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An Overview of the Biological and Chemical Perspectives of *Croton tiglium*

Simran Sinsinwar, Indhumathi Paramasivam and Meenakshi Sundaram Muthuraman*

Department of Biotechnology, School of Chemical and Biotechnology, SASTRA University, Thirumalaisamudram, Thanjavur 613401, India

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ABSTRACT

Plants and their extract have the potential to cure the infirmity of mankind. From ancient times herbal plants are used for treatment. Croton tiglium Linn belongs to the family of Euphorbiaceae is widely distributed throughout the plain of India. The various part of Croton tiglium possess different biological and chemical perspectives such as anti- tumor, anti- HIV, anti- inflammatory, antidermatophytic, antioxidant activities in case of biological perspective and Toxicity, Phytochemistry, cytotoxic, detoxification activities in chemical perspectives. This plant has great prospects for development of Ayurvedic and modern medicines.

Keywords: *Croton tiglium*, Anti-HIV, Anti- tumor, Antioxidant, Phytochemistry, Cytotoxic.

INTRODUCTION

Plants are one of the most important sources of medicines. The use of herbal plant for treatment was in practices from ancient times. India was a rich heritage for use of medicinal plant in clinical practices. According to WHO, 80% of world population rely on herbal plants based medicine due to diversity of medicinal plant and herbal medicine it is difficult for WHO, to continue to develop more monographs [1]. Alternative medicine has become very common in western culture, it focuses on the idea of using plant for medicinal purpose. Medicinal plant frequently used as raw material for extraction of active ingredients which used in different drugs like laxative, antibacterial, anti-fungal [2]. A drug such as NSAIDS analgesia is not useful, because of liver dysfunction and other side effects.

Croton tiglium L commonly known as Jamalgota and Mukula (Sanskrit) is widely distributed in Tropical Asia, New Guinea, Japan, Indonesia, China, and Southern California. This plant is shrubby 12 m tall, leaves arranged in alternative, ovate to broadly rounded 4 - 9.5 cm. Flowers are generally small, male flowers are generally star in shape, hair, leaves oblong ovate and 15- 20 stamen, Female flowers- apetalous, the capsule is scared with star shape hairs, triangular, 10-15 mm broad and 15- 20 mm long [3]. *Croton tiglium* oil contains 0.3% steers, 1.5% arachidic, 19.0% linoleic, 37.0% alike, 3.4% toxic resin of the acids [4]. Hence, the present study, review the pharmacological activities which have been recently explored.

Phytochemistry

Xiao-Long Zhang et al., 2016 conducted a study to identify phytochemical investigation of the seed of *Croton tiglium* resulted in isolation and structural explanation of 4-deoxy-4 β phorbol diester compound, the structure of this compound established by 1-D, 2-D Nuclear magnetic resonance (NMR) and HR-ESI-MS (High-resolution electrospray ionization mass spectrometry) [5]. The medicinal plant they screened for phytochemical constituent. Phytochemical analysis discloses tannins, alkaloids, saponins, steroids [6]. This project ensures the quality and safety of Karpoora Cinthamani Mathirai (KCM). It contains *Croton tiglium* seed as detoxified, characterization was carried out using FTIR, SEM. They conclude KCM have therapeutic property and trace elements revealed that heavy metals are below deduction limit [7]. They focused, on the influence of *tiglium* seeds on pharmacokinetics of

rhein in Radix et Rhizoma Rhei and performed comparison within monomer. Results indicated AUC and C_{max} of Rhein in RCE are quite disparate as comparable to Rhein [8]. They focused on analysis of 8 Ethnomedicinal plants. The result revealed presence of compounds like alkaloids, flavanoids, tannins in the aqueous leaf extract of *tiglium* and it can traditionally used for medicinal purpose [9]. This study proved that crotonoside, the nucleoside of tiglium seed, is d- riboside of iso-guanine, by measurement of UV absorption it showed that it occupies 9- position of purine and it conformed aglycone is isoguanine [10].

BIOLOGICAL ACTIVITIES

Antioxidant activity

Shahid M et al., 2012 showed highest specific activities of peroxidase (POD) in leaf extract and high concentration of Zn. Statistics data showed antioxidant and enzymatic activities were notably ($p< 0.05$) different between medicinal plant, leaf and seed extract [11].

Antitumor activity

Xiao- Long- Zhang et al., during 2016 conducted a study to identify a cytotoxic effect of seed of *tiglium* and they evaluated the compound 1-4 against hepatic tumor cell line (SNU 387 and SNU 398), and compound 4 exhibited most potent activity against SNU 387 with IC_{50} value 0.17 µm [5,12]. Researchers studied twig and leaves and isolated 11 new tigliane- diterpenoid (1-11) and their result proved that HL- 60 cell line with IC_{50} value 1.61µm show strongest activity [13]. They have isolated 5 new phorbol ester as well as 4 known phorbol ester analogues. The result showed that compound 3 exhibited cyclooxygenases -1 and -2 inhibition with IC_{50} values of 0.14 and 8.5 µM [14]. Researchers studied Veeramezhugu, Siddha formulation which prescribed in cancer therapy. Results proved Siddha formulation established herbo-metallic preparation [15]. They studied the cytotoxic effect on hepatic tumor cell line. Croton seeds contain 8 new phorbol diester and the activity evaluated against hepatic tumor cell line (SNU387), compound III with IC_{50} values 1.2 µm show effective result [16]. Investigated anti-tumor activity of aloe-Vera gel, oral treatment with aloe Vera extract and topical, DMBA and Croton oil. Results showed that in group I (DMBA+ CROTON OIL) 78.6% body weight was increased, occurrence of tumor development and the number of pipelines also increased from 4.9 to 5.23, decrease in another group. They concluded aloe-Vera protects mice against Croton oil [17]. Researchers use *tiglium* for evaluating brine shrimp toxicity, their results proved *tiglium* had high toxicity to brine shrimp with LC_{50} value 0.0924 g/ml [18]. They focused to find the toxicity of *tiglium* against *M. obese* bacteria and result showed, no tunnelling in seed extract at 100% concentration of this species [19]. They discussed isoguanosine which isolated from *tiglium*, showed antitumor activity against S-180 associates mice. Results proved that isoguanosine inhibit the growth of S-180 and Ehrlich solid tumor in mice at optimal dose of 96mg/kg/day ×12 and 48mg/kg/day×12 with a 1-T/C value of 65% and 60% [20]. Researchers find the effective result of *tiglium* on Nasopharyngeal carcinoma (NPC). The NPC led to induction of EBV in human lymphoblastoid cell lines. This genome carrying cell line which exerted high in EBV antigen, they combine treatment with Croton oil, and the results are good, they conclude Croton tiglium used as herbal drug [21].

Anti HIV activity

Nakamura N, et al., 2004 reported that the extract of *Croton tiglium* showed inhibitory effects on proliferation of HIV-1 [22]. They studied the compound 12-O-Acetylphorbol-13-decanoate and 12-O-decanoyl phorbol-13 inhibited the cytopathic effect of HIV at IC_{100} value is 7.6ng/ml and 7.81µg/ml and minimum cytotoxic concentration (CC_o) value is 62.5 and 31.3 µg/ml. 12-O-Acetyl phorbol -13-decanoate showed no activation of Protein kinase C [23].

Antidermatophytic activity

Han Chien Lin et al., 2016 conducted a study to evaluate the activity of stem, leaves and seeds of *C.tiglium*. Activity was evaluated by disc diffusion and microdilution assay against Trichophyton mentagrophytes. Results showed the ethanolic stem extract had great inhibitory activity with MIC at 0.16 mg/ml oleic and hexadecanoic acid have a major constituent in the stem and demonstrate strong Antidermatophytic activity [24].

Antitermitic activity

Sohail Ahmed et al, 2007 studied about change in tunnelling behavior such as number of bacterial colonies in hindgut activation of enzyme in midget. Results showed that the low LT_{50} (12.85 % and 2.65 h) at a concentration of 50% and 100%. There was no tunnelling in soil treated with 100% [25].

Antimicrobial activity

Shahid M et al., 2008 studied antifungal and antibacterial activities and determined by purification and their results showed by SDS-PAGE and it revealed that the purified protein was monomer, which possess a strong and broad spectrum antimicrobial activity [26].

Antileukemia activity
Kupchan S, M et al., 1976 studied antileukemic activity against p388 lymphatic leukemia in mice. Results proved that systematic fraction of Croton oil led to interpret 13- decanoate and phorbol-12 tailgate as an active principle [27].

Anticonvulsant activity
Mudium R, et al., 2014 evaluated the anticonvulsant effect of hydro-alcoholic seed extract of *tiglium* in rats and mice and results showed the effect was less as compared to sodium valproate. There was the high percentage of mortality in *tiglium* group in chemically induced convulsion when compared to sodium valproate [28].

Gastrointestinal activity
Mi Seong Kim et al., 2014 studied the effect of croton fructus extract (CFE) and croton oil (CO) on Lipolysis in OP9 adipocytes, results showed CFE and CO play important role in the development of Lipolysis- stimulating agent in adipocytes [29]. They showed comparison between raw *tiglium* and processed *tiglium* to test GI motility. The LD_{50} value of raw *tiglium* is 888mg/kg and processed *tiglium* 2139mg/kg. It proved this processing procedure is simple, affordable and safe [30]. Studied pharmacological effect and fraction on the GI tract, results proved that the n-BuOH and water fraction show spasmolytic activity with methanol extract, Polyethylene and ethyl acetate were showed spasmogenic effect. Data indicate the ethyl acetate fraction on GI are mediated, activation of M3 muscarinic receptor and Ca^{2+} influx through L-type Ca^{2+} channel [31]. Croton oil has dual action (contracting and relaxing) intestinal muscle contraction were induced by Croton oil, it implies that the action on gastrointestinal motility is moderated by calcium channel results also suggested that Croton oil possess spasmolytic and spasmogenic property [32]. Studied ethanol extracts as laxative material using the intestinal transit method. Results showed that ethanol extract of *tiglium* seed at dosage 0.06ml/30g is effective as a laxative, the LD_{50} was 0.0707 [33]. Investigated the effect of tiglium on intestinal transists mice, low dose of croton tiglium oil increased GI transists of charcoal and high dose exerted an inhibitory effect. Colonic longitudinal stripes in treated mice were less delicate to electric field stimulation as compared to control mice modulates GI motility and induced inflammation [34]. Studied showed the effect of ion transportation in rat epithelial, the extract affects chlorine movement were more direct than sodium movement in intestinal epithelial cell [35]. Examined the effect of *croton* extract on human intestinal epithelial cells(in-vitro). Results showed *Croton* was directly related to dose, high concentration affects the growth of cell but low concentration had not any influence. Cells cultivated chronically with *croton* extract shows high proliferation [36].

Larvicidal activity
Dophutica M et al., 2015 studied mosquito larvicidal potential against several mosquito vectors and results revealed that the crude petroleum ether extracts of the root *Croton tiglium* have remarkable larvicidal activity [37].

Detoxification activity
Shanavaskhan A E, et al., 1997 studied detoxification technique used by the traditional physician of Kerala, India to purify toxic herbal drug. Ten toxic herbs and relevant detoxification technique they discussed [38].

Tumor- Enhancing activity
Ji-Young Kim et al., 2015 investigated mutagenic responses in five *Salmonella typimurium* strain. *Tiglium* extract inhibited gap junction intracellular communication (GJIC) related to the tumor- promoting potential. The results proved that *tiglium* seed contains mutagenicity, tumor-promoting potential along the dysfunction of GJIC [39].

Sivak A et al., 1969 they discussed the tumor promoting phorbol ester from *tiglium* alter the permeability and structural properties of the cell membrane of mouse embryo fibroblast of 3T3 line, results proved that exposure of mouse skin to phorbol ester would not lead to lysosomal damage [40]. The study focused on the mode of action of this phorbol ester on cellular and intracellular membrane, these are: inhibition of tumorigenesis in two stage carcinogenesis and the relationship between initiating agents [41]. Studied the phenotypic expression of transformation, results showed that untreated cells have increased the number of transformed clones, but in the presence of a phorbol ester number of transformed clones did not increase [42]. They showed *Croton* resin give rise to very few tumors. *Croton* oil is reported to elicit a decrease incidence of malignancy, increase incidence of tumor regression and when applied alone is notably tumorigenic. The chemical composition play important role in determining the biological activity [43]. Investigate the extraction and isolation of the active carcinogenic agent and their long- term biological testing, results showed materials are potentially co-carcinogen at low dosage phorbol myristate acetate show promoting activity [44]. Studied structure elucidation of pure crystalline, highly active tumor-enhancing principle of seed *Croton tiglium*, prepared crystalline derivatives of the active compound and discussed active material [45].

Molluscidal activity

Yadav R P, et al., 2006 investigated the bark of the stem of *Croton tiglium* have strong molluscicidal activity against the snail Lymneae acuminate. The result showed that exposure of low doses of aqueous extract altered total protein, total free amino acid, glycogen and activities of enzyme acetylcholinesterase. The effect was dose dependent and there was significantly recovered in snail's tissue [46].

Chobchuenchom W et al., 2004 discussed total 91 Thai indigenous plant samples from 78 different species. Results showed LC_{50} value of *Croton tiglium* have strong molluscicidal activity as compared to other species. (LC_{50} 73.60 mg/l) [47].

Others

Ariharan V N, et al., 2015 focused on utilization of a commonly available bio energy crop, evaluate the Physio-chemical method, analysis property by blending with conventional diesel at 10% (B10) and 20% (B20), both values were compared with ASTMT standard of biodiesel and they found blended 20% (B20) with ASTMT standard have a potential source of biodiesel [48].

CONCLUSION

Natural products identified from traditional medicinal plants have always paved the way for development of new types of therapeutics [49]. *Croton tiglium* has been used to treat various diseases for more than hundreds of years. The present review reports the various pharmacological potentials which are explored by various researchers. The active exploration of natural sources has provided new developments based on the understanding of complex and redundant physiological mechanisms [50]. Such exploration will lead to a safe and effective pharmacological treatment.

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