ORIGINAL ARTICLE

Strychnos nux-vomica: A Poisonous Plant with Various Aspects of Therapeutic Significance

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ABSTRACT

Strychnos nux vomica (Family: Loganiaceae) is a widely distributed poisonous medicinal plant. Different parts of this plant mainly seeds have been used in traditional Chinese and Indian systems of medicine. Although nux vomica is extremely poisonous, still it considered to be useful for treating many diseases such as paralytic and neuralgic affections, dyspepsia, itching, urinary disorders, joint pain, dysentery, emotional disorders, epilepsy, rheumatism and insomnia. Phytochemical studies of different parts revealed the presence various constituents mainly alkaloids together with flavonoids, iridoids and phenolic glycosides. Various types of preparations and constituents of nux vomica exerted hepatoprotective, antioxidant, antinociceptive, anti-allergic, anti-inflammatory, antimicrobial, anticancer, antipyretic, gastroprotective, antidiabetic, antialcoholic, anti-snake venom and neuropharmacological properties. Moreover, clinical studies on nux vomica preparations showed positive outcome against sinusitis, insomnia and rhinitis. However, most of the pharmacological and clinical studies are too preliminary to conclude the effectiveness of nux vomica. In the future, more efforts should be required on *in vitro* and *In vivo* studies and also on clinical trials to confirm clinical efficacy and to determine the active constituent(s) and mode of actions involved in each activity of nux vomica. Moreover, nux vomica is extremely toxic and this is attributed to the presence of alkaloids, mainly strychnine and brucine. Therefore, more attention should also be paid to minimize its toxic potential through advanced detoxification processes without altering the therapeutic potential. Through this review, the authors are intended to integrate traditional ethno medicinal knowledge and modern scientific findings about nux vomica in order to understand its phytochemical, therapeutic potential as well as toxicity and future perspective.

Key words: *S. nux vomica*, phytoconstituents, pharmacology, clinical studies, toxicity

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INTRODUCTION

Strychnos nux vomica Linn (Family: *Loganiaceae*), a medicinally important toxic plant, commonly known as nux vomica, poison nut, has diverse therapeutic and clinical applications. This plant is commercially cultivated in the different part of world such as United States, European Union, Fujian, Guangdong, Guangxi, Hainan, North Australia, Taiwan, and throughout tropical Asia.[1] Different parts of this plant especially seeds and bark possesses a wide variety of indications in traditional and folklore medicines of different countries. This plant is known to be a highly toxic to human and most domestic animals due to the abundance of highly toxic alkaloids especially strychnine. Since, at small dose, it has diverse clinical applications in traditional Indian (e.g., Ayurveda, Unani and Homeopathy) and Chinese medicines.[2]

Presently, nux vomica is utilized in more than 60 formulations of Indian systems of medicine of which 30 formulations are used in the disorders of *vata dosha*.[3] Various compounds of different phytochemical categories especially alkaloids have been identified in different parts of this plant. Different parts of this plant are rich in indole alkaloids strychnine and brucine which are responsible for a wide range of therapeutic potential and toxicity as well. Besides the toxic properties, a wide range of pharmacological and biological activities have been reported for this plant. Over the past decades, considerable progresses have been made on phytochemical, pharmacological and toxicological investigation of this plant. Since, there is no detail review on therapeutic and pharmacological aspects as well as phytochemistry of this ancient medicinal plant. Therefore, the present review emphasizes collective information on the ethno medicinal uses, pharmacological and phytochemical aspects of nux vomica, to provide a scientific source to future natural drugs development from this plant for managing various disorders.

ETHNOMEDICINAL USES

The medicinal properties of nux vomica are substantially due to the abundance of alkaloids strychnine and brucine. In India the fruits are used in both the Ayurvedic and Unani systems of medicine as appetizer, tonic, aphrodisiac and antipyretic. It has been also claimed to be a curative medicine for leucoderma, blood diseases, itching, ringworm, piles, ulcer, anemia, jaundice, urinary disorders, joint pain, lumbago and limb weakness.[4] In India, nux vomica seeds are used in the treatment of dyspepsia, nervous system disorders, chronic dysentery, atonic diarrhea, cholera, diabetes, emotional disorders, hysteria, epilepsy, intermittent fevers, gout, rheumatism, hydrophobia, insomnia, urinary incontinence, spermatorrhoea, paralytic and neuralgic affections and as antidote to alcoholism.[5,6] The juice of the stem and root barks are claimed to be useful in intermittent fevers, cholera and acute dysentery. Internally, the infusion of barks is used to treat epilepsy and is externally applied for the treatment of ulcers and leprotics. Leaves are externally applied as poultice and promote healthy action in sloughing wounds or ulcers especially when maggots have formed.[5]

PHYTOCHEMISTRY

The detail phytochemical profile of nux vomica has not reported comprehensively. It is rich in different classes of phytochemicals of which mostly indole alkaloids with different structural patterns [Figure 1]. In the last few decades more than 90 chemical compounds have been identified from different parts of this plant. Detailed phytochemical profile and their chemical configuration of nux vomica are as follows.

Fruits and seeds

The dried seeds contain 2.6-3% alkaloids of which strychnine(1)

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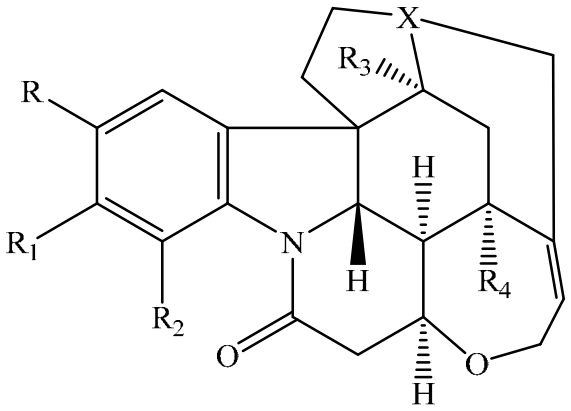
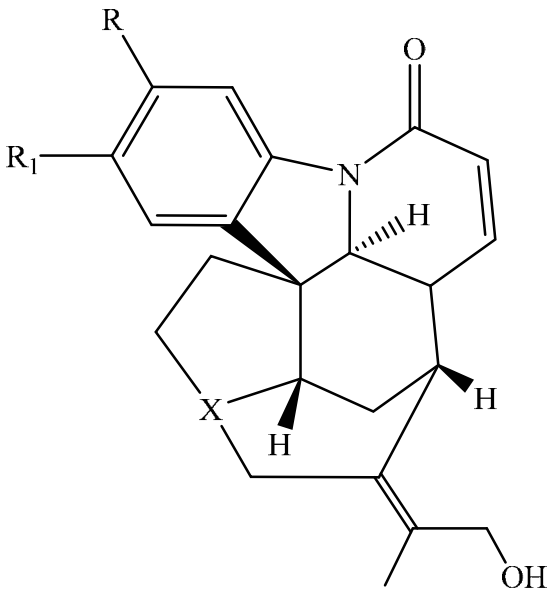
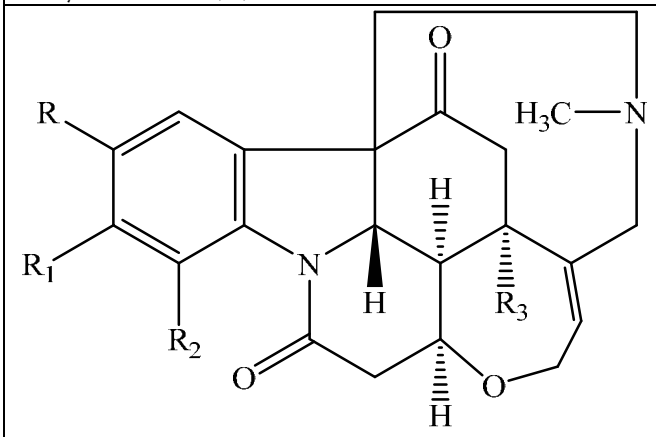


Strychnine (**1**); R=R_1=R_2=R_3=R_4=H, X=N
Brucine (**2**); R=R_1=OCH_3, R_2=R_3=R_4=H, X=N
Pseudostrychnine (**3**); R=R_1=R_2=R_4=H, R_3=OH, X=N
Pseudobrucine (**4**); R=R_1=OCH_3, R_2=R_4=H, R_3=OH, X=N
β-colubrine (**5**); R=OCH_3, R_1=R_2=R_3=R_4=H, X=N
α-colubrine (**6**); R=R_2=R_3=R_4=H, R_1=OCH_3, X=N
Strychnine *N*-oxide (**7**); R=R_1=R_2=R_3=R_4=H, X=N^+→O
Brucine *N*-oxide (**8**); R=R_1=OCH_3, R_2=R_3=R_4=H, X=N^+→O
2-hydroxy-3-methoxystrychnine (**9**); R=OH, R_1=OCH_3, R_2=R_3=R_4=H, X=N
15-hydroxystrychnine (**10**); R=R_1=R_2=R_3=H, R_4=OH, X=N
15-acetoxystrychnine (**11**); R=R_1=R_2=R_3=H, R_4=OAc, X=N
3-hydroxy-*α*-colubrine (**12**); R=OCH_3, R_1=R_2=R_4=H, R_3=OH, X=N
3-hydroxy-*β*-colubrine (**13**); R=R_2=R_4=H, R_1=OCH_3, R_3=OH, X=N
4-hydroxystrychnine (**65**); R=R_1=R_3=R_4=H, R_2=OH, X=N
10-hydroxystrychnine (**83**); R=OH, R_1=R_2=R_3=R_4=H, X=N
12-hydroxystrychnine (**84**); R=R_1=R_3=R_4=H, R_2=OH, X=N
12-hydroxy-11-methoxystrychnine (**85**); R=R_3=R_4=H, R_1=OCH_3, R_2=OH, X=N
4-hydroxy-3-methoxystrychnine (**86**); R=R_3=R_4=H, R_1=OCH_3, R_2=OH, X=N

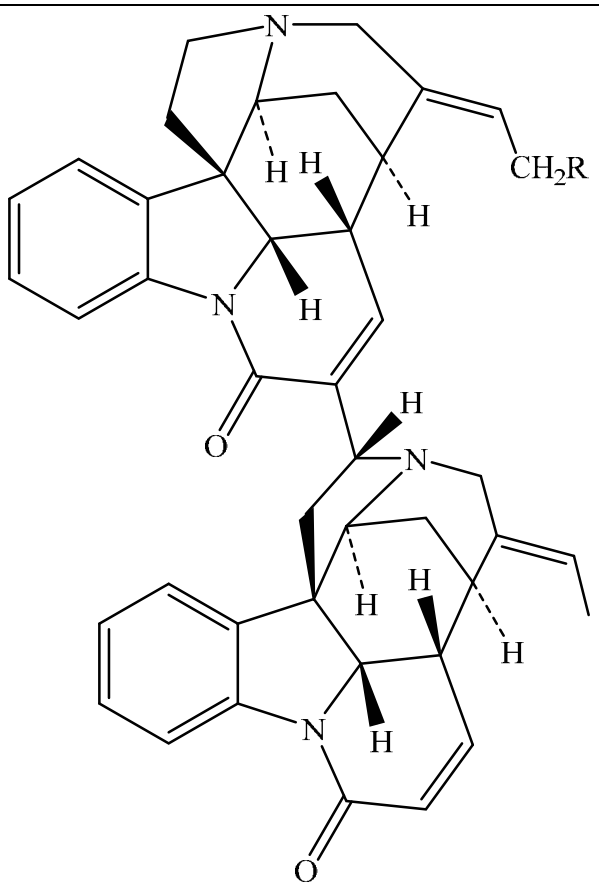
12-hydroxystrychnine *N*-oxide (**88**); R=R_1=R_3=R_4=H, R_2=OH, X=N^+→O
12-hydroxy-11-methoxystrychnine *N*-oxide (**89**);
R=R_3=R_4=H, R_1=OCH_3, R_2=OH, X=N^+→O
10,11-dimethoxystrychnine *N*-oxide (**90**); R=R_1=OH, R2=R_3=R_4=H, X=N^+→O
3-hydroxystrychnine (**91**); R=R_1=R_2=R_4=H, R_3=OH, X=N
3,12-dihydroxystrychnine (**92**); R=R_1=R_4=H, R_2=R_3=OH, X=N
3,12-dihydroxy-11-methoxystrychnine (**93**); R=R_4=H, R_1=OCH_3, R_2=R_3=OH, X=N
3-hydroxy-10,11-dimethoxystrychnine (**94**); R=R_1=OCH_3, R_2=R_4=H, R_3=OH, X=N



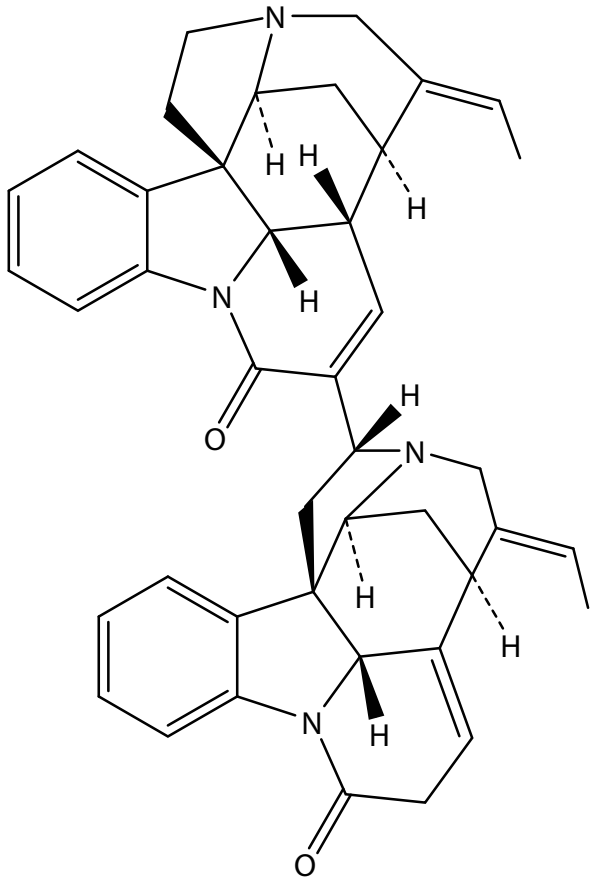
Isostrychnine (**14**); R=R_1=H, X=N
Isobrucine (**15**); R=R_1=OCH_3, X=N
Isobrucine N-oxide (**16**); R=R_1=OCH_3, X=N^+→O
Isostrychnine *N*-oxide (**17**); R=R_1=H, X=N^+→O



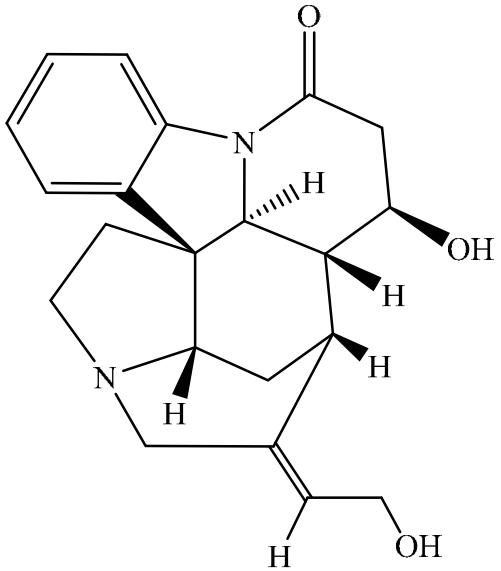
Icajine (**18**); R=R_1=R_2=R_3=H, X=N-CH_3
Vomicine (**19**); R=R_1=R_3=H, R_2=OH, X=N-CH_3
Novacine (**20**); R=R_1=OCH_3, R_2=R_3=H, X=N-CH_3
15-hydroxyicajine (**21**); R=R_1=R_2=H, R_3=OH, X=N-CH_3
3-methoxyicajine (**22**); R=R_2=R_3=H, R_1=OCH_3, X=N-CH_3
Icajine *N*-oxide (**47**); R=R_1=R_2=R_3=H, X=X=N^+→O
N-methyl-*sec*-pseudo-*β*-colubrine (**66**); R=OCH_3, R_1=R_2=R_3=H, X=N-CH_3



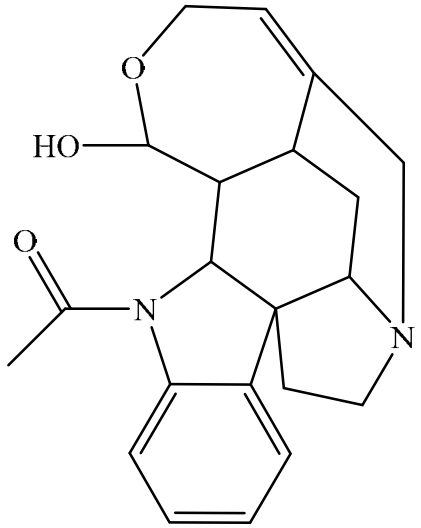
Sungucine (**23**); R=H
18-hydroxysungucine (**30**); R=OH



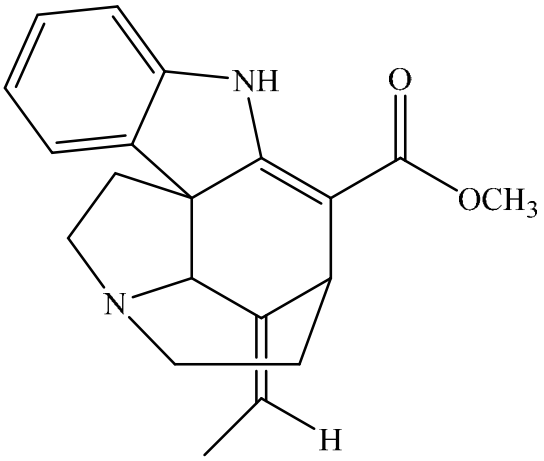
Isosungucine (**24**)



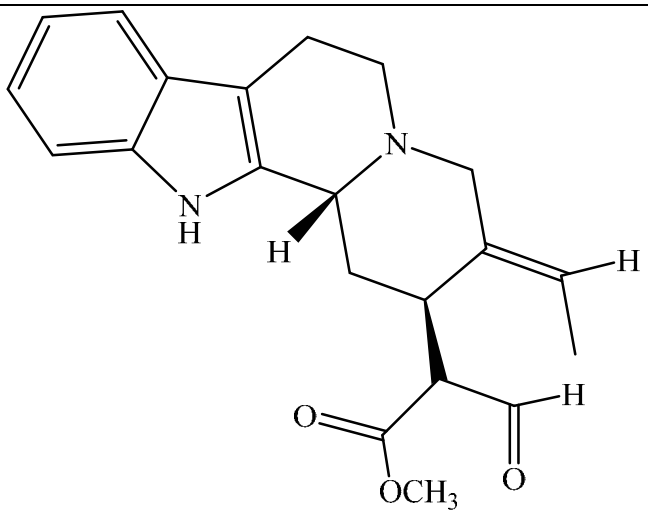
Protostrychnine (**25**)



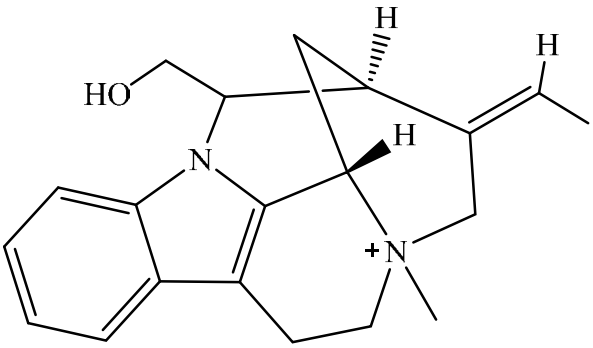
Diaboline (**26**)



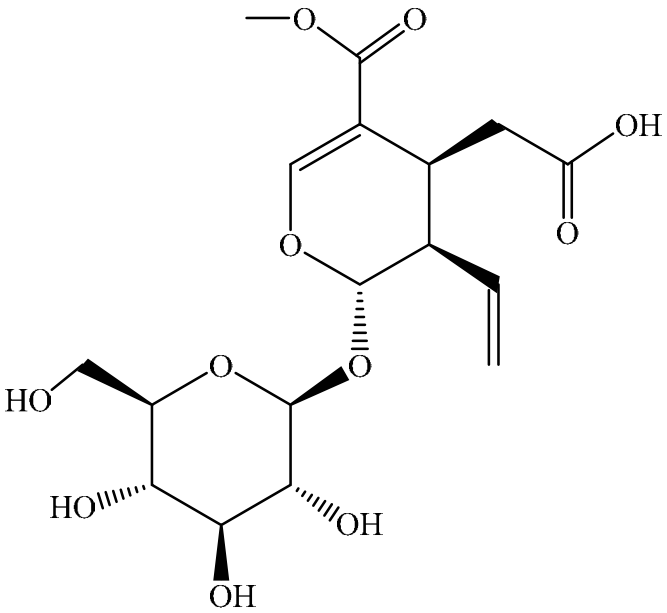
Condylocarpine (**27**)



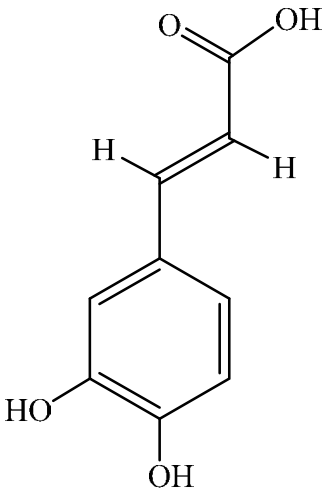
Geissoschizine (**28**)



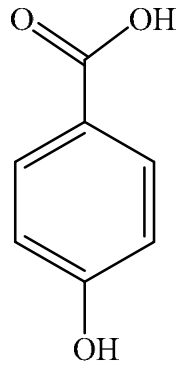
Mavacurine (**29**)



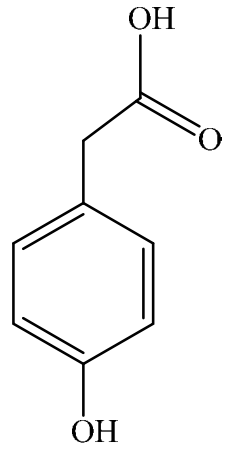
Secoxyloganin (**31**)



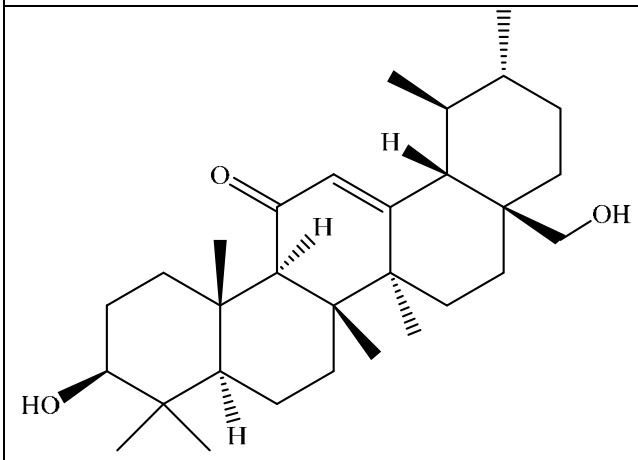
Caffeic acid (**32**)



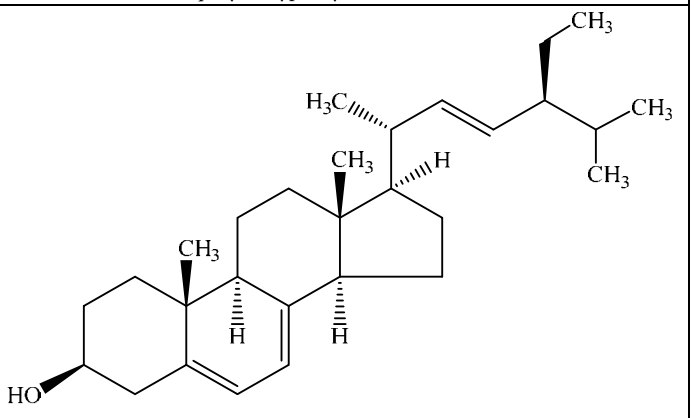
p-hydroxybenzoic acid (**33**)



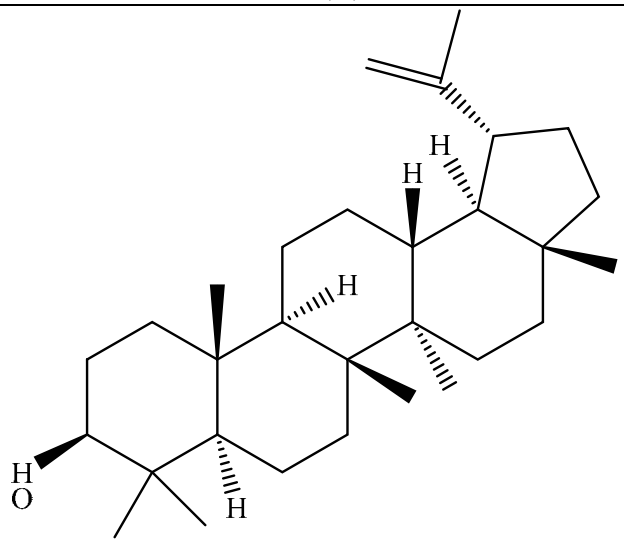
p-hydroxyphenylacetic acid (**34**)



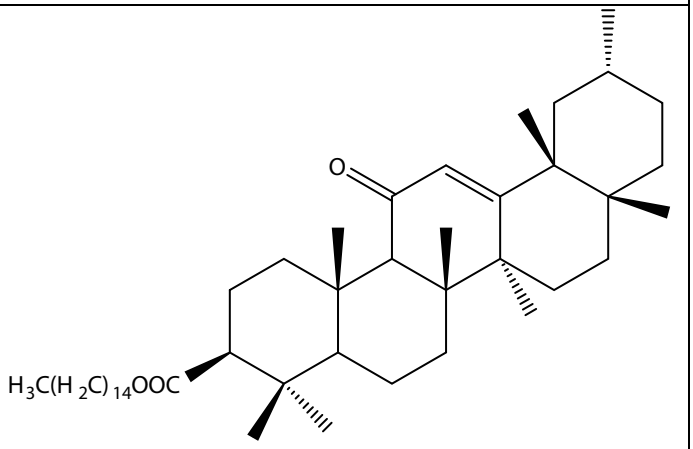
Uvaol (**35**)



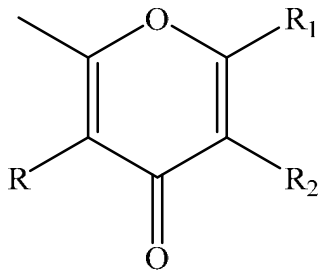
Stigmasta-7,22,25-triene-3-ol (**36**)



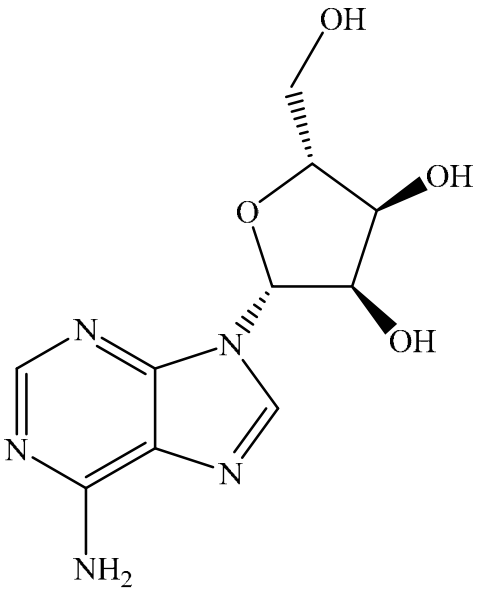
Lupeol (**37**)



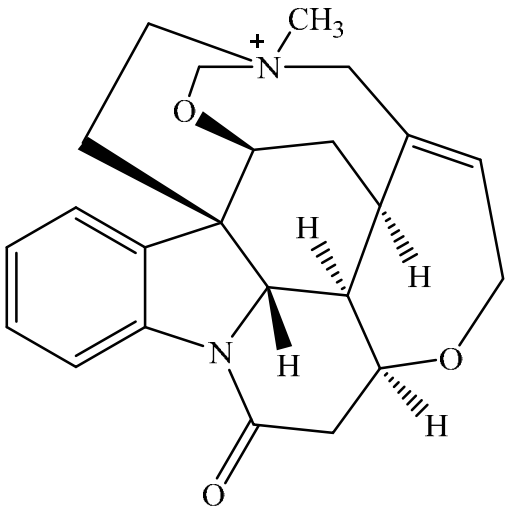
11-*oxo*-α-amyrin palmitate (**38**)



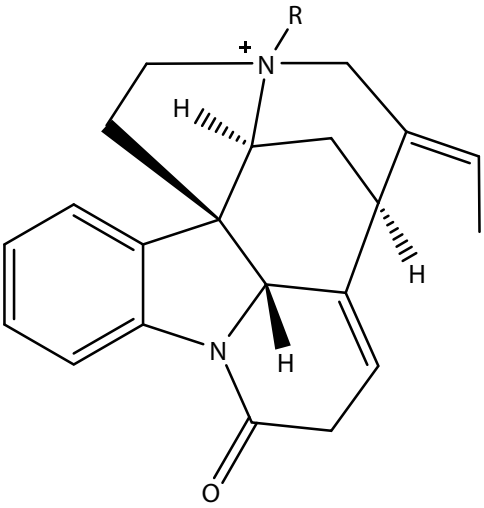
Catechol (**39**); R=H, R_1=CH_3, R_2=OH
Maltol (**40**); R=OH, R_1=R_2=H



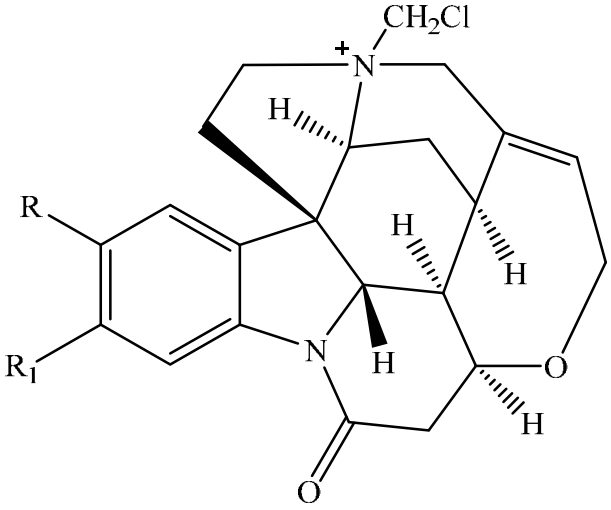
Adenosine (**41**)



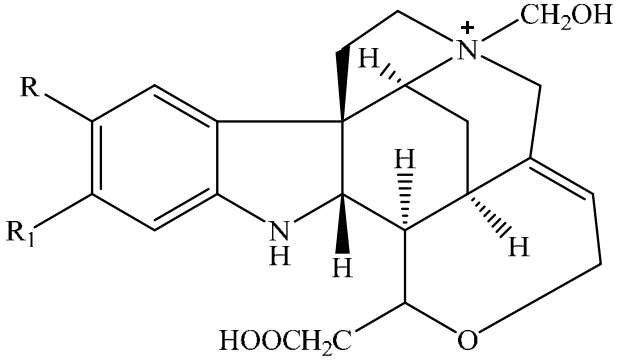
Stryvomicine A (**42**)



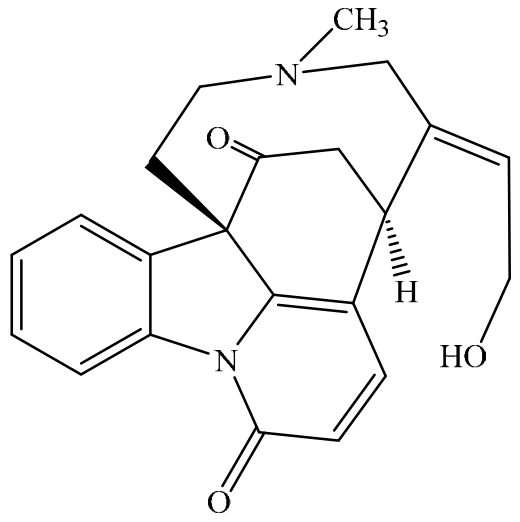
Deoxy-isostrychnine (**43**); R=CH_3
Deoxy-isostrychnine-chloromethochloride (**44**); R=CH_2Cl



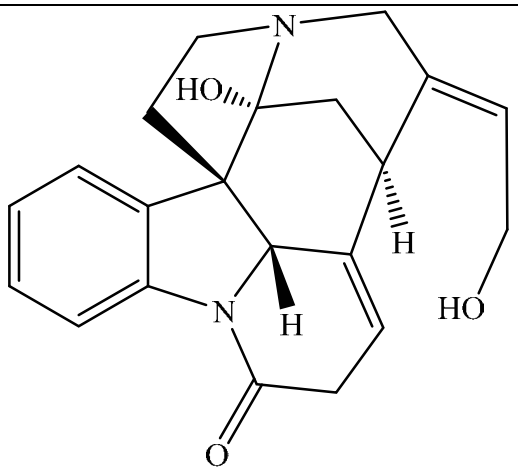
β-colubrinechloromethochloride (**45**); R=OCH_3, R_1=H
α-colubrine-chloromethochloride (**46**); R=H, R_1=OCH_3



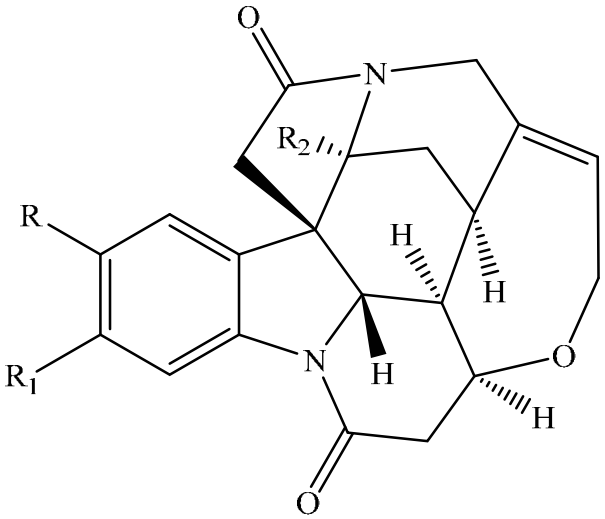
4-*N*-hydroxymethyl strychnidin-17-acetic acid (**48**); R=R_1=H
10,11-dimethoxy-4-*N*-hydroxymethyl
strychnidin-17-acetic acid (**49**); R=R_1=OCH_3



Stryvomitine (**50**)

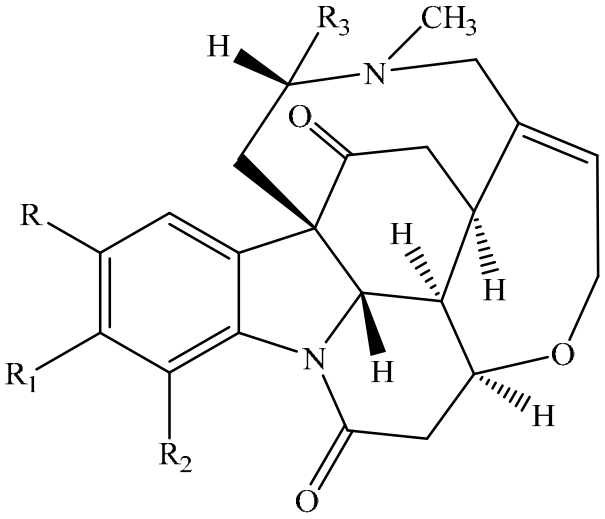


Isopseudostrychnine (**51**)



5-oxobrucine (**52**); R=R_1=OCH_3, R_2=H

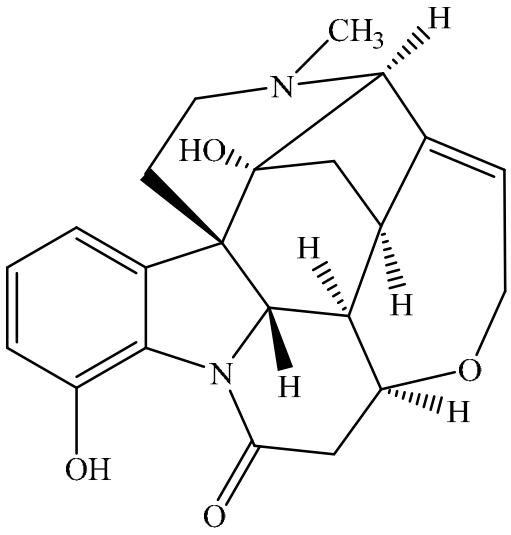
5-oxopseudostrychnine (**53**); R=R_1=H, R_2=OH



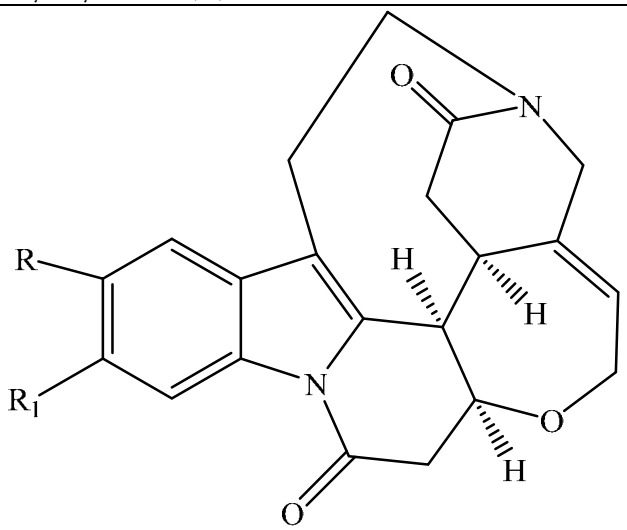
11-hydroxyl-icajine (**54**); R=R_2=R_3=H, R_1=OH

10-hydroxyl-icajine (**55**); R=OH, R_1=R_2=R_3=H

5-hydroxyl-vomicine (**56**); R=R_1=H, R_2=R_3=OH

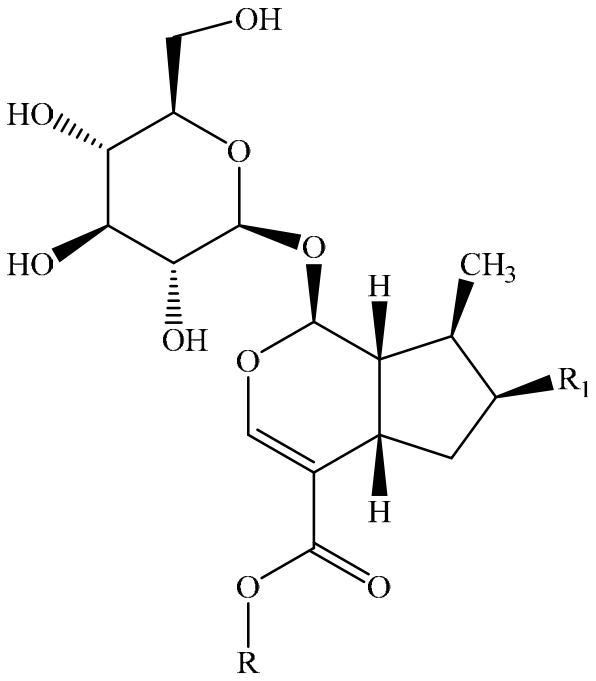


Stryvomicine (**57**)

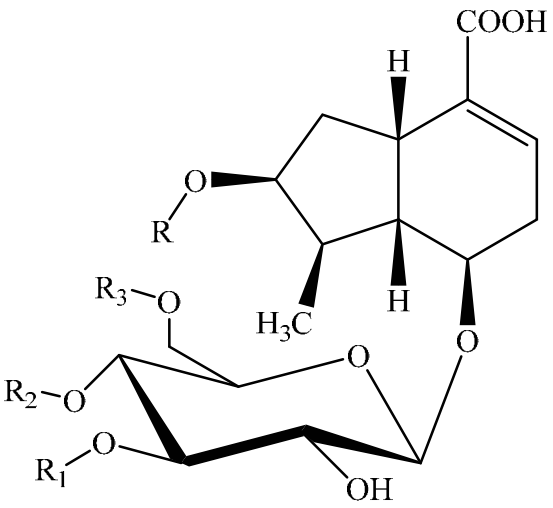


Strynuxline A (**58**); R=R_1=OCH_3

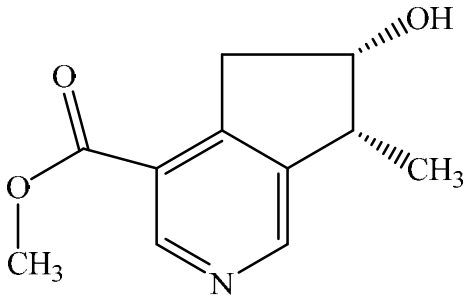
Strynuxline B (**59**); R=R_1=H



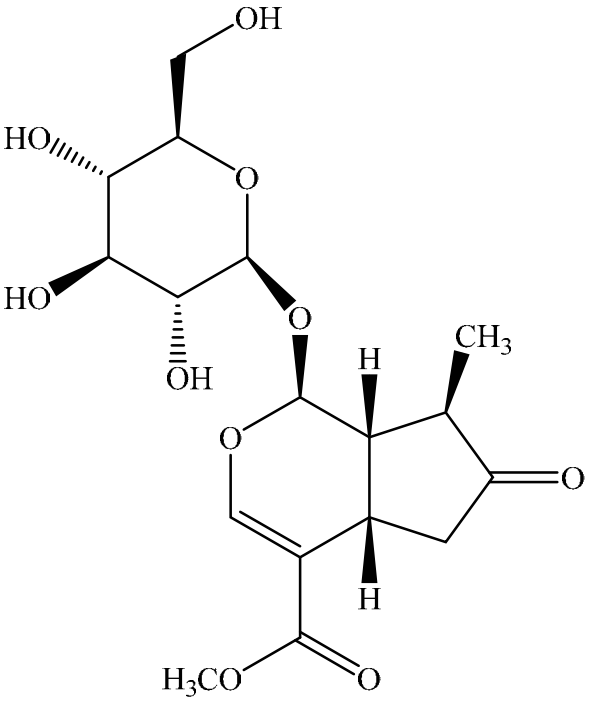
Loganin (**60**); R=CH_3, R_1=OH, H
Loganic acid (**68**); R=H, R_1=OH, H Deoxyloganin (**69**); R=CH_3, R_1=H, H



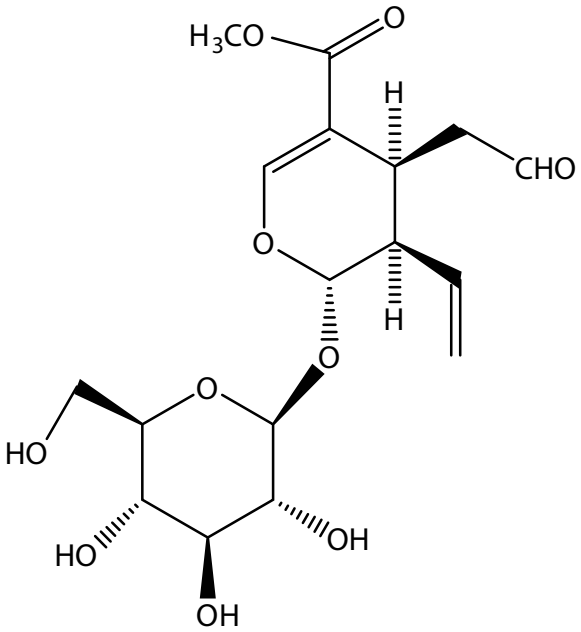
6-*O*-acetylloganic acid (**61**); R=R_1=R_2=H, R_3=CH_3CO
4-*O*-acetylloganic acid (**62**); R=R_1=R_3=H, R_2=CH_3CO
3-*O*-acetylloganic acid (**63**); R=R_2=R_3=H, R_1=CH_3CO
7-*O*-acetylloganic acid (**64**); R=CH_3CO, R_1=R_2=R_3=H



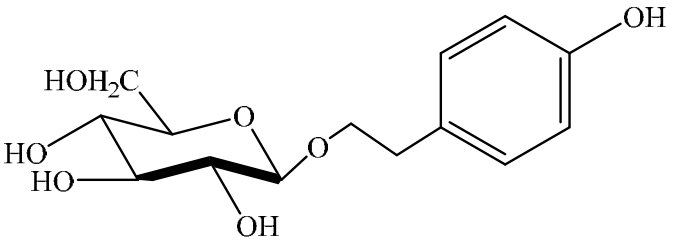
Cantleyine (**67**)



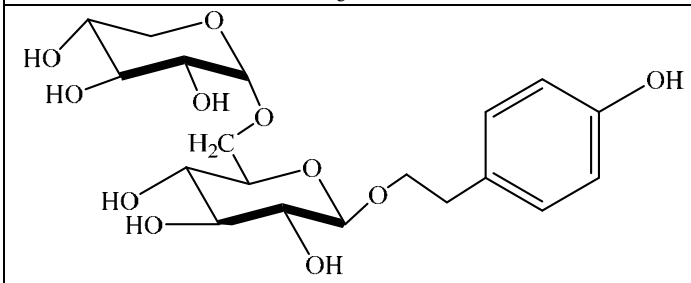
Ketologanin (**70**)



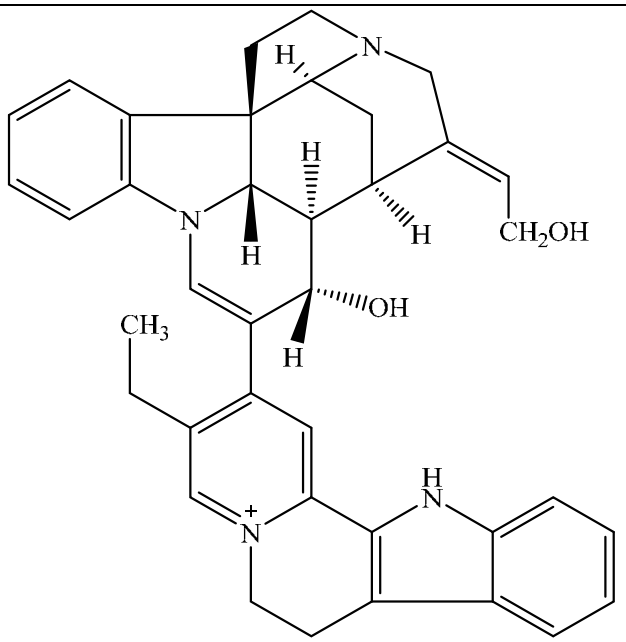
Secologanin (**71**)



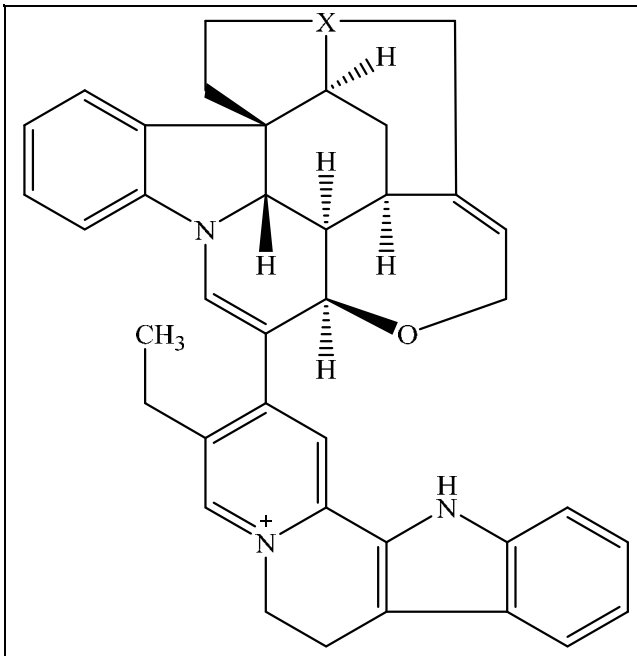
Salidroaide (**72**)



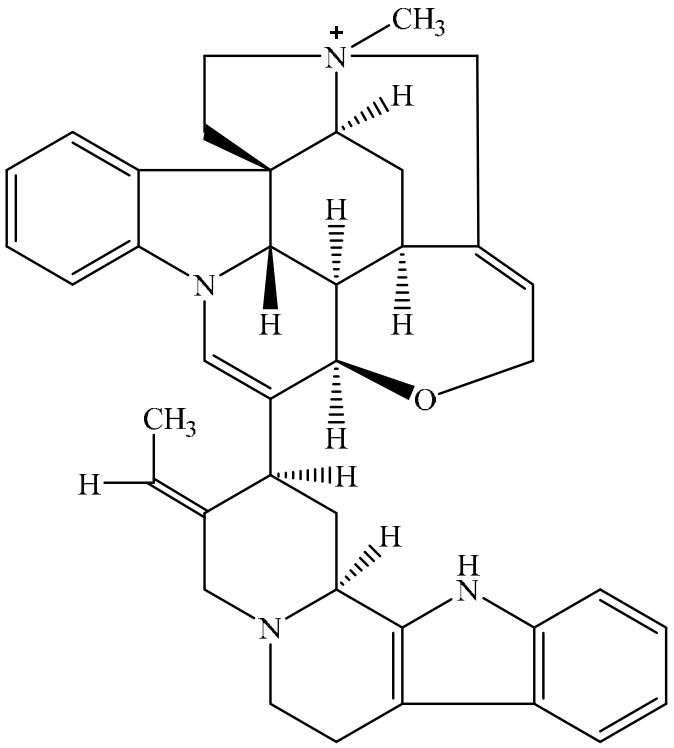
Cuchiloside (**73**)



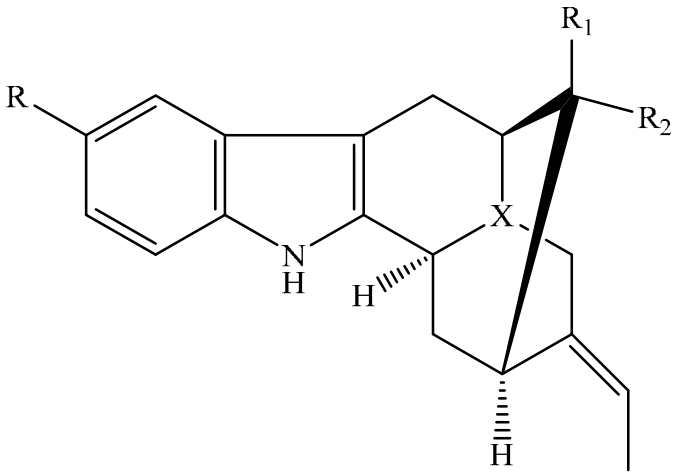
Strychnochrysine (**74**)



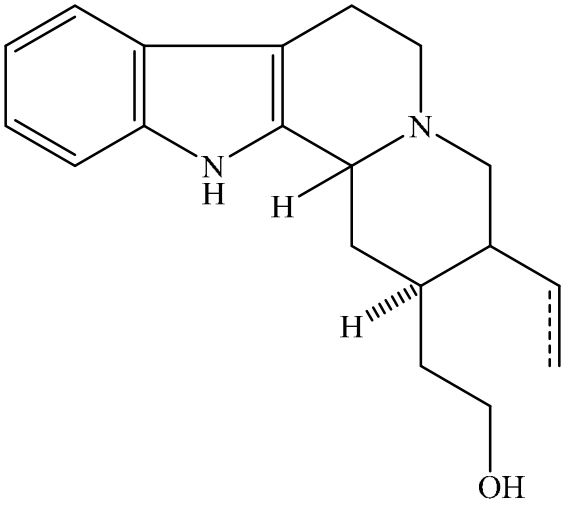
Demethoxyguiaflavine (**75**), X=N^+–CH_3
Strychnoflavine (**76**), X=N
Artefact from strychnoflavine (**77**), X=N^+–Cl



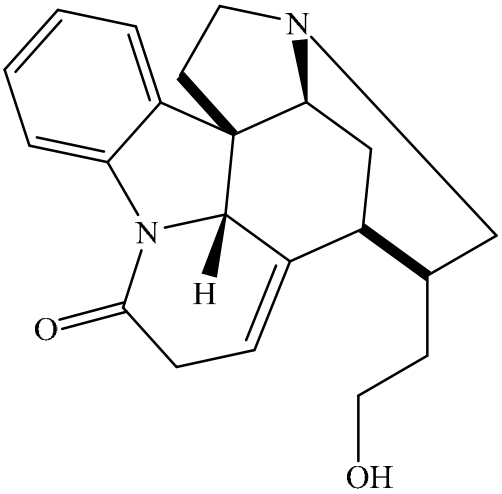
N-methyl-longicaudatine (**78**)

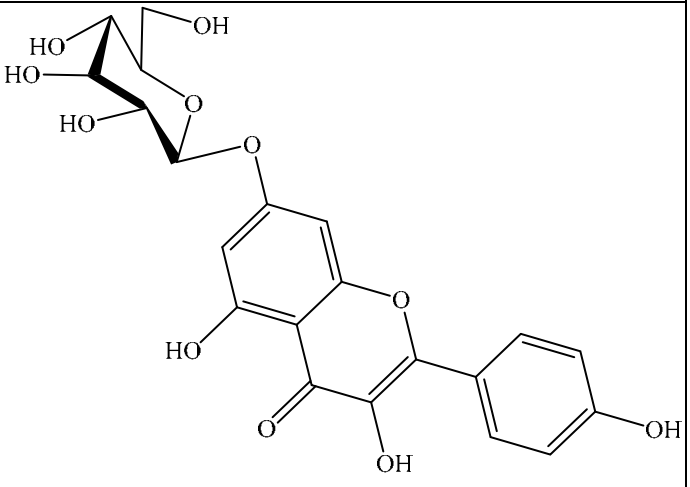


Nor-macusine B (**79**); R=R_1=H, R_2=CH_2OH, X=N
O-methylmacusine B (**80**); R=R_1=H, R_2=CH_2-OCH_3, X=N^+-CH_3
16-*epi*-*O*-methylmacusine B (**81**); R=R_2=H, R_1=CH_2-OCH_3, X=N^+-CH_3

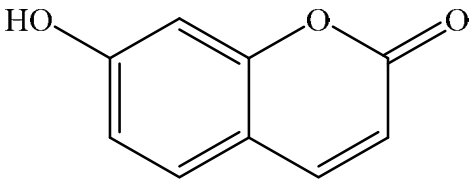


Nor-melinonine B (**82**)



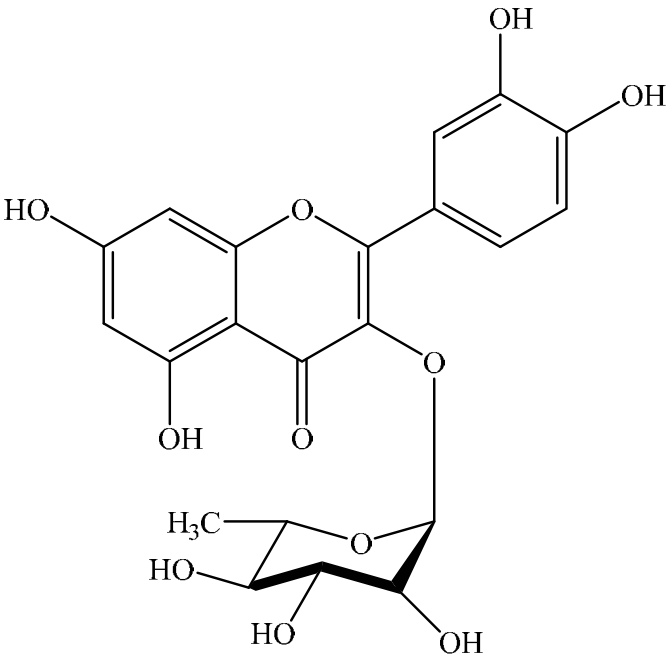


19,20-dihydroisostrychnine (**87**)

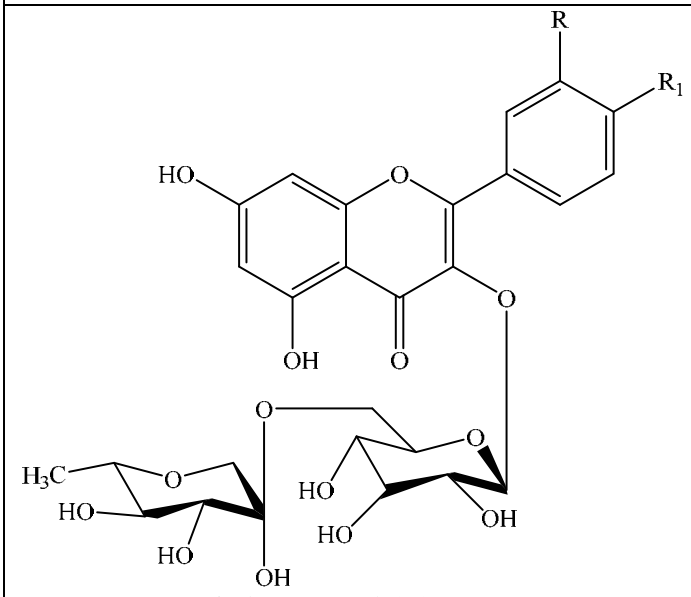


Umbelliferone (**96**)

Kaempferol-7-*O*-*β*-*D*-glucopyranoside (**95**)



Quercetin-3-rhamnoside (**97**)



Kaempferol-3-*O*-rutinoside (**98**); R=H, R_1=OH

Rutin (**99**); R=R_1=OH

Figure 1: Chemical structures of nux vomica phytoconstituents

(1.25-1.5%) and brucine (2)(1.7%) are the major active constituents.[7] Besides, various minor alkaloids such as pseudostrychnine (3), pseudobrucine (4), *β*-colubrine (5), α-colubrine (6), strychnine N-oxide (7), brucine N-oxide (8), 2-hydroxy-3-methoxystrychnine(9), 15-hydroxystrychnine(10), 15-acetoxystrychnine(11), 3-hydroxy-*α*-colubrine (12), 3-hydroxy-*β*-colubrine (13), isostrychnine (14), isobrucine (15), isobrucine N-oxide(16), isostrychnine N-oxide (17), icajine (18), vomicine (19), novacine (20), 15-hydroxyicajine (21), 3-methoxyicajine (22), sungucine (23), isosungucine (24), protostrychnine (25), diaboline (26), condylocarpine (27) and geissoschizine (28).[6,8-11] Most of these alkaloids were also present in the processed seed extract along with some other alkaloids such as mavacurine (29), 18-hydroxysungucine (30),[9,11] secoxyloganin (31), caffeic acid (32), *p*-hydroxybenzoic acid (33), *p*-hydroxyphenylacetic acid (34), uvaol (35), stigmasta-7,22,25-triene-3-ol (36), lupeol (37), 11-*oxo*-*α*-amyrin palmitate (38), catechol (39), maltol (40) and adenosine (41).[12] Recently, few minor alkaloids such as stryvomicine A (42), deoxy-isostrychnine (43), deoxy-isostrychnine-chloromethochloride (44), *β*-colubrinechloromethochloride (45), *α*-colubrine-chloromethochloride (46) and icajine-N-oxide (47),[13] 4-*N*-hydroxymethyl strychnidin-17-acetic acid (48), 10,11-dimethoxy-4-*N*-hydroxymethyl strychnidin-17-acetic acid (49),[14] stryvomitine (50), isopseudostrychnine (51), 5-oxobrucine(52), 5-oxopseudostrychnine (53), 11-hydroxyl-icajine (54), 10-hydroxyl-icajine (55), 5-hydroxyl-vomicine (56) and stryvomicine (57),[15] strynuxlines A (58) and B (59)[16] were isolated from the unprocessed seed extract of nux vomica. Besides, some iridoid glucosides such as loganin (60), 6′-*O*-acetylloganic acid (61), 4′-*O*-acetylloganic acid (62),

3'-*O*-acetylloganic acid (63) and 7-*O*-acetylloganic acid (64) were also identified in the seed extract.[17]

Similar alkaloidal profiles were also observed in pericarp and pulp of the nux vomica fruits. Fruit pericarp was found to contain strychnine, 4-hydroxystrychnine (65), *β*-colubrine, brucine, pseudostrychnine, pseudobrucine, strychnine N-oxide, brucine N-oxide, icajine, vomicine, *N*-methyl-*sec*-pseudo *β*-colubrine (66), novacine and cantleyine (67).[18] Alkaloidal profile of fruit pulp was found to be same as fruit pericarp except *β*-colubrine and N-methyl-*sec*-pseudo *β*-colubrine.[18] Besides, some iridoids such as loganin, loganic acid (68), deoxyloganin (69), ketologanin (70), secologanin (71) and two phenolic glycosides salidroaide (72) and cuchiloside (73) were identified in the fruit pulp.[18,19]

Barks

Preliminary phytochemical analysis of stem bark revealed the presence of flavonoids, phenols, alkaloids, carbohydrates, tannins, steroids, triterpenoids and glycosides. Phytochemical analysis exhibited the presence of brucine, strychnine, *α*-colubrine, loganin, mavacurine, vomicine, pseudobrucine, pseudostrychnine, 16-hydroxycolubrine and caffeic acid ester in the stem bark,[10,20] while the root bark contains *β*-colubrine, brucine, caffeic acid ester, strychnine,[10] strychnochrysine (74),[21] pseudostrychnine, pseudobrucine, vomicine, icajine and novacine.[22] Recently, 13C NMR and mass spectrometry analysis of stem bark revealed the presence of four new dimeric bisindole alkaloids viz. demethoxyguiaflavine (75), strychnoflavine (76), artefact from strychnoflavine (77), *N*-methyl-longicaudatine (78), with the known dimeric bisindole alkaloid, strychnochrysine.[23] Root bark of nux vomica from Sri Lankan origin were reported to contain nor-macusine B (79), *O*-methylmacusine B (80), 16-*epi*-*O*-methylmacusine B (81), nor-melinonine B (82), isostrychnine, protostrychnine, strychnine, 10-hydroxystrychnine (83), 12-hydroxystrychnine (84), *β*-colubrine, 12-hydroxy-11-methoxystrychnine (85), brucine, 4-hydroxy-3-methoxystrychnine (86) and 4-hydroxystrychnine.[24,25]

Leaves

Presence of four alkaloids such as strychnine, brucine, colubrine and vomicine in the leaves of nux vomica was first established by Quirin *et al.*[26] However, phytochemical analysis of the leaves from Sri Lankan origin reported to contain sixteen alkaloids and the alkaloids were include strychnine, brucine, nor-macusine B, isostrychnine, 19,20-dihydroisostrychnine(87), 12-hydroxystrychnine, 12-hydroxy-11-methoxystrychnine, strychnine N-oxide, 12-hydroxystrychnine N-oxide (88), 12-hydroxy-11-methoxystrychnine N-oxide (89), 10,11-dimethoxystrychnine N-oxide (90), 3-hydroxystrychnine (91), 3,12-dihydroxystrychnine (92), 3,12-dihydroxy-11-methoxystrychnine (93), 3-hydroxy 10,11-dimethoxystrychnine (94) and vomicine.[25] Recently, Eldahshan and Abdel-Daim isolated five phenolic compounds viz. kaempferol-7-*O*-*β*-*D*-glucopyranoside (95), umbelliferone (96), quercetin-3-rhamnoside (97), kaempferol-3-*O*-rutinoside (98) and rutin (99) from the hydro-methanolic extract of leaves.[27]

Flowers

Five tertiary indole alkaloids were isolated by thin layer chromatographic (TLC) analysis of nux vomica flowers. Isolated alkaloids were identified as strychnine, brucine, vomicine, icajine and novacine.[28]

PHARMACOLOGICAL ACTIVITIES

Nux vomica is a toxic plant since the processed extract of this plant has been used in various traditional formulations of different countries. Various extracts, fractions as well as pure compounds obtained from different parts of this plant have been studied to identify their possible pharmacological effects in both *In vivo* and *in vitro* models. The pharmacological activities observed by different authors is presented in the following section which are including antioxidant, hepatoprotective, antinociceptive, anti-allergic, anti-inflammatory, antibacterial, anticancer, gastroprotective and so on. In addition, the pharmacological activities of some active constituents are also summarized in Table 1.

Hepatoprotective

Nux vomica is listed as a toxic drug; however its processed extract still used in various herbal formulations for the treatment of various ailments including liver diseases and jaundice. Recent, *In vivo* study demonstrated the hepatoprotective potential of processed seed extract in assays involving CCl_4-induced liver injury in rats. Oral administration of varying doses of processed seed extract for 5 days resulted in the reduction of serum levels of glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), alkaline phosphatase (ALP), bilirubin, cholesterol in addition with the restoration of glutathione (GSH) and reduced lipid peroxidation in liver tissue.[29] In a study performed by Visen *et al.* loganin was isolated from the fruit of nux vomica and was showed excellent hepatoprotective potential in *ex vivo* and *In vivo* models of liver injury induced by galactosamine.[30] This hepatoprotective potential of loganin was confirmed by ameliorating the galactosamine-mediated reduction of hepatocytes viability as well as bile volume and bile contents.[30]

Antioxidant

Antioxidant property of nux vomica seeds was first reported by Tripathi and Chaurasia.[31] The ethanol extract of nux vomica dose dependently inhibited the $FeSO_4$-induced lipid peroxidation through the chelation of Fe++/Fe+++ ions not by tapping the hydroxyl radicals.[32] In further studies, Chitra *et al.* established that the methanol extract of seeds showed significant antioxidant activity by reducing lipid peroxidation and increasing the levels of antioxidant enzymes like super oxide dismutase (SOD) and catalase in the liver of alloxan-induced diabetic rats.[33] Antioxidant potential of nux vomica seed extract may be attributed to the presence of antioxidant compounds such as loganin, uvaol, secoxyloganin, maltol, lupeol, hydroxybenzoic acid and caffeic acid [Table 1].

Besides, chloroform, ethyl acetate and methanol extracts (100 µg/ml) of nux vomica leaves showed significant *in vitro* antioxidant capacity in terms of scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals; however the methanol extract had higher scavenging activity (IC50 73.41 µg/ml) than ethyl acetate and chloroform extracts.[34] Another studies established that the nux vomica leaves contain high levels of non-enzymatic (superoxide dismutase, ascorbate peroxidase, catalase, peroxidase and polyphenol oxidase) and enzymatic (ascorbic acid, α-tocopherol and reduced glutathione) antioxidants.[35] Hence, it was postulated that the antioxidant effect of nux vomica leaves might be predominantly due to the abundance of non-enzymatic and enzymatic antioxidant contents. However, further studies are warranted to evaluate the antioxidant potential of these individual anti-oxidant components. In order to investigate the antioxidant potential, the methanolic flower extract of nux vomica also showed significant DPPH free radicals scavenging activity.[36]

Antinociceptive

Nux vomica seeds extract has been used in various analgesic preparations of traditional Chinese medicine. Using tail-pressure, hot-plate and acetic acid-induced writhing tests models, the intraperitoneal administration of crude alkaloid fractions (CAF) and processed alkaloidal fractions (PAF) of nux vomica seeds extract exhibited antinociception potential in mice; however PAF showed stronger antinociception than CAF.[37] Using the same models, the transdermal administration of modified total alkaloid fractions (MTAF) containing low strychnine and high brucine was significantly improved the

Table 1: Pharmacological activities of nux vomica constituents

Active Constituent	Pharmacology
Strychnine	Anticancer,[67] reduced locomotor activity,[68] antagonist of glycine, and acetylcholine receptors[69]
Isostrychnine	Anticancer[67]
5-oxopseudostrychnine	Autophagy inducer[13]
Brucine	Analgesic, anti-inflammatory,[39] and anticancer.[53]
Brucine *N*-oxide	Analgesic, anti-inflammatory,[39] and anti-HIV.[70]
Icajine	Antimalarial[71]
11-hydroxyl-icajine	Anticancer[15]
10-hydroxyl-icajine	Anticancer[15]
Loganin	Hepatoprotective,[30] antioxidant,[72] acetylcholinesterase (AChE) inhibitor,[73] anti-inflammatory,[74] and neuroprotective[75]
Loganic acid	Anti-inflammatory[76]
Caffeic acid	Antimutagenic[77], anti-hepatitis B virus[78], AChE activity inducer[79], anticancer[80], anti-inflammatory[81], antibacterial,[82] and antioxidant.[83]
Cantleyine	Spasmolytic[84]
p-hydroxybenzoic acid	Hypoglycemic,[85] antioxidant,[86] antidepressant,[87] antimicrobial,[88] and anticancer.[89]
p-hydroxyphenylacetic acid	Inhibit platelet monoamine oxidase[90]
Sungucine	Antimalarial,[91] and anticancer.[92]
Isosungucine	Antimalarial,[91] and anticancer.[93]
Lupeol	Hepatoprotective,[94] antiangiogenic,[95] cardioprotective,[96] antiarthritic,[97] wound healing,[98] antiurolithic,[99] nephroprotective,[100] gastroprotective,[101] antidiabetic, antioxidant,[102] antitumor,[103] antinociceptive,[104] **anti-acne,**[105] anti-inflammatory,[106] and anticancer.[107]
Nor-macusine B	Anti-hypertensive, and spasmolytic.[108]
Maltol	Antioxidant,[109] antitumor,[110] and neuroprotective.[111]
Secoxyloganin	Anti-allergic,[112] antibacterial,[113] and antioxidant.[114]
Uvaol	Cardiotonic, antidysrhythmic,[115] anti-inflammatory, antioxidant,[116] and vasodilatory.[117]
Rutin	Antioxidant,[118] anti-inflammatory,[119] anti-asthmatic,[120] and antinociceptive.[121]

analgesic activity in compared to the total alkaloidal fractions (TAF).[38] Strychnine possessed little antinociceptive property; however brucine and brucine N-oxide showed strong antinociceptive potential.[39] It has been also demonstrated that the transdermal absorption of brucine of MTAF was significantly higher than brucine alone, which might account somewhat for the higher antinociceptive potential of MTAF. Therefore, it has been postulated that antinociceptive potential of nux vomica seed extract might be due to a synergistic effect of low level strychnine with brucine and brucine N-oxide which might attributed by the inhibition of cyclooxygenase (COX) and monoamine oxidase activities.[38,39]

In a recent studies, oral administration hydro-methanolic leaves extract of nux vomica also showed promising dose dependent (100, 200 and 400 mg/kg) analgesic activity in various animal models and the extract dose of 400 mg/kg showed highest analgesic potential which was comparable to that of the standard analgesic drug, diclofenac (100 mg/kg).[27] This pharmacological activity of the leaves extract was due to the presence of strychnine, brucine, brucine N-oxide in association with analgesic flavonoid compounds. The postulated mechanisms of this activity might involve peripheral analgesic (inhibition of COX and/or lipoxygenases) and central analgesic (inhibition of central pain receptors) effects of these compounds.[27]

Anti-allergic

In folk medicine nux vomica has been used for alleviating inflammation, arthritis, joint pain and allergic symptoms. *In vivo* study demonstrated that the intraperitoneal administration of aqueous stem extract of nux vomica significantly suppressed the induction of ovalbumin (OVA)-specific IgE antibody response in different haplotypes of mice viz. BALB/C, C57BL/6 and SWR/J without any significant change in the total IgG antibody response against OVA.[40]

Anti-inflammatory

The seeds of nux vomica are used in various Ayurvedic and Unani formulations for the treatment of pain, inflammation and rheumatism. A number of different solvent extracts from different parts of S. nux vomica have shown anti-inflammatory activity in different test models. Mitra *et al.* reported the significant anti-inflammatory activity of raw and purified seed extract of this plant against formaldehyde induced hind paw edema in rats.[41] In a more recent study, the MTAF of nux vomica seeds extract with a low strychnine content showed 1.8 times higher anti-inflammatory potential than that of total alkaloid fraction (TAF) at the dosage of 1 mg/kg body weight against xylene-induced ear edema in rats.[38,42] Alkaloids of nux vomica seeds such strychnine, brucine and brucine N-oxide were reported as primary active compounds exhibited significant anti-inflammatory activity. Brucine and brucine N-oxide showed higher anti-inflammatory potential than that of strychnine; since brucine N-oxide was found to more active than that of brucine.[38,39] Both, brucine and brucine N-oxide were found to inhibit the release of prostaglandin E2 in inflammatory tissue, reduced acetic acid-induced vascular permeability and the content of 6-keto-PGF1a in blood plasma of Freund's complete adjuvant (FCA) induced arthritis rats. In addition, both compounds were also shown to reduce 5-hydroxytryptamine (5-HT), while increased 5-hydroxytryindole-3-acetic acid (5-HIAA) contents in blood plasma.[39] On the other hand, orally administered hydro-methanolic leaves extract (100, 200 and 400 mg/kg) was also showed dose dependent anti-inflammatory potential against carrageenan-induced paw edema in rats. In this acute inflammation model, the extract dose of 400 mg/kg showed maximal inhibitory effect against carrageenan-induced paw edema and the result was comparable to that of the reference drug, diclofenac (100 mg/kg).[27] In order to understand the mechanism of anti-inflammatory potential leaves extract, paw tissue exudates and plasma were analyzed and found that the leaves extract significantly lowered the high levels of prostaglandin E2 (PGE_2), TNF-α, malonaldhyde (MDA) with higher superoxide dismutase (SOD) content in paw tissue exudates with the reduction of elevated levels of PGE_2, TNF-α, IL-1β, and IL-6 in serum. It was suggested that these effects of leaves extract could be mediated through the inhibition of COX and subsequent inhibition of PGE2 synthesis.[27]

Antimicrobial

In disc diffusion and minimal inhibitory concentration (MIC) assay methods, the ethyl acetate extract of nux vomica bark was found to exhibit potent antimicrobial activity against both, gram positive (*Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus faecalis* and *Staphylococcus albus*) and gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes* and *Protieus vulgaris*), pathogenic bacterial strains.[20] Similarly, different extracts (such as hexane, chloroform, ethyl acetate and ethanol) of the leaves were also reported to possess different degree of growth inhibitory potential against *Shigella flexneri, P. mirabilis, P. vulgaris, Vibrio cholera*, *E. coli*, *P. aeruginosa*, *S. aureus*, *Salmonella typhimurium*, *K. pneumoniae* and *Enterobacter faecalis;* however the methanol extract was found to be most active against these pathogenic bacterial strains.[42-44] In a similar study, Gnanavel *et al.* reported that the n-butanol extract of leaves showed strong inhibitory potential against some pathogenic bacterial (*S. aureus*, *K. pneumonia*, *B. subtilis*) and fungal (*Aspergillus terreus*, *A. flavus* and *A. niger*) strains.[45] In another study, the methanolic extract of nux vomica flowers showed significant anti-microbial activity against both pathogenic bacterial and fungal strains viz. *P. aeruginosa*, *S. aureus*, *B. subtilis*, *K. pneumoniae* and *Candida albicans* in disc diffusion method.[36] It has been also reported that the nux vomica dilution 200C showed strong antiviral potential against Chicken Embryo Virus of fowls.[46]

Anticancer

A preliminary *in vitro* screening study by Eldahshan and Abdel-Daim revealed that the methanolic leaves extract of nux vomica exhibited potent anti-proliferative activity against human epidermoid larynx, breast and colon carcinoma cells with IC50 value of 17.8, 36.3 and 41.2 µg/ml, respectively.[27] Angiogenesis is an important step of cancer development. It has been found that the methanol extract of nux vomica leaves (5-20 µg/ml) showed significant dose dependent anti-angiogenic potential in a chick chorioallantoic membrane assay model.[47] The aqueous extract of nux vomica roots have also been showed dose and time dependent anti-proliferative activity against human multiple myeloma cell lines with IC50 value of 11 mg/ml. This finding indicated that the root extract induced apoptosis of myeloma cells in addition with the disruption of mitochondrial membrane potential and subsequent leakage of mitochondrial cytochrome c and these effects were likely caused by strychnine and brucine.[48,49] Besides, the studies with TAF and MTAF of nux vomica seeds extract showed potent anticancer potential against variety of human carcinoma cells such as hepatoma (HepG2; IC50 70.71 and 38.58 µg/ml, respectively), gastric (MGC-803; IC50 77.62 and 40.20 µg/ml, respectively), lung (A549; IC50 80.02 and 76.52 µg/ml, respectively), colon (LoVo; IC50 14.89 and 6.57 µg/ml, respectively) and ovarian (A2780; IC50 32.79 and 15.67 µg/ml, respectively) cancer cells.[50] However, MTAF exhibited higher anticancer potential than that of TAF.

Several biologically active alkaloids such as strychnine, brucine, *β*-colubrine, strychnine N-oxide, brucine N-oxide, 2-hydroxy-3-methoxystrychnine, isostrychnine, isostrychnine N-oxide, isobrucine, isobrucine N-oxide, pseudostrychnine, and icajine have been isolated from nux vomica and were showed different degree of inhibitory effects against various cancer cell lines.[51,52] Among these alkaloids, brucine has been studied extensively for its anticancer potential. *In vivo* and *in vitro* studies showed that the brucine suppressed VEGF-induced tumor angiogenesis via inhibiting VEGFR2 signaling pathway.[53,54] In addition, brucine showed strong anticancer activity against various human carcinoma cells through caspase dependent apoptotic programmed cell death which was characterized by the formation of apoptotic bodies, DNA fragmentation, cell cycle arrest, phosphatidylserine externalization, caspase-3 activation, elevation of intracellular Ca2+ and suppression of Bcl-2 protein overexpression.[55-57] Studies also demonstrated that the brucine inhibited the migration of hepatocellular carcinoma and lung metastasis via hypoxia inducible factor 1 (HIF-1) pathway.[58]

Antipyretic

Antipyretic activity of nux vomica leaves extract against yeast induced pyrexia in rats was studied by Eldahshan and Abdel-Daim.[27] The methanolic leaves extract showed dose dependent antipyretic activity; however higher dose of extract (400 mg/kg) showed comparable efficacy as compare to the standard drug, paracetamol (150 mg/kg).[27]

Gastroprotective

In Ayurvedic as well as in homeopathic medicines various forms of nux vomica seeds extract are often clinically used as important remedy for gastritis, gastric ulcers, atony and relaxation of the stomach and bowels. Recent investigation with highly diluted form of nux vomica seeds extract (10c) prepared in ethanol was found to reduce *Helicobacter pylori* induced up-regulation of HB-EGF gene expression in KATO-III cells even in dilutions beyond Avogadro's number.[59]

Antidiabetic

Seeds of nux vomica are traditionally used to treat various disorders including diabetes. Recently, it has been found that the oral administration of ethanolic (50%) and aqueous extracts (3.6 mg/kg) of nux vomica seeds showed significant hypoglycemic potential in alloxan-induced diabetic rats. Effective and significant results for both extracts were observed in reducing the blood glucose level and the results were comparable with that of standard (gliclazide, 10 mg/kg).[7] In a similar study, the methanolic seed extract of nux vomica also reduced the blood glucose level in addition with the reduction of serum levels of total protein, cholesterol, creatinine and blood urea nitrogen (BUN) in alloxan induced diabetic rats.[33] Besides, the methanol extract of nux vomica leaves also exhibited dose dependent antidiabetic potential via inhibition α-amylase activity and non-enzymatic glycosylation of haemoglobin.[34]

Neuropharmacological

Nux vomica crude extract rarely used in clinical practice, as such due to the high content of strychnine, but still it widely used in the alternative medicine system after processing. Studies showed that the sub-convulsive dose of processed seed extract (125 mg/kg) significantly inhibited the pentylenetetrazole-induced convulsions and potentiated barbiturate induced hypnosis in animals and the facts are indicative of CNS depressant action of processed seed extract of nux vomica. It was also seen that processed seed extract antagonized the morphine-induced catalepsy in rats which may justify the clinical use of nux vomica in muscular rigidity.[60] Further, the brucine was found to allosteric enhancers of acetylcholine binding to the muscarinic 1 receptor by 2-fold.[61] Therefore, it was postulated that nux vomica seeds extract might useful in the development of drugs for the treatment of various neurological disorders such as Parkinson's and Alzheimer's diseases.

Anti-snake Venom

Anti-snake venom potential of nux vomica seeds extract was evaluated by Chatterjee *et al.*[62] In low doses, nux vomica seeds extract was found to effectively neutralized Daboia russelii venom induced lethal, haemorrhage, defibrinogenation, phospholipase A2 (PLA2) enzyme activity and Naja kaouthia venom induced lethal, cardiotoxicity, neurotoxicity, PLA2 enzyme activity.[62]

Antialcoholic

Different dilutions (30C, 200C and 1000C) of nux vomica were reported to exhibit antialcoholic effect in mice. Administration of all three potencies of nux vomica restored ethanol-induced loss of righting

reflex in mice more quickly than the controls.[63] Despite, other *In vivo* studies on toads and mice revealed that the nux vomica dilution 30C and 200C significantly reduced ethanol induced sleep time.[64-66]

CLINICAL STUDIES

Effect on rhinitis

In an open, multicenter clinical trial in children with acute rhinitis has demonstrated the usefulness of homeopathic nux vomica dilution (potency) in the treatment of acute rhinitis. The nux vomica 6C dilution was applied in 109 children with acute rhinitis. Among them, 79.82% of children were completely cured and 14.68% of children were remarkably improved, while 5.50% of children improved moderately within 7 days of trail period.[122] However, controlled studies are needed to investigate the effectiveness nux vomica dilution.

Effect on sinusitis

An open, multi-center, observational study was carried out to determine effectiveness of nux vomica dilutions (potencies) in acute and/or chronic, frontal, fronto-maxillary, sphenoidal, ethmoidal and maxillary sinusitis. Nux vomica 30C, 200C and 1000C dilutions were applied on 16 different sinusitis cases and these dilutions were found to be useful in 14 different sinusitis patients in relieving sinusitis indications.[123]

Effect on insomnia

The high dilutions of nux vomica extract are known to be clinically useful for the treatment of insomnia. A clinical study on 10 human subjects showed that the nux vomica dilutions (3C and 15C) significantly lowered the serum cortisol levels in 38% patients.[124] However, the study was performed on too small number of subjects to conclude the clinical efficacy of nux vomica dilutions. Therefore, further studies on statistically significant numbers of patients are required to prove the efficacy of nux vomica dilutions in chronic insomnia.

TOXICITY

Nux vomica is a poisonous plant due to the presence of toxic alkaloids, strychnine and brucine. Both compounds are neurotoxic and competitive antagonists of the glycine receptors on postsynaptic membrane in the spinal cord, brain stem, and higher centers.[125] It was found that the lethal doses of strychnine induce convulsions of the central nervous system and death through respiratory or spinal paralysis or cardiac arrest.[126] However, the general symptoms of strychnine poisoning with low or moderate doses are including agitation, restlessness, abnormal eye movements, photophobia, stiff joints, myalgia, dark urine and painful muscle spasms.[125] Strychnine and brucine can also directly damage the epithelia of renal tubules and hepatic microsomal enzymes that lead to the acute renal failure, uremia and liver injury.[125] Through brucine is a weaker alkaloid; however its lethal concentration causes life threatening complications like rhabdomyolysis and acute renal failure.[127] The lethal dose of strychnine and brucine was found to be 30-120 and 1000 mg for an adult individual.[128] *In vivo* toxicity studies in quail and ducks produced various typical signs of strychnine poisoning such as ataxia, muscle spasms, balance loss, wing-beat convulsions and tremors and the lethal concentrations (LC_{50}) of strychnine were found to be 4.974 and 0.680 mg/g per body weight in quail and duck, respectively.[129] LD_{50} oral doses of strychnine and brucine were found to be 2.0 and 150 mg/kg body weight in mice.[130,131]

CONCLUSION AND FUTURE PERSPECTIVES

This review describes a comprehensive summary on traditional uses, phytochemistry, pharmacology, and toxicity of nux vomica. It has long been used in Traditional Chinese Medicines (TCM) and in traditional Indian systems of medicine like Ayurveda, Unani and Homeopathy for the treatment of various diseases most notably in inflammation, jaundice, urinary disorders, dyspepsia, dysentery, epilepsy, rheumatism, insomnia, paralytic, and neuralgic affections. It has been used in various herbal and homeopathic formulations that are used clinically against various ailments. Seeds and leaves of nux vomica are mainly exploited for pharmacological research; however other parts such as bark, flowers and stems need to be investigated for effective utilization of nux vomica. A close scrutiny of literatures infers that various types of preparations, extracts, and individual compounds derived from different parts of nux vomica have been found to possess a number of pharmacological activities e.g., hepatoprotective, antioxidant, antinociceptive, anti-allergic, anti-inflammatory, antimicrobial, anticancer, antipyretic, gastroprotective, antidiabetic, neuropharmacological and anti-snake venom properties. In this context, no clinical trials have been done so far on nux vomica. Therefore, well-controlled, double-blind clinical trials on nux vomica using a statistically significant number of patients are mandatory in order to validate pre-clinical data and traditional knowledge in the light of a rational phytotherapy. Few preliminary pharmacological activities of nux vomica such as antidiabetic, gastroprotective, antipyretic, antimicrobial, anti-allergic, antioxidant and hepatoprotective need to be investigated further to determine the active constituent(s) and mode of actions involved in each activity. Despite, pre-clinical evidence for antirheumatic, antidiarrheal, antiulcer, anticonvulsant, antileprotic, antianxiety and antidyspeptic actions is not yet available, while this is essential to validate the ethno pharmacological data.

To date, more than 90 chemical compounds have been isolated from different parts of nux vomica and some active compounds exhibit various pharmacological effects such as anticancer, analgesic, anti-inflammatory, antimicrobial, antioxidant, neuroprotective, hepatoprotective, antidepressant, vasodilatory, spasmolytic, and so on. However, the strychnine and brucine

were found to be the major active principles, responsible for its therapeutic potential and toxicity. As nux vomica is categorized as potential toxic plant, much attention should be required to reduce its toxic effects using appropriate and validated detoxification techniques. Pharmacological studies on processed extract of nux vomica (detoxified) exhibited greater efficacy with low toxicity than unprocessed extract. However, further research should be designed to determine safe and effective dose ceiling limit of processed extract for its therapeutic properties.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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