Volume 2 • Issue 3 • 2020

Review Article

Journal of Medicine and Surgical Sciences

Physiological Role of Some Alkaloids

Arun Kumar Srivastava[1]* and Vinay Kumar Singh[2]

[1]Department of Zoology, Shri Guru Goraksha Nath P.G. College, Ghughli, Maharajganj-273151, U.P. India

2Department of Zoology and Environmental Science, DDU Gorakhpur University, Gorakhpur - 273009 U. P. India

***Corresponding Author:** Dr. Arun Kumar Srivastava, Department of Zoology, Shri Guru Goraksha Nath P.G. College, Ghughli, Maharajganj-273151, U.P. India.

Received: August 29, 2020; **Published:** September 08, 2020

Abstract

Alkaloids are low-molecular-weight nitrogen-containing compounds. It is widely accepted that the main role of alkaloids in plants is toxicity against predators and pathogens. Plant alkaloid toxicity can be quite diversified, but often involves neurotoxicity or cell signaling disruption. The same toxic properties observed in the plant defense scenario can often be used in prospection for new drugs. A very specific toxicity may be used to fight certain tumor cell types, or also be used to control specific microorganisms or pests. Alkaloid papain is also used in topical formulations as a proteolytic debriding agent for the treatment of open, extensive wounds and burnings. Toxicity may arise by enzymatic alterations affecting physiological processes, inhibition of DNA synthesis and repair mechanisms by intercalating with nucleic acids, or affecting the nervous system. This alkaloid inhibits choline acetyltransferase, affecting neurotransmission. It also affects several other neuroreceptors and DNA synthesis.

Keywords: *Alkaloids; Toxicity; Papain; Antioxidants; Anti-reproductive*

Introduction

Alkaloids are among the most important drugs in human history and contain the largest groups of secondary metabolites, being extremely diverse in terms of structure and biosynthetic pathways, including more than 20,000 different molecules distributed throughout in known vascular plants [1]. Dey et al. [2] reported that alkaloids are low-molecular-weight nitrogen-containing compounds and, due to the presence of a heterocyclic ring containing a nitrogen atom, are typically alkaline. Matsuura and Neto [3] reported that alkaloids are known by their numerous pharmacological effects on vertebrates. These metabolites can be divided into different classes according to their precursor (e.g., indole alkaloids are alkaloids derived from tryptophan), encompassing more than 20 different classes (e.g., pyrrolidine alkaloids, tropane alkaloids, piperidine alkaloids, pyridine alkaloids, quinolizidine alkaloids, and indole alkaloids, among others).

The presence of alkaloids and other secondary metabolites in plants enhances plant reproductive rates, either by improving defenses against biotic and abiotic stresses or by affecting pollinators and seed/fruit disperser visitation [4]. It is widely accepted that the main role of alkaloids in plants is toxicity against predators and pathogens. The same toxic properties observed in the plant defense scenario can often be used in prospection for new drugs. For example, a very specific toxicity may be used to fight certain tumor cell types, or also be used to control specific microorganisms or pests [5]. There is also evidence for allelopathic activity of some plant alkaloids against target species mostly in laboratory assays

[6]. Demasi et al. [7] reported the Inhibition of *Lactuca sativa* and *Lepidium sativum* seedling growth by berberine, sanguinarine, and gramine, among other alkaloids, has been recorded. Somanah et al. [8] tested papaya leaf extracts (alkaloids) against human pathogenic microbes. Bacteria such as *Bacillus subtilis, Clostridium tetanus, Escherichia coli, Proteus vulgaris, Stapylococcus aureus* and fungi such as *Aspergillus conicus, spergillus flavus, Aspergillus niger, Aspergillus sulphureus* and Rhizopus by agar well diffusion method. All the leaf extracts of *Carica papaya* L. exhibited greater activity towards bacteria and fungi. The extract demonstrated higher activities against all the bacteria and fungi tested, with the highest activity (acetone extract of 13 mm zone of inhibition) demonstrated against *Saphylococcus aureus* and (ethanol extract of 18 mm zone of inhibition) demonstrated *against Aspergillus flavus. Carica papaya* may be used for the treatment of gastroenteritis, uretritis, otitis media, dengue fever, typhoid fever and wound infections. Pinto et al. [9] reported that alkaloid papain is also used in topical formulations as a proteolytic debriding agent for the treatment of open, extensive wounds and burnings. It is also employed as an enhancer for cutaneous permeation of active compounds, chemical peeling and as a progressive depilatory agent.

Amri and Mamboya [10] reported that papain (alkaloids) preferentially cleaves peptide bonds involving basic amino acids, particularly arginine, lysine and residues following phenylalanine. The unique structure of papain gives its functionality that helps to understand how this proteolytic enzyme works and it's useful for a variety of purposes [11] Srivastava and Singh [12] reported that papain is bactericidal, bacteriostatic, anti-inflammatory and debridement material and shows a broad proteolytic activity against the protein, short chain peptides, amino acid ester and amid. Caffeine found in *C. Arabica* (Rubiaceae) and various other plant species is often toxic and paralyzes insects feeding on the plant. Invertebrates, the interaction of the alkaloid with adenosine receptors of the nervous system is responsible for stimulating effects [13]. Nicotine effect lies on the ability of some alkaloids to bind various neuroreceptors and block or displace endogenous neurotransmitters. Nicotine acts as an agonist or antagonist targeting nicotinic acetylcholine receptors in insects, which are the most abundant excitatory postsynaptic receptors, causing continual neuronal excitation, leading to insect paralysis and death [13]. In this review, we will systematically summarize the chemistry, identification techniques and their biological activities along with potential applications in a single platform.

Sources of Alkaloids

The presence of plant alkaloids chimonanthine, calycanthine, and nicotine, or its enantiomers, has been reported in the skin of Dendrobatidae frogs [14]. Native Indians from the Amazon use the secretion of poison frogs to contaminate the point of darts used in hunting and rapidly kill or impair birds and little mammals. Bufonidae frogs were believed to produce alkaloids instead of accumulating them from a food source, but recent studies showed that Bufonidae frogs also obtain alkaloids from the diet [15]. Some species of Phyllobates (Dendrobatidae) can secrete batrachotoxins, which are the most potent known non-peptide neurotoxins [16]. Pyrrolizidine alkaloids of species of Crotalaria (rattlebox), which serve as hosts to the moth Utetheisa ornatrix (bella moth), can be stored by larvae, making them poisonous and frequently repellent to predators, a feature that remains through the pupae and adult stages. In addition, the alkaloids and biotransformation products of these are given to females as a nuptial gift, which is transferred to eggs, presumably making these protected against predators [3].

Johannsen and Kayser [17] reported that the Plants containing tropane alkaloids (TAs) are found in numerous and important plant families such as Solanaceae, Brassicaceae, Erythroxylaceae, Convolvulaceae, and Euphorbiaceae. TAs are alkaloids derived from ornithine, and in many parts of the world, TA-containing plants have been used for folkloric and medicinal purposes due to their powerful anticholinergic (e.g., scopolamine) and hallucinogenic effects (e.g., hyoscyamine and atropine), causing constipation, photophobia, pupil dilatation, vision disturbance, and dryness of upper digestive and respiratory tract mucosa. Contaminations with TAs often occur via ingestion of food containing Datura, which accumulates high concentrations of scopolamine and hyoscyamine [18]. Vasquez et al. [19] reported that in Solanum plants (Solanaceae), the commonly present glycoalkaloids, solanine and chaconine, can be found in species such as nightshades (*S. nigrum*), potato (*S. tuberosum*), tomato (*S. lycopersicum*), eggplant (*S. melongena*), pepper (*Capsicum annuum*), and petunia (*Petunia sp*.), carrying fungicidal and pesticidal properties participating in plant defense mechanisms.

Mechanisms of Action of Alkaloids

Thawabteh et al. [20] reported that alkaloids affect different metabolic systems in animals, and the toxic mechanism of action of alkaloids may vary considerably. Torgovnick and Schumacher [21] reported that Toxicity may arise by enzymatic alterations affecting physiological processes, inhibition of DNA synthesis and repair

mechanisms by intercalating with nucleic acids, or affecting the nervous system. Several alkaloids may affect multiple functions. Taxines are calcium channel antagonists, increasing cytoplasmic calcium [22]. Pyrrolizidine alkaloid toxic effects are mainly due to their biotransformation into strong reactive pyrrole structures by oxidases from the mammalian liver. The reactive pyrroles act by alkylating nucleic acids and proteins [23]. Alkaloid mechanisms of action as antibacterial agents differ among alkaloid classes. Synthetic quinolone alkaloids may have respiratory inhibition effects; isoquinolines, such as berberine, sanguinarine, protoberberine, and benzophenanthridine, inhibit cell division by perturbing the Z-ring; the phenanthridine isoquinoline alkaloid ungeremine acts by inhibiting nucleic acid synthesis; pergularinine and tylophorinidine, which are indolizidine alkaloids, inhibit nucleic acid synthesis as well, by targeting dihydrofolate reductase [24].

Molluscicidal Activity

Jaiswal et al., [25] reported that lyophilized latex from the skin of unripe fruits and pure papain show about similar toxicity against *L. acuminata* at all exposure period whereas column purified fraction of *C. papaya* seed shows lower toxicity than lyophilized latex. It is due to the presence of high concentration of papain in *C. papaya* latex than seed. Srivastava et al. [26] tested sublethal treatment (40% and 80% of 24h LC_{50}) of alkaloid piperine (*Piper nigrum*) on level of different biochemical parameters viz. protein, amino acid, nucleic acids and phospholipids and rate of lipid peroxidation in nervous tissue of *L. acuminata*. and found that treatment of 80% of 24h LC_{50} of piperine caused maximum reduction in protein, DNA, RNA and phospholipids in the nervous tissue of *L. acuminata* and concluded that the alkaloid, piperine, found in *P. nigrum* destroys the cytochrom P-450 and inhibits monooxygenase activity [27]. Phospholipids are needed for the growth of endoplasmic reticulum or other cellular membranes [28]. It has been reported that all classes of phospholipids decrease markedly following high dose piperine treatment [29]. The enhancement of lipid peroxidation might be due to oxidative degradation of polyunsaturated fatty acids of the biomembrane leading to pathological infestation [30].

Formation of activated oxygen can have extremely detrimental consequence not only for phospholipids but also protein, nucleic acids, polysaccharides and inhibition of vital enzymes [31]. Srivastava and Singh [32] reported that feeding of snail attractant pellets containing alkaloid papain (40% of 24 h LC_{50}) caused significant reduction in the level of protein, amino acids, DNA, RNA and AChE activity in the gonadal/nervous tissue of *Lymnaea acuminata*. Jaiswal and and Singh [33] reported that *Carica. Papaya* seed and latex are potential source of botanical molluscicides. *C. papaya* lyophilized latex is more effective than seeds against *L. acuminata*. The molluscicidal activity of *C. papaya* seed and latex may be due to the presence of papain (Srivastava et al. [34]. Srivstava et al. [34] reported that sub-lethal treatment of papain in bait formulation (24hLC50) caused a significant inhibition of AChE activity in the nervous tissue of *L. acuminata*. Jaiswal et al. [35] noted that papain is uncompetitive inhibition of AChE. AChE inhibition result in accumulation of acetylcholinesterase at the nerve synapses so that the post synaptic membrane is in a state of permanent stimulation producing paralysis, ataxia and general lack of coordination in neuromuscular system and eventual death.

Anti-Reproductive Activity

Plant alkaloid toxicity can be quite diversified, but often involves neurotoxicity or cell signaling disruption [36]. Croaker et al. [37] reported that alkaloid sanguinarine from *Sanguinaria canadensis* (Papaveraceae) presents multiple toxic effects. This alkaloid inhibits choline acetyltransferase, affecting neurotransmission and also affects several other neuroreceptors and DNA synthesis. Srivastava [38] reported that sub-lethal (40% and 80% of 24h LC_{50}) of feeding of bait containing plant alkaloid papain and piperine, significantly reduced the fecundity of the snail *L. acuminata*. Because the caudo dorsal cells in the brain of the snail *L. acuminata* release ovulation hormone. The cerebral neurosecretory caudo dorsal cells of the fresh water pulmonates snail *Lymnaea stagnalis* control egg laying, an event that involves a pattern of stereotyped behaviour [39]. The CDCS synthesize and release multiple peptides, among which is the ovulation hormone (CDCH). It is thought that each peptide controls a specific aspect of the processes involved in egg laying [38]. It is also noted that after sublethal treatment of alkaloid papain caused the decrease the level of serotonin and inhibits prostaglandins synthesis by inhibiting 5-lipoxygenase and leukotriene directly or indirectly CDCs. Possibly, the alkaloid papain affect the CDCs and reduce the release of ovulation hormone, resulting a decrease in the fecundity of treated snail [39].

Other Function

Senchina et al. [40] reported that Alkaloids consumed to improve immune functions, nutrition, and physical performance, being present in daily foods, beverages, and supplements. Azam et al. [41] reported that some alkaloids include the caffeine from coffee (or guaranine and mateine from other plants) with antioxidant, anti-inflammatory, and stimulatory properties; theobromine

and paraxanthine from cocoa as antioxidants; and gingerol and shogaols (phenolic alkanones) present in ginger bearing antioxidant, anti-inflammatory, antimicrobial, and antitumoral properties. Mitochondria are the major intracellular sources of reactive oxygen species (ROS) in animal cells. Conjugates of the plant alkaloids berberine and palmatine with the antioxidant plastoquinone can be used as a strategy in therapies focusing mitochondria-targeted antioxidant activity [42]. Baracchi et al. [43] reported that various alkaloids display antioxidant properties, some of which being effective skin sunscreens, some negative consequences, such as reduced ovary development, mobility, and survivorship, are documented for several pollinators visiting alkaloid-containing plants, but, in some cases, secondary compounds present in nectar can be beneficial to the pollinator, reducing gut pathogens.

Toxicity to Humans and Other Vertebrates

Adibah and Azzreena, [44] reported that animal intoxication by alkaloids is mostly caused by accidental ingestion of food contaminated with alkaloid-containing plants, Clearly, the amount of ingested alkaloid and the sensitivity of the target animal are key factors leading to intoxication. James et al. [45] reported that some alkaloids can be extremely harmful to mammals, which is the case of the steroidal alkaloid cyclopamine in lambs, identified as the compound in *Veratrum californicum* (Liliaceae) responsible for teratogen effects resulting in craniofacial birth defects causing a cyclops aspect in offspring of sheep grazing *V. californicum*. The mechanism of action can be due to inhibition of acetyl cholinesterase and calcium transport, which occur in micromolar range. The plant families Asteraceae, Boraginaceae, and Fabaceae often produce pyrrolizidine alkaloids, which are also ornithine-derived alkaloids, estimated to be present in more than 6,000 plants and known to be efficient against predators, including human and livestock [46]. Pyrrolizidine alkaloids acute and chronic liver toxicity in humans and other animals is well known, and some symptoms of acute poisoning are abdominal pain, nausea, vomiting, diarrhea, and edema [44]. Highly toxic carcinogenic and genotoxic effects are reported as the main mechanism of action of pyrrolizidine alkaloids [47]. Some quinolizidine alkaloids, as the case of lupin alkaloids, are toxic to humans in acute doses, which may occur when consuming lupin beans that were not previously debittered, causing dry mouth, blurry vision, facial flushing, and confusion [48]. Cortinovis and Caloni [49] reported that adult livestock animals, piperidine alkaloids (derived from lysine) can be acutely toxic causing musculoskeletal deformities in neonatal individuals. Signs of acute intoxication by piperidine alkaloids in livestock include frequent urination and defecation, muscle weakness, tachycardia, ataxia, muscle fasciculations, collapse, and death by respiratory failure. Green et al. [50] reported that the teratogenic effect of some piperidine alkaloids, such as ammodendrine, N-acetylhystrine, anabaseine, coniine, and g-coniceine, include multiple congenital contracture deformities and cleft palate in pigs, goats, cattle, and sheep.

Poisonous plants containing teratogenic piperidine alkaloids include some *Lupinus* sp., *Laburnum* sp., *N. tabacum*, *N. glauca*, and *Conium maculatum* [50]. Taxines are a mixture of active alkaloids from yew trees (Taxus sp., Taxaceae), which have been implicated in several animal and human poisonings with predominant cardiovascular effects. Although some taxines are related to the antitumor drug Taxol, they are distinct molecules [51]. Willson [52] reported that excess of daily-consumed metabolites such as caffeine can also be considerably toxic. Some overdose symptoms include tachycardia, arrhythmia, convulsions, vomiting, and eventually coma and death. Bonnie et al. [53] reported in his book that ue to stimulatory and addictive effects of nicotine from tobacco, the popularity of tobacco products and their widespread use remain, causing billions of people around the world to use it, despite the fact that almost all users are aware of the numerous negative health and economic impacts of smoking. He also reported that nicotine is also important as a treatment to help quit smoking, in the form of skin patches and gums.

Rockville [54] reported that cocaine and its derivatives are extremely addictive and harmful drugs, with devastating effects in health and behavior of users, carrying economical and social disorders to society. Iturriaga et al. [55] reported that alkaloid-mimicking sugars are efficient inhibitors of several sugars and glycosidases metabolizing enzymes by inhibition of trehalase in some tissues and sucrose in the midgut, leading to toxic effects and affecting growth once the insect becomes disabled to use threalose or uptake sucrose. Colchicine from *Colchicum autumnale* (Colchicaceae) is toxic to honey bee (Apis mellifera) and inhibits microtubule polymerization by binding to tubulin and inhibiting mitosis [56]. He also reported that plant alkaloid toxicity can be quite diversified, but often involves neurotoxicity or cell signaling disruption. Caffeine found in *C. Arabica* (Rubiaceae) and various other plant species is often toxic and paralyzes insects feeding on the plant. Caffeine inhibits phosphodiesterase activity and promotes increase in intracellular cyclic AMP level [57]. Souza and Markou [58] reported that in vertebrates, the interaction of the alkaloid

with adenosine receptors of the nervous system is responsible for stimulating effects. Nicotine effect lies on the ability of some alkaloids to bind various neuroreceptors and block or displace endogenous neurotransmitters. Nicotine acts as an agonist or antagonist targeting nicotinic acetylcholine receptors in insects, which are the most abundant excitatory postsynaptic receptors, causing continual neuronal excitation, leading to insect paralysis and death.

Conclusion

Alkaloids are structurally unique bioactive molecules. They are a large and diverse group carrying a broad range of physiological activities of great importance to plants, animals, and humans, with highly significant pharmaceutical properties. Alkaloids are often viewed as "villains," due to their high toxicity, may be reassessed as holding the cues for combating specific diseases. New emerging ecological roles for alkaloids are also surfacing, such as their activity as antioxidants and general stress protectants. The primary functions of alkaloids may differ in the various plant species, and their metabolic profiles can be linked to specific environmental factors and developmental signals, often conferring a clear adaptive value.

References

1. Bribi N. (2018). Pharmacological activity of Alkaloids: A Review. Asian Journal of Botany. 1, doi:10.63019/ajb.v1i2.467.
2. Dey P, Kundu A, Kumar A, Gupta M, Lee BM, Bhakta T, Dash S, Kim HS. (2020). Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). Recent Advances in Natural Products Analysis. 505–567.
3. Matsuura HN, Neto AGF (2015). Plant Alkaloids: Main Features, Toxicity, and Mechanisms of Action. Plant Toxins, DOI 10.1007/978-94-007-6728-7_2-1, 2015.
4. Mazid M, Khan TA, Mohammad F (2011) Role of secondary metabolites in defense mechanisms of plants. Biology and Medicine, 3(2): 232-249
5. Atanasov AG, Waltenberger B, Wenzig EMP, Linder T, Wawrosch C, Uhrin P, Temml V, Wang I, Schwaiger S, Heiss EH, Rollinger JM, Schuster D, Breuss JM, Bochkov V, Mihovilovic MD, Kopp B, Bauer R, Dirsch VM, Stuppner H (2015) Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 33(8): 1582–1614.
6. Cheng F, Cheng Z (2015) Research Progress on the use of Plant Allelopathy in Agriculture and the Physiological and Ecological Mechanisms of Allelopathy. Front Plant Sci. 6: 1020.
7. Demasi S, Caser M, Fogliatto S, Vidotto F, Trotta F, Scariot V (2019) Ailanthone inhibition data on seed germination and seedling growth of *Lepidium sativum L*. and *Raphanus sativus* L. Data Brief. 104550.
8. Somanah J, Bourdon E, Bahorun T, Aruoma OI (2013) The inhibitory effect of a fermented papaya preparation on growth, hydrophobicity, and acid production of *Streptococcus mutans, Streptococcus mitis,* and *Lactobacillus acidophilus*: its implications in oral health improvement of diabetics. Food Sci Nutr 1(6): 416–421.
9. Pinto CASDO, Lopes PS, Sarruf FD, Polakiewicz B, Kaneko TM, Baby AR, Velasco MVR (2011) Comparative study of the stability of free and modified papain incorporated in topical formulations. Brazilian Journal of Pharmaceutical Sciences, 47: 4.
10. Amri E, Mamboya F (2012) Papain, a Plant Enzyme of Biological Importance: A Review. American Journal of Biochemistry and Biotechnology 8(2): 99-104.
11. Srivastava AK, Singh VK (2016) Carica Papaya- A Herbal Medicine. International Journal of Research Studies in Biosciences. 4(11): 19-25.
12. Srivastava AK, Singh VK (2017) Antimicrobial activity of papain. In: Antimicrobial activity of natural substances. Karpiński TM, Adamczak A, eds." JB Books, Poznań, Poland Ch. 2: pp. 19-34.. ISBN: 978-83-947078-2-8.
13. Costenla AR, Cunhab RA, Mendonc AD (2010) Caffeine, Adenosine Receptors, and Synaptic Plasticity. Journal of Alzheimer's Disease. 20: S25–S34.
14. Saporito RA, Donnelly MA, Spande TF, Garraffo HM (2012) A review of chemical ecology in poison frogs. Chemoecology 22: 159–168.
15. Jeckel AM, Saporito RA, Grant T (2015) The relationship between poison frog chemical defenses and age, body size, and sex. Front Zool 12 : 27.
16. Ribeiro CTD, Roussilhon C (2016) On frogs, toxins and true friendship: an atypical case report. Journal of Venomous Animals and Toxins including Tropical Diseases 22:3.
17. Johannsen KLK, Kayser O (2019) Tropane Alkaloids: Chemistry, Pharmacology, Biosynthesis and Production. Molecules 24(4): 796.
18. Ally F, Mohanlall V (2020) An overview of tropane alkaloids from *Datura stramonium* L. Journal of Pharmacognosy and Phytochemistry 9 (3): 05-13.

19. Vasquez AO, Arzola VA, Ramos MADG, Baca VHU, Obando FS (2019) Toxicity, teratogenicity and anti-cancer activity of solanine: A perspective on anti-cancer potential. Int. J. Pharmacol 15: 301-310.
20. Thawabteh A, Juma S, Bader M, Karaman D, Scrano L, Bufo SA, Karaman R. (2019). The Biological Activity of Natural Alkaloids against Herbivores, Cancerous Cells and Pathogens. Toxins (Basel) 11(11): 656.
21. Torgovnick A, Schumacher B. (2015). DNA repair mechanisms in cancer development and therapy. Front Genet 6: 157.
22. Vriese KD, Costa A, Beeckman T, Vanneste S. (2018). Pharmacological Strategies for Manipulating Plant Ca2+ Signalling. Int J Mol Sci. 19(5); 1506
23. Schramm S, Köhler N, Rozhon W. (2019). Pyrrolizidine Alkaloids: Biosynthesis, Biological Activities and Occurrence in Crop Plants. Molecules. 24 (3): 498.
24. Mabhiza D, Chitemerere T, Mukanganyama S. (2016). Antibacterial Properties of Alkaloid Extracts from Callistemon citrinus and Vernonia adoensis against Staphylococcus aureus and Pseudomonas aeruginosa. International Journal of Medicinal Chemistry Volume 2016, Article ID 6304163, 7 pages.
25. Jaiswal P, Kumar P, Singh VK, Singh DK. (2010). Review Article. Carica papaya Linn: A Potential source for various health problems. Journal of Pharmacy Research 3(5): 998-1003.
26. Srivastava P, Kumar P, Singh VK, Singh DK. (2010). Effect of Piper nigrum and Cinnamomum tamala on biochemical changes in the nervous tissue of fresh water snail Lymnaea acuminata. Bioscan. 1: 247-256.
27. Atal CK, Dubey RK, Singh J. (1985). Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J Pharmacol Exp Ther. 232: 258- 262.
28. Moore TS. (1982). Phospholipid biosynthesis. Ann Rev Plant Physiol. 33: 235-259.
29. Malini T, Arunakaran J, Aruldhas MM, Govindarajulu P. (1999). Effects of piperine on the lipid composition and enzymes of the pyruvate –malate cycle in the testis of the rat in vivo. Biochem Mol Biol Int 47: 3: 537-545.
30. Dillard CJ, Tappel AL. (1971). Fluorescent products of mitochondria and microsomes. Lipids. 6: 715-721.
31. Singh DK, Singh VK, Kumar P. (2012). Pestiferous gastropods and their control. "LAP Lambert. Academic Publication GmbH and Co. Germany page 1-72.
32. Srivastava AK, Singh VK. (2015). Feeding of snail attractant pellets (SAP) containing papain on certain biochemical parameters in the gonadal/nervous tissue of the vector snail (*Lymnaea acuminata*), Singapore Journal of Scientific Research 5(1): 12-19.
33. Jaiswal P, Singh DK. (2008). Molluscicidal activity of *Carica papaya* and *Areca catechu* against the freshwater snail *Lymnaea acuminata*. Vet Parasitol. 152 (3-4): 264-70.
34. Srivastava AK, Singh DK, Singh VK. (2014). Influence of Abiotic Factors on Anti-reproductive Activity of Bait-containing Papain in *Lymnaea acuminata*. Annual Research & Review in Biology 4 (1): 223-237.
35. Jaiswal P, Singh VK, Singh DK. (2008). Enzyme inhibition by molluscicidal components of *Areca catechu* and *Carica papaya* in the nervous tissue of vector snail *Lymnaea acuminata*. Pesticide Biochem Physiol. 92: 164-68.
36. Diaz GJ. (2015). Toxicosis by Plant Alkaloids in Humans and Animals in Colombia. Toxins (Basel). 7(12): 5408–5416.
37. Croaker A, King GJ, Pyne JH, Dukie SA, Liu L. (2016). *Sanguinaria canadensis*: Traditional Medicine, Phytochemical Composition, Biological Activities and Current Uses. Int J Mol Sci. 2016; 17(9): 1414.
38. Srivastava AK. (2013). Effect of certain attractant bait formulations, containing plant molluscicides on the reproduction of *Lymnaea acuminata* with reference to seasonal variation in abiotic factors. Ph.D. Thesis, DDU Gorakhpur University, Gorakhpur.
39. Srivastava AK, Singh VK. (2018). The egg-laying behaviours of the gastropod mollusks. Adv Tissue Eng Regen Med Open Access 4(2): 22–26.
40. Senchina DS, Hallam JE, Kohut ML, Nguyen NA, Perera MAN. (2014). Alkaloids and athlete immune function: Caffeine, theophylline, gingerol, ephedrine, and their congeners. Alkaloids and athlete immune function 68-93.
41. Azam S , Hadi N, Khan NU, Hadi SM. (2003). Antioxidant and prooxidant properties of caffeine, theobromine and xanthine. Med Sci Monit. 9(9): 325-330.
42. Zielonka J, Joseph J, Sikora A, Hardy M, Ouari O, Vivar JV, Cheng G, Lopez M, Kalyanaraman BB. (2017). Mitochondria-Targeted Triphenylphosphonium-Based Compounds: Syntheses, Mechanisms of Action, and Therapeutic and Diagnostic Applications. Chem. Rev. 117(15): 10043–10120.
43. Baracchi D, Marples A, Jenkins AJ, Leitch AR, Chittka L. (2017). Nicotine in floral nectar pharmacologically influences bumblebee learning of floral features. Sci Rep 7: 1951.

44. Adibah KJM, Azzreena MA. (2019). Plant toxins: alkaloids and their toxicities. GSC Biological and Pharmaceutical Sciences 06 (2) : 021–029.
45. James LF, Panter KE, Gaffield W, Molyneux RJ. (2004). Biomedical Applications of Poisonous Plant Research. Agric. Food Chem. 52 (11): 3211–3230.
46. Moreira R, Pereira DM, Valentao P, Andrade PB. (2018). Pyrrolizidine Alkaloids: Chemistry, Pharmacology, Toxicology and Food Safety. Int J Mol Sci. 19 (6): 1668.
47. Seremet OC , Olaru OT, Gutu CM , Nitulescu GM , Ilie M, Negres S, Zbarcea CE, Purdel CN, Spandidos DA, Tsatsakis AM, Coleman MD, Margina DM. (2018). Toxicity of plant extracts containing pyrrolizidine alkaloids using alternative invertebrate models. Molecular Medicine Reports 17: 7757-7763.
48. Frick KM, Kamphuis LG, Siddique KHM, Singh KB, Foley RC. (2017). Quinolizidine Alkaloid Biosynthesis in Lupins and Prospects for Grain Quality Improvement. Front Plant Sci 8: 87.
49. Cortinovis C, Caloni F. (2015). Alkaloid-Containing Plants Poisonous to Cattle and Horses in Europe.Toxins (Basel). 7 (12); 5301–5307.
50. Green BT, Lee ST, Panter KE, Brown DR. (2012). Piperidine alkaloids: Human and food animal teratogens. Food and Chemical Toxicology 50 (6): 2049-2055.
51. Handeland K, Vikoren T, Josefsen TD, Madslien K, Valdecanas B, Uhlig S. (2017). Yew (Taxus) intoxication in free-ranging cervids. PLoS One. 12 (12): e0188961.
52. Willson C. (2018). The clinical toxicology of caffeine: A review and case study. Toxicol Rep. 5: 1140–1152.
53. Bonnie RJ, Stratton K, Kwan LY. (2015). Editors; Committee on the Public Health Implications of Raising the Minimum Age for Purchasing Tobacco Products; Board on Population Health and Public Health Practice; Institute of Medicine. ISBN 978-0-309-31624-8. 2015.
54. Rockville MD. (2009). Substance Abuse and Mental Health Services Administration, Treatment Improvement Protocol (TIP) Series 51. HHS Publication No. (SMA) 09-4426. 2009.
55. Iturriaga G, Suárez BNF. (2009). Trehalose Metabolism: From Osmoprotection to Signaling." Int. J. Mol. Sci 10: 3793-3810.
56. Alkadi H, Khubeiz MJ, Jbeily R. (2018). Colchicine: A Review on Chemical Structure and Clinical Usage. Infect Disord Drug Targets 18 (2): 105-121.
57. Javier A, Navarro C, Vega FE, Karaoz U, Hao Z, Jenkins S, Lim HC, Kosina P, Infante F, Northen TR, Brodie EL. (2015). Gut microbiota mediate caffeine detoxification in the primary insect pest of coffee. Nature Communications 6: 7618.
58. Souza MSD, Markou A. (2011). Neuronal Mechanisms Underlying Development of Nicotine Dependence: Implications for Novel Smoking-Cessation Treatments. Addict Sci Clin Pract. 6(1): 4–16.