate) is even more active than the mentioned phorbol esters against HIV-1 (EI-Mekkawy et al., 1999 and 2000).

Antinociceptive effect

Seeds of *C. tiglium* are known to have antinociceptive effect and an *in vitro* and *in vivo* study was done to evaluate the antinociceptive effect using the seed oil of *C. tiglium* through writhing test in mice (Liu et al., 2012).

Gastrointestinal activity

C. tiglium oil (CO) increase or decrease gastrointestinal motility by affecting contractile frequency and amplitude of intestinal smooth muscle depending on the dose of oil and also induce intestinal inflammation related to immunological milieu and motor activity which may affect intestinal motility (Wang et al., 2008). These findings confirm the purgative and inflammational properties of *C. tiglium*, and justify its inhibitory effects on intestinal motility. Hu et al. (2010) reported the effect of croton oil on spontaneous smooth muscle contractions in isolated rabbit jejunum and the underlying mechanisms. Liu et al. (2012) investigated the effects of seeds of *C. tiglium* on spontaneous smooth muscle

contractions of isolated rabbit jejunum and examined the *in vitro* results through the *in-vivo* small intestine propulsion. The ethanol extract of the dried nuts elicit a purgative effect by increasing the gut motility, partially *via* muscarnic receptor activation (Pillai, 1999).

Analgesic activity

From the Chinese record we know that *C. tiglium* was used as traditional medicine due to its analgesic effect but the underlying mechanism was remained unclear until the isolation of a pyragine derivative crotonine from the leaves which showed significant analgesic effect.

Haemagglutinating and haemolytic activity

Banerjee and Sen (1981) described the purification of a lectin from *C. tiglium* seeds and physicochemical properties of the lectin. Lectin exhibits haemagglutinating activity towards erythrocytes of sheep, cow and a few other animals and haemagglutinating as well as haemolytic activity towards rabbit erythrocytes (Banerjee and Sen, 1981 and 1983).

Genotoxic activity

The aqueous extract of *C. tiglium* have the potentiality to cause genotoxic activity and it was observed that the exposure of aqueous extract cause increase plasmid DNA strand breakage in a dose dependent manner (Yumnamcha et al., 2014).

Conclusion

From the above review it is clear that *C. tiglium* is used for treatment of various ailments in developing countries but as the plant contains some poisonous compound, therefore, side effects and safety measures should be taken before administration to human. Extensive and indiscriminate use may cause serious threat to human health and therefore, proper evaluation of the toxicity and phytochemical screening of the plant is essential before it could be used for therapeutic medicinal interventions.

Due to its tremendous medicinal importance this plant is extensively used in traditional medicine which leads to definite threat to the genetic stocks and to the diversity of this medicinal plant. The inevitable ruthless exploitation leading to their rapid depletion from the wild is a cause of concern. In fact the pace of depletion has outpaced the pace of conservation. New strategies are being therefore introduced for rapid multiplication and conservation of this medicinal plant.

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