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Review Article: Brucine as Anticancer Agent, Characterization and Medical Applications

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***Abstract*:** Brucine (BRU) is considered as an effective anti-carcinogenic agent toward several cancer cell lines such as liver cancer, breast cancer, colon cancer and lung cancer; however, its low solubility represents a great obstacle in its formulation. In this review a brief description about physicochemical properties of Brucine including its origin, chemical and physical properties. In addition to the Pharmacological properties that illustrates the mechanism of action, Further, the pharmacology of Brucine that shows its pharmacodynamics and pharmacokinetics. Eventually, the usage, dose and administration, adverse reactions and contraindications will be summarized.

Keywords: *Brucine, Anticancer, Characterization, Medical application.*

I. INTRODUCTION

BRU, is an alkaloids, considered an effective analgesic and anti-inflammatory agent for rheumatic arthritis and in treating diseases, such as tumor (Junling et al., 2009). However, due to high incidence of side effects, such as violent convulsion and even lethal poisoning, BRU, until now, has never been widely used in clinic (Wu et al., 2003). Therefore, it is obvious that, for a therapeutic application of this drug, there is a need for a better formulation for BRU that is less toxic and possibly enhancing its therapeutic efficacy (Yan et al., 2007).

II. PHYSICOCHEMICAL PROPERTIES

A. Origin

Strychnos nux-vomica L. (Loganiaceae) is a deciduous tree that distributed in tropical areas and throughout India and Southeast Asia. The dried seed of this plant, nux vomica, has been used clinically in China as a folk medicine for hundreds of years. Aalkaloids are representing the main active constituents of nuxvomica that are responsible for the pharmacological and toxic properties of the seed. 16 alkaloids have been separated from the seed and identified, among them BRU (Jun et al., 2014).

B. Chemical properties

BRU is a white, odorless, crystalline solid with a molecular weight of 394.45 and molecular formula $C_{23}H_{26}N_2O_4$•$4H_2O$ (Gupta and Chaphalkar, 2015). It is known to chemists as dimethoxy strychnine. Its Chemical name is 2,3-Dimethoxystrychnidin-10-one.

C. Physical properties

The melting point of the anhydrous base is 178 °C and of the hydrated form is 105 °C (Anthony et al., 2004). pH (saturated water solution) 9.5. It is very bitter, freely soluble in alcohol, chloroform, slightly soluble in water, glycerol and ether. soluble (USP) in 850 parts of cold water. Solubility of one gm in different solvents are (0.8 ml methanol, 1.3 ml alcohol, 5 ml chloroform, 25 ml ethyl acetate, 36 ml glycerol, about 100 ml benzene, 187 ml ether, 1320 ml water, 750 ml boiling water) (Jun et al., 2014).

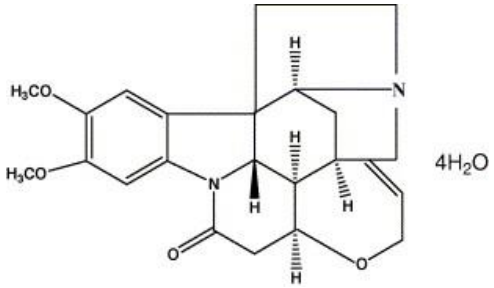

Figure 1: Chemical structure of brucine

III. PHARMACOLOGICAL PROPERTIES

A. Mechanism of action

Mechanism of action of BRU is similar to that of strychnine. It acts as an antagonist at glycine receptors and paralyzes the inhibitory neurons. Glycine binds to receptors on inhibitory neurons to terminate action potentials by causing an influx of chloride ions into the neuron, repolarizing its binding does not trigger an influx of chloride ions. Toxicity of BRU occurs because glycine is blocked from binding to its receptors, making inhibition of an action potential more difficult (Xukun et al., 2006).

HepG2 cell proliferation has been significantly inhibited by BRU and caused dose-dependent apoptosis of HepG2 cells through cell cycle arrest at G0/G1 phase, thus preventing cells entering S or G2/M phase (Deng et al., 2006). Immunoblot results revealed that BRU markedly decreased the protein expression level of cyclooxygenase-2, but increased the expression caspase-3.

Another mechanism suggested that BRU cause cell death via apoptosis (Agrawal et al., 2011). In addition, BRU can cause decrease in tumor weight and volume as a result of suppressing vascular endothelial growth factor (VEGF). The inhibitory effect of BRU may be due to inhibiting the migration of the endothelial cells (Saraswati and Agrawal, 2013).

Shu et al., 2013 investigated the effect of BRU on migration and metastasis of hepatocellular carcinoma cell. The study revealed that BRU strongly suppressed hepatocellular carcinoma (HCC) cell migration and cause decrease in lung metastasis of ascetic hepatoma cells. They suggested that this is may be due to BRU caused decrease in levels of hypoxia-inducible factor 1 (HIF-1) which is a responsive gene that is important for the formation of a vascular system in tumors. Further study revealed that Ca2+ and Bcl-2 mediated mitochondrial pathway were involved in BRU-induced HepG2 cell apoptosis (Deng et al., 2006).

IV. PHARMACOLOGY OF BRU

A. Pharmacodynamics

The main pharmacodynamics actions of BRU are relieving pain, reducing swelling, and promoting circulation. The possibility of using BRU is limited because of its side

effects, so a novel BRU formulations were developed and under investigations (Junling et al., 2009).

B. Pharmacokinetics

Pharmacokinetic parameters of BRU after intravenous injection of dose rate 0.4 mL/100 g to rats were found to be as follow, the half-life of normal BRU solution is about 0.9 hours, the elimination rate constant (Ke) is 0.8 1/hours, clearance (CL) is 3.88 L/hours/kg and area under the curve (AUC) is 1.2 mg/L. hours (Bai-can et al., 2011).

1. Absorption and distribution:

BRU is rapidly absorbed from the gastrointestinal tract following ingestion or intravenous use and widely distributed in different organs and tissues but with different concentrations (Qin et al., 2012).

2. Metabolism

BRU yields BRU-N-oxide in bacillus, and yields 2-hydroxy-3-methoxystrychnine and 3- hydroxy-2-methoxystrychnine in rabbits. Metabolism and excretion of BRU is similar to strychnine as it undergoes oxidative biotransformation in the liver via microsomal enzymes. The major enzyme responsible for metabolism was the cytochrome P450 mono-oxygenase. BRU can be metabolized by hydrolysis, demethylation and methoxylation

3. Excretion

Strychnine is excreted in the urine and can be detected there 24 h or more following ingestion. Only 20% or less is excreted unchanged in the urine.

V. INDICATION AND USAGE

Seed of Strychnos nux-vomica is used to improve blood circulation, to treat gastrointestinal disorders, and as an analgesic. In addition, they possess anti-inflammatory and antioxidant activity. Previous reports proved that BRU is mainly responsible for the anti-inflammation properties and analgesic effects produced by nux vomica and highlights the necessity of inspecting targeted drug delivery technologies in order to take advantage of drugs such as BRU which has cytotoxic effect in cancer therapy.

Recent studies found that BRU has antitumor and antiangiogenic effects and reported its cytotoxic and anti-proliferative activities as it acts via multiple and specific molecular targets to emerge anti-carcinogenic activity in different cancer cell lines (Agrawal et al., 2011). It was found that BRU possess more antitumor activity compared to strychnine. Anil et al, 2016 reported that, recent investigations highlighted the cytotoxic activity of BRU and Strychnos nux vomica as well. In addition, the study done by Wenjuan et al., 2013 evaluated the action of BRU in inhibiting the colon cancer. In vitro and in vivo examinations done by Qin et al., 2018 have shown that BRU immuno nanoparticles has the ability to inhibit the proliferation of liver cancer cells and growth of animal tumors, and may be a promising targeted drug for the treatment of hepatocellular carcinoma. Furthermore, many studies have shown that BRU is an effective agent for the treatment of breast cancer (Zhao et al., 2013). Deng et al., 2006 assessed the cytotoxicity of four main alkaloids found in nux-vomica where the investigation suggested that significant inhibition of cell proliferation was found in these alkaloids especially BRU.

Mamatha et al., 2014 reported that BRU possess cytotoxic, anti-inflammatory and anti-cancer activities and has been used as anticancer agent in various types of cancers including hepatoma and lung cancer. Nux vomica has antioxidant property and antibacterial activity (Glad et al., 2015). Moreover, nux-vomica extracts show antihyperglycemic activity in experimental animals.

VI. DOSE AND ADMINISTRATION

The appropriate dose of nux vomica depends on several factors such as the user's age, health, and several other conditions. The LD50 of BRU following oral administration to mice was determined to be 78 mg/kg (Malone et al., 1992), however the corresponding value of strychnine was 6.62 mg/kg. Li and Xu, 2000) reported that the LD50 of strychnine and BRU for mice are 3.27 and 233 mg/kg (orally) and 1.53 and 19 mg/kg (intraperitoneal), respectively. It is evident that BRU is much less toxic than strychnine.

VII. ADVERSE REACTIONS AND CONTRAINDICATIONS

In excessive doses, strychnos is a virulent poison, producing stiffness of muscles and convulsions, ultimately leading to death. Nux vomica is taken with caution in case of liver disease, as it can cause liver damage. It shouldn't be taken in high doses, or used as a long-term treatment as it may cause serious symptoms, including restlessness, anxiety, dizziness, back stiffness, liver failure, breathing problems and seizures (Vijayakumar et al., 2009). Oral ingestion of BRU leads to lethal intoxication (Jörg et al., 2011).

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