

A short review on anticancer investigations of *Strychnos nux-vomica*

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Abstract

Herbs used in traditional medicine have provided a nidus for the discovery of various new molecules having therapeutic viability. With the advent of various diseases, the science has also armed itself to combat the ever-evolving family of diseases with the help of these new molecules. Cancer is one such area which has limited scope for management through conventional therapy. Recent research advances in herbal medicine have opened new horizons in the medicinal chemistry sector. *Nux-vomica*, a medicinal plant, has a long history of use in traditional medicine. Recently, this plant has been extensively researched on for its anti-cancer potential. By the virtue of the alkaloids, viz., strychnine and brucine in *nux-vomica*, it has shown promising results as an anti-cancer agent. The present review paper will comprehend such research including their possible mechanism of action.

Key words: Angiogenesis, anticancer, brucine, *Strychnos nux-vomica*, strychnine

INTRODUCTION

Cancer is a group of diseases described by an uncontrolled development and spread of abnormal cells.^[1] According to the WHO, cancer is a leading cause of morbidity and mortality worldwide. Approximately, 14 million new cases and 8.2 million cancer deaths are reported in 2012.^[1] In India every year about 850,000 new cancer cases being diagnosed, resulting about 580,000 cancer related death every year.^[2] Furthermore, cancer was mainly a disease of old ages. Worldwide median age at diagnosis was about 60 years. Average life span was about 58 years in India compared to 75 years in the developed world. At present, cancers are a serious health problem and create a significant social and economic impact on the health-care system. Cancer is a degenerative disease. An accumulation of toxins through carcinogenic food such as fast food, cigarette smoking, paan chewing, stressful lifestyle, toxic medicines, and environmental pollution lowers immunity causing cancer. The control of cancer, one of the leading causes of death worldwide, may benefit from the potential that resides in alternative therapies. Conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Better cancer treatments

with milder side effects are desperately needed. There is thus the need to utilize alternative concepts or approaches to the prevention of cancer.^[3] Delineation of cancer cell progression includes mainly surgery, radiotherapy, and chemotherapy.^[4] Chemotherapy is widely used to treat the early and later stage of cancers whereas surgery and radiotherapy are limited to early stage cancer treatment. However, chemotherapy has multiple side effects such nerve degeneration, bone marrow depression, gastrointestinal disorders, fatigue, hair loss, and skin disorders.^[5] Nowadays, most of the researchers/scientists using medicinal plants have been important resources in the traditional medicine.^[6] The use of plants in the treatment of cancer has played a significant role in nearly every culture on earth and is the basis of modern medicine.^[7] Hence, plant-based drugs can be a better substitute for the treatment of cancer. Discovery of the vinca alkaloids and podophyllotoxins started the search for an anti-cancer agent from plant sources, there after numerous natural entities having a wide range of cytotoxic activities have been

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Received: 03-05-2016

Revised: 29-06-2016

Accepted: 09-07-2016

discovered including taxanes and camptothecins [Figure 1].^[8] *Strychnos nux-vomica* is an established drug in Indian system of medicine having multidimensional therapeutic activities including antidiabetic,^[9] analgesic, anti-inflammatory,^[10] hepatoprotective,^[11] anti-oxidant,^[12] antiarrheal,^[13] and anti-snake venom.^[14] Moreover, recent investigations highlighted its cytotoxic activity as well, which was discussed in the present review in detail.

PLANT DESCRIPTION OF *S. NUX-VOMICA*

S. nux-vomica belongs to the Loganiaceae family is a tree. The size of the tree is medium tree having a short and thick trunk, white hardwood, and bitter roots. Irregular branches are covered with ash colored smooth bark; shiny and dark green colored young shoots; leaves about 10 cm long and 8 cm broad, opposite, smooth, oval, short-stalked, and shiny at both

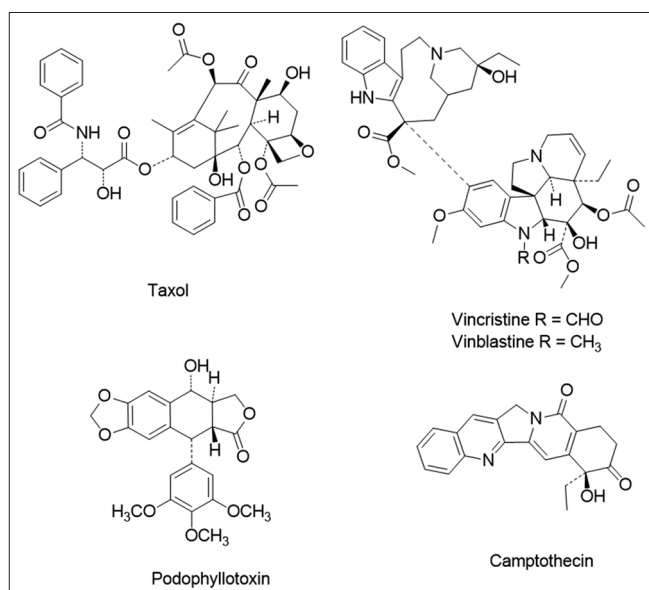


Figure 1: Plant based anticancer agents



Figure 2: Fruit of *Strychnos nux-vomica*

side; flowers greenish white, small in size, funnel-shaped, terminal cymes, having unpleasant odor, and blooming in winter. The size of fruit is like a big apple with a smooth and hard shell. Shell having bright orange color when ripe and filled with white pulp containing five seeds [Figure 2]. The seeds are removed from the ripe fruit. They are generally exported from ports of South India; Cochin and Madras. The seeds have the shape like a flat disk, covered with dense silky hairs, radiating from the center, and giving a characteristic shine to the seed; they are very hard with a dark gray horny endosperm embedded with a small embryo; odorless and bitter in taste [Figure 3].^[15]

PHYTOCHEMICAL CONSTITUENTS OF *S. NUX-VOMICA*

In general, seeds of *S. nux-vomica* are used as a medicine. 2.6-3% total alkaloids are present in seeds. The major alkaloids are strychnine (1.25-1.5%) and brucine (1.7%) whereas minor alkaloids are vomicine and igasurine^[16] including loganin, α -colubrine, β -colubrine, n-oxystrychnine, 3-methoxycajine, isostrychnine, protostrychnine, pseudostrychnine, novacine, and chlorogenic acid.^[17] Strychnine and brucine are the main bioactive molecules which are responsible for the cytotoxic activity of *S. nux-vomica* [Figure 4].



Figure 3: Seeds of *Strychnos nux-vomica*

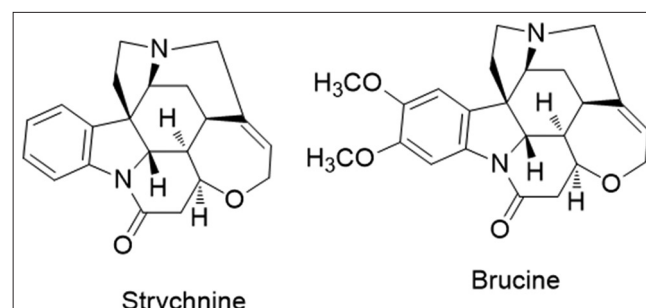


Figure 4: Main bioactive chemical constituents of *Strychnos nux-vomica*

ANTICANCER ACTIVITIES OF *S. NUX-VOMICA*

Recent investigations have been reported by various eminent scientists for cytotoxic effect of *S. nux-vomica* *in vitro* as well as *in vivo* [Tables 1 and 2]. Deng *et al.* assessed the cytotoxicity of four main alkaloids of *S. nux-vomica*, i.e. brucine, strychnine, brucine *N*-oxide, and isostrychnine using SMMC 7721 cells to understand their probable mechanisms. The investigation suggested that significant inhibition of HepG2 cell proliferation was found in brucine, strychnine, and isostrychnine except brucine *N*-oxide. In addition, brucine caused apoptosis of HepG2 cells may be due to the participation of caspase 3 and cyclooxygenase 2.^[18] Further observations highlighted that brucine producing distinctive characteristics of apoptotic programmed cell death including cell shrinkage, nucleus condensation formation of the apoptotic body, and membrane blebbing. Furthermore, the flow-cytometry analysis reported that phosphatidylserine externalization and formation of subdiploid DNA caused cells apoptosis.^[19]

Table 1: *In vitro* anti-cancer studies of *Strychnos nux-vomica*

Test drugs	Mechanism of action	Dose (mg/ml)	References
Brucine	Inhibits VEGF-induced cell proliferation	0.5	[21]
Root extract	Apoptosis triggered by extrinsic and intrinsic pathways	11	[20]
Seed alkaloids	Apoptosis via participation of caspase-3 and cyclooxygenase-2	1	[18]

VEGF: Vascular endothelial growth factor

Table 2: *In vivo* anti-cancer studies of *Strychnos nux-vomica*

Test drugs	Mechanism of action	Dose	References
Brucine	Inhibits VEGF-induced cell proliferation	10 mg/kg	[22]
Brucine	Decreasing VEGF and TNF- α and increasing IL-12 expression	0.5 mg/ml	[21]
Brucine and brucine- <i>N</i> -oxide	Inhibition of the HIF-1 pathway	15 mg/kg	[23]

TNF- α : Tumor necrosis factor α , HIF-1: Hypoxia inducible factor 1, w VEGF: Vascular endothelial growth factor, IL-12: Interleukin12

Rao *et al.* used root extract of *S. nux-vomica* for screening human MM-cell line and RPMI 8226 to establish a plant drug as anticancer agents. Cells lines (3×10^4) were plated in 200 μ l growth medium in the root extract (0, 5.5, 11, 22, 44 and 100 mg/ml) in 96 well culture plates for 24-72 h. A significant decrease was observed in proliferation after 48 and 72 h. The IC₅₀ value of extract was reported as 11 mg/ml.^[20]

Agrawal *et al.* isolated brucine from the seeds of *S. nux-vomica* and studied *in vitro* MTT assays using MCF-7 cell lines in various concentrations (0.125, 0.25, 0.5, 1, 2 mM) for 24, 48 and 72 h. Efficacy of brucine was confirmed by an *in vivo* study using Swiss albino mice by implanting ehrlich ascites carcinoma (EAC) cells. The dose of brucine was given i.p. at 12.5, 25, and 50 mg/kg for 14 days in ascites tumor and 50 mg/kg in the solid tumor for 30 days. Tumor volume, cell viability, angiogenic, antiangiogenic, anti-inflammatory factors, and antioxidant parameters were assessed, and results suggested that inhibition of the MCF-7 cell line was found time and dose-dependent *in vitro* and EAC tumors *in vivo*. Hence, brucine can be used as a potent anti-cancer agent.^[21]

Saraswati *et al.* carried out *in vitro* and *in vivo* studies to elucidate the mechanism of brucine in tumor angiogenesis. An *in vitro* study conducted to check the inhibition effect of brucine on vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase activity revealed that VEGF-induced angiogenesis may be due to the inhibition the migration, invasion and tubular structure formation of endothelial cells. In *in vivo* studies, EAC was injected (15×10^6 cell/mouse) into the right limbs of all the mice to induce cancer, and anti-angiogenic effects of brucine were evaluated using mouse matrigel plug model of angiogenesis. A considerable microvessel formation was observed in VEGF-supplemented matrigel plug. Brucine significantly suppressed the tumor volume, tumor weight, and VEGF-induced angiogenesis.^[22]

Shu *et al.* have studied the effect of brucine on hepatocellular carcinoma cell migration and metastasis. For *in vitro* study, the authors used MTT assay using human HepG2 and SMMC-721 HCC cells which revealed that brucine strongly suppressed HCC cell migration, whereas *in vivo* anti-metastasis activity showed that an intraperitoneal injection of 5 and 15 mg/kg of brucine resulted in dose-dependent decreases in the lung metastasis of H22 ascitic hepatoma cells. The effect may be due to brucine caused decreased expression levels of hypoxia-inducible factor 1 (HIF-1) responsive genes, hence is concerned in the anti-metastasis activity.^[23]

Saraswati and Agarwal used murine cannulated sponge implant angiogenesis model to reveal the effect of strychnine in inhibition of inflammatory angiogenesis. Strychnine (0.25, and 0.5 mg/kg/day) was administered by cannulas for 9 days in Swiss albino mice. The assessment was done by evaluating the hemoglobin, *N*-acetylglucosaminidase, myeloperoxidase, and collagen as indexes for angiogenesis, neutrophil

and macrophage accumulation and extracellular matrix deposition, respectively. Results showed that strychnine had suppressive effect as pro-inflammatory, profibrogenic cytokines, and pro-angiogenic.^[24]

CONCLUSIONS

This review strongly suggests that the *S. nux-vomica* having anticancer activities which could be used as anticancer agents. Anti-cancer drug suffers from generally inadequate efficacy and number of serious adverse effects in human health. *S. nux-vomica* is widely used in the traditional system of medicines for various ailments and has been researched extensively for various anticancer activities. Various reported works conclude that different parts of *S. nux-vomica* plant possess anti-cancer activities by the virtue of its alkaloids, *viz.*, strychnine and brucine. *In vivo* and *in vitro* studies indicate that the mode of action may be either due to inhibition of VEGF-induced cell proliferation or by decreasing VEGF and tumor necrosis factor- α and increasing IL-12 expression or by inhibition of the HIF-1 pathway. These leads should be further assessed and validated for results on clinical trials. Owing to the fatal nature of cancer and associated complications with its treatment, *S. nux-vomica* can definitely provide more promising prospects in the management of this disease.

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Source of Support: Nil. **Conflict of Interest:** None declared.