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A REVIEW ON BIOLOGICAL ACTIVITIES OF TROPANE ALKALOIDS

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ABSTRACT

Secondary metabolites of *Solanaceae* plants, sharing tropane skeleton as a common structural feature, are sharply divided into two groups: tropine and ecgonine derivatives. The first group includes atropine and scopolamine (anticholinergic drugs). The second group includes one of the principal drugs of abuse, cocaine. Contemporary pharmaceutical industry manufactures over 20 active pharmaceutical substances containing tropane moiety in their structure, which are Biologically having most importance. So they are applied as mydriatics, antiemetics, antispasmodics, anticholinergics, anesthetics , bronchodilators, antiasthamatic, antinociceptives, hypoglycemics, antiparkinsons, antialzhemerics etc.

Keywords: Solanaceae, Tropine, Alkaloids, Medicinal Uses.

INTRODUCTION

Tropane alkaloids have been found in different plant families, *Brassicaceae (Cruciferae), Convolvulaceae, Erythroxylaceae, Euphorbiaceae, Olacaceae, Proteaceae*, and *Rhizophoraceae*, but they are best known for their occurrence in the family *Solanaceae*. This plant family comprises about 100 genera and 3000 species. Particularly the genera *Datura*, *Brugmansia*, *Hyoscyamus*, *Atropa*, *Scopolia*, *Anisodus*, *Przewalskia*, *Atropanthe*, *Physochlaina*, *Mandragora*, *Anthotroche*, *Cyphantera*, and *Duboisia* are known as being rich intropane alkaloids .They havein common a two-ringed structure characterized by a pyrrolidine and a piperidine ring sharing a single nitrogen atom and two carbons atoms.

The nitrogen atom at the end of the molecule, which characterizes the compounds as alkaloids, is in this group characteristically methylated. The most important natural tropane alkaloids are hyoscyamine and scopolamine (hyoscine) known to have anticholinergic, antiemetic, parasympatholytic (competitively antagonize acetylcholine), anaesthetic, and many other actions.

High concentrations of these alkaloids have been found particularly in *Datura stramonium* and *Datura ferox*, as well as in *Datura innoxia.* The pattern of tropane alkaloids differs significantly and in *Datura stramonium(*thorn apple or Jimson weed) hyoscyamineprevails in most parts of the plant, whereas in *Datura ferox* scopolamine is the major alkaloid produced [1,2,3].

Chemistry of tropane alkaloids

The wide range of tropane alkaloids occurring in the *Solanaceae* family arises from the esterification of acids, such as acetic acid, propanoic acid, isobutyric acid, isovaleric acid, 2- methylbutyric acid, tiglic acid, (+)-α-hydroxy-β-phenylpropionic acid, tropic acid, and atropic acid) with various hydroxytropanes (α-tropanol, α−tropane-diol or α-tropane-triol). The alkaloid part of tropane alkaloids is a two-ringed structure characterized by a pyrrolidine and a piperidine ring sharing a single nitrogen atom and two carbons atoms. Thus, the common structural element of the tropane alkaloids is the bicyclic azabicyclo-octane skeleton.

The most important natural tropane alkaloids hyoscyamine and scopolamine are esters oftropane-3α-ol (and the 6-7 epoxide of tropane-3α-ol) and tropic acid. The asymmetric α-carbon of tropic acid allows the formation of two stereoisomers. 6βHydroxy hyoscyamine (anisodamine), the intermediate between hyoscyamine and hyoscine has been detected in some of the scopolamine containing plant species.

Upper panel: common ring system of tropane alkaloids; lower panel: scopolamine and hyoscyamine with the asymmetric α- carbon of tropic acid marked in bold giving rise to stereoisomers.

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The chemical and physical characteristics of (±)-atropine, (-)-hyoscyamine and (-)-scopolamine, which all are readily soluble in organic solvents and fat [4].

BIOLOGICAL ACTIVITIES OF TROPANE ALKALOIDS

Anti-cholinergic activity

The all tropane alkaloids and their derivatives are used clinically as anticholinergic agents. Jimson weed (Jamestown weed, thorn apple and stinkweed) has been reported as a drug of abuse and has been involved in the accidental poisoning of humans and animals. Symptoms of acute jimson weed poisoning included dryness of the mouth and extreme thirst, dryness of the skin, pupil dilation and impaired vision, urinary retention, rapid heartbeat, confusion, restlessness, hallucinations, and loss of consciousness.

Mydriaic activity

Tropane alkaloids mentioned above (considering, according tothe medical tradition, hyoscyamine and its racemate –atropine as separate entities), are known to cause the pupil dilatation (mydriasis), which is accompanied by impairment of the lens accommodation (cycloplegia).This biological activity, pronounced even after topical application of minute amounts of the substance, makes them useful as agents aiding ophthalmic examinations. The strength of this effect diminishes from hyoscyamine through atropine to scopolamine, but atropine became the substance of choice for ophthalmologic applications because it is more stable and easier to standardize than hyoscyamine [5].

Anti-emetic activity

There is a growing body of evidence that tropane alkaloids and their synthetic analogs can interact effectively with receptors other than acetylcholinergic MR. The synthetic tropeine: 1-H-indole-3-carboxylic acid ester of tropine, tropisetron was developed as a selective serotonin type 3 receptor antagonist, and it is used clinically for treatment of postoperative and chemotherapy-induced emesis [1].

Anti-spasmodic activity

scopolamine butylbromide can be applied safely as an antispasmodic, without risk of such central effects as disorientation, hallucinations and loss of memory, which are characteristic of scopolamine itself. The antispasmodic activity of tropane alkaloids are useful in treatment of bladder spasms, irritable bowel disease, peptic ulcer, colic, cystitis and pancreatitis [1,6].

Anesthetic activity

Cocaine has presently very limited medicinal use, particularly in ophthalmologic surgery, where its topical anesthetic and vasoconstrictive properties are particularly advantageous. Around that time, cocaine was supposed to be very closely structurally related to atropine, in part because both exhibited mydriatic and local anesthetic activity [1].

Bronchodilator activity

Inhibition of the respiratory tract secretory activity and bronchodilation,

Anti-ulcer activity

Well known tropane alkaloid cocaine shows antiulcer activity against ulcers induced by reserpine at a dose of 10 mg/kg by oral route of administration. This substance is obtained of the *Erythroxylum coca* leaves and has multiple actions in the central and peripheral nervous system. It is a psychomotor stimulant with a strong abuse potential and has ability to dominate or decreasing behaviors such as eating and sleeping [7].

Anti-inflammatory activity

Datura stramonium Linn. is commonly known as Shivapriya (Solanaceae). Its chemical constituents are tropane, hyoscyamine. This ethanolic extracts were tested for anti-inflammatory activity by carrageenan induced rat paw edema [8].

Tropisetron also is a nicotinic AChR selective partial agonist. Another unexpected feature of this drug is anti-inflammatory action, probably by targeting the calcineurin pathway, which is likely to find a clinical application in immunomodulation [1].

Analgesic& antinocicetive activity

D.stramonium seed extract has an analgesic effect on both acute & chronic pain which were produced by hot plate and formalin tests. It is likely that, this effect can be attributed to the alkaloids which interact with opioid system [9].

Hyoscyamus reticulatesL. extract produced significant analgesic effect and this effect may be due to inhibition of the synthesis of the arachidonic acid metabolite. The antinociceptive effect of intra peritoneally administered methanol extract of *Hyoscyamus reticulatus L.* leaves was demonstrated in this study by two different test (chemical and thermal nociceptive test). The present study showed that the antinociceptive effect of *Hyoscyamus reticulatus L.* extract in different nociceptive responses generated by a chemical or thermal noxious stimulus [10].

Antiasthamatic

D.stramonium is used frequently as an anti asthmatic treatment. The widely reported medicinal uses include the use of the dried leaves of the plant as an anti-asthmatic agent. As the cure for the asthma mixture of the leaves and seeds is taken orally as a decoction or smoke [11].

Herbicidal Activity

Aqueous and organic solvent (methanol and nhexane) 0, 5, 10 and 15% (w/v) extracts of shoot and root of *Datura metel* L. (Syn, *Datura alba* Nees.) were studied against *Phalaris minor* Retz. one of the most problematic weeds of wheat. 5-15% of methanol and 15% n hexane root extract significantly reduced the germination, shoot and root length was significantly suppressed by all the

employed concentrations of aqueous as well as organic solvent extracts in fact reduce the biomass a lot.

Insecticidal

Different percentages of methanolic extract of *Datura metel* seeds, were tested against *Helicoverpa armigera* (Hubner), the cotton bollworm, is a moth, the larvae of which fed on a wide range of plants, including many important cultivated crops. The 1.5 and 2.0% fractions of methanolic extract showed significant adverse effects on various biological parameters viz. larval survival, weight and duration, pupal period, % of pupation and adult emergence [12].

Antibacterial Activity

Crude aqueous and ethanol extracts of leaf, stem bark and roots of *D. metel* were investigated against eight clinical bacterial isolates (*Streptococcus betahemolytic, S.dysenteriae Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Bacillus cereus* and *Salmonella typhi*). The leaf and stem bark extracts was antagonistic against the test bacteria species with inhibitory zones and *Staph. aureus* was the most inhibited majorly with the ethanol extract [13].

Antifungal

The ethanol extract was found as highly effective against the three fungal strains and zone of inhibition measured against *S. cerevisiae* was about 16±0.2mm, 13±0.7mm against *A. fumigatus* and was10±0.3mm against *A. niger* [12].

Hypoglycemic Activity

The seeds of *D. metel* were investigated for hypoglycemic and antihyperglycemic activities in normal Wistar albino rats and diabetic rats. *D. metel* seed powder was suspended in 1% sodium Critical Micellar Concentration and given to normal (in the form of mucilage), diabetic rats, blood glucose levels above 300 mg/dL (orally) at doses of 25, 50 and 75 mg/kg body weight. Blood sampling indifferent time frame within 24h and dose dependent hypoglycemia was observed in animals treated. The dose dependent antihyperglycemic activity was also observed with *D. metel* in alloxan-induced diabetic rats. Seed powder of *D. metel* possessed blood glucose lowering effect in normoglycemic and in alloxan-induced hyperglycemic rats. Thus, the folk usage of the seeds of *D. metel* for controlling diabetes may be validated by this study and the seeds offer promise for the development of potent phytomedicine for diabetes [14].

Free radical scavenging activity

D. metel seeds were analysed for the fatty acids and fat-soluble bioactive compounds. The amount of total lipid in *D. metel* seeds was 55g/kg in weight and mainly linoleic acid followed by oleic, palmitic and stearic acids. The crude n-hexane extract was characterized by a relatively high amount of phytosterols along with stigmasterol, β-sitosterol, lanosterol, P5-avenasterol and sitostanol. In this extract, γ- tocopherol was the major component present accounting for more than 80% of total tocopherols detected. n-hexane extract of *D.metel* seeds was able to quench only 40 % of DPPH radical. *D. metel* seeds contain a considerable amount of oil and may be a good source of essential fatty acids and lipid-soluble bioactives. The presence of tocopherols and sterols may have medicinal importance for human being [15].

Antioxidant Activity

The aqueous extracts of leaf, stem bark and roots of *D. metel* showed phytochemical and antioxidant activities. The aqueous extract of the plant displayed antioxidant activity of between 49.30-23.82% and can consider the plant as a natural source of antioxidants [13].

Toxicities and Cytotoxicity Activity

All of the plant parts of Datura are poisonous. Even a small dose is very poisonous because of the presence of toxic tropane alkaloid or the presence of anticholinergic substances such as scopolamine, hyoscyamine and atropine can cause neural toxicity. The toxicity sign and symptoms include acute confusion, fever, tachycardia, hot flushed dry skin, dilated pupils, dry mouth, urinary retention, hallucinations, headache, delirium, rapid and weak pulse, convulsions, and coma and even death . Using the MTT [3-(4,5-dimethylthiazol- 2-yl)-2,5-diphenyltetrazolium bromide] assay cytotoxic activity of withametelins I, J, K, L, M, N, O, P, 12-β-hydroxy-1,10-secowithametelin B and 1,10-seco-withametelin B isolated from methanolic extracts of *D. metel* were investigated. The withametelins I, K, L and N exhibited cytotoxic activities againstA549 (lung), BGC-823 (gastric), and K562 (leukemia) cancer cell lines, with IC50 valuesranging from 0.05 to 3.5 μM. Withamilin J showed moderate cytotoxic activity against BGC-823 and K562 but less cytotoxicity against A549 [16-17].

Antidote

Atropine is also useful as an antidote against poisoning with organic phosphorous derivatives used as insecticides and also against some nerve gases applied as military weapons.

Antiparkinson

Benztropine (1-5mg/day) is used to treat the parkinson's disease due to their centrally acting cholinergic activity [18].

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