ABSTRACT

Anamirta Cocculus (Linn.) belongs to the family Menispermaceae is commonly known as fish berry or crow killer, also known as Garalaphala in Sanskrit and kakamari in Hindi. The plant is well known for producing poisonous seeds. Anamirta Cocculus is found in Southeast Asian and Indian subcontinent. This wild medicine is being exploited by human beings for several purposes including medication, hunting and fishing. In traditional Ayurvedic system of medicine in India, Anamirta Cocculus (Linn.) has been used as a (Rasayan) drug in vitiated condition of vata and kapha. This plant is also used in the treatment of bronchitis, chronic skin diseases, foul ulcers, dermatophytosis, phthisis, inflammation, vertigo, flatulence, nocturnal epilepsy, chorea, paralysis of pharynx, leg and respiratory center etc. It has also been suggested to possess anti inflammatory, antifungal, anthelmintic antioxidant, antimicrobial, insecticidal, germicidal, CNS actions, a nervine tonic and a best antidote to morphine poisoning. The Phytochemical screening of this plant has shown the presence of alkaloids, steroids, phenolic terpenoids, fixed oils, carbohydrates and proteins. The active constituents like picrotoxinin, picrotin, menispermine, paramenispermine etc., present in Anamirta Cocculus (Linn.) have been found to be responsible for the therapeutic potentials. Isolation of anticancer constituents from this plant was also reported newly and moreover, the most useful and immense medicinal values that require more exploration in all the pharmaceutical aspect.

Keywords: Ethnobotany; menispermaceae; pharmacology; phytochemistry.

INTRODUCTION

Anamirta Cocculus L. is commonly known as fish berry or crow killer. It is a wild woody climber producing poisonous seeds, found in Southeast Asian and Indian subcontinent and belongs to the family Menispermaceae. This wild medicine is being exploited by human beings for several purposes including hunting and fishing (Kirtikar K R et al., 1991). The dried berries of A. cocculus have been used in India to stupefy fish (Drury H, 1973) and are reported to contain picrotoxin (Agarwal SK et al., 1999). This plant is distributed throughout India in dense forests (Orient longmanm, 1996).

BOTANICAL DESCRIPTION (James A Duke et al., 2002)

Botanical Source and History
The seeds furnishing this body are known as Cocculus indicus (Fructus cocculi), Fish berries or Indian berries. The plant furnishing them is a strong, climbing shrub, with a corky, ash-colored bark, with deep cracks or fissures. The leaves are dense, smooth, shining, coriaceous, roundish, acute, very slightly cordate, if at all, sometimes truncate at the base, with 5 digitate ribs, about 6 inches long, and as many broad. The stalks are a little shorter than the leaves, tumid at both ends, especially the lower. Flowers dioecious, the female flowers being in lateral compound racemes. The calyx is composed of 6 sepals in a double series, with 2 closely-pressed bractioles. The stamens are united into a central column dilated at the apex. The stamens are united into a central column dilated at the apex. The stamens are united into a central column dilated at the apex. The stamens are united into a central column dilated at the apex. The stamens are united into a central column dilated at the apex.
and 1-seeded. The seed is globose and deeply excava-
ted at the hilum. Albumen fleshy, cotyledons very thin, linear-oblong, distant, diverging, and very mem-
branous (L.—W.—A.). The plant is large-stemmed (up
to 10 cm in diameter); the bark is "corky gray" with
white wood. The "small, yellowish-white, sweet-
scented" flowers vary between 6 to 10 centimeters
across; the fruit produced is a drupe, "about 1 cm in
diameter when dry". The Fruit (Fructus cocculi).—The
fruit, as met with in commerce, consists of a dry, light,
roundish nut, nearly 1/2 inch in diameter, of a grayish-
black color, wrinkled, inodorous, subreniform, and
composed of an external, slightly bitter shell or layer,
beneath which is a white, thin, ligneous endocarp,
containing an oleaginous, whitish-yellow, odorless, but
intensely bitter nucleus or seed of a semilunar form,
within which arises a central placenta contracted at the
base, but enlarged and divided into two cells superior-
ly.

TRADITIONAL/ FOLKLORIC USES

Cocculus indicus is occasionally given internally, though
very poisonous. Given to animals it acts on the cere-
bro-spinal system, causing giddiness, staggering, tetan-
ic convulsions, and coma. It also produces gastric irri-
tation. The powder, or an ointment, has been applied in
barber’s itch, scald-head, itch, and other unyielding
diseases of the skin, as well as to kill lice. Given to fish,
it poisons them, depriving them of sensibility, and has
been used for the purpose of catching them. Extraor-
dinary claims have been made by planat for cocculus,
as an agent in spasmodic disorders, including epilepsy,
infantile convulsions, chorea, etc. Others, however,
claim that it aggravates epilepsy. It has likewise been
employed in paralysis of the sphincters and limbs. By
some physicians, cocculus and picrotoxin, in minute
doses, are recommended in disorders for which strychnine
and nuxvomica are employed. It is also an
antagonist to these drugs, and may be used in cases of
poisoning by them. Nervous debility, paresis, mild
forms of paralysis, facial paralysis, paralysis agitans,
and alcoholic tremor are conditions in which minute
doses have rendered good service. Spasms of the mus-
cles of locomotion, with cold skin and deficient capil-
larary circulation, are said to be benefited by cocculus. It
has also been advised in gastric atony and intestinal
dyspepsia, with torpor of the parts involved. It was
reported that 2-grain doses of the 3 x titration as a
certain remedy for profuse sweating. It has been en-
dorsed by others as exceedingly efficient in night-
sweats, the above doses being given every 2 hours, in
the evening, for 3 or 4 days. An attenuation of co-
cculus, as employed by Homoeopaths, is an efficient re-
medy to prevent the nausea and sickness incident to
travel by rail and upon water (sea-sickness). The dose
of picrotoxin ranges from 1/150 to 1/64 grain (M L
Mayer, D W Straughan 1881). Seeds of A. cocculus are
being exploited by human beings for several purposes
including hunting and fishing .The dried berries of A.
cocculus have been used in India to stupefy fish (N Jo-
and Arn., Menispermaceae, used in Breast cancer and
mastitis (Eat 1 cup fruit/day, better if fresh, collected in
summer, Picked by herbalist) (Evan Mati and Hugo de
Boe, 2011). Anamirta Cocculus Seeds used in treating
scabies and epilepsy (Alluri V Krishnaraju, 2006). In
India, the leaves are inhaled as a snuff to relieve mala-
ria, and the leaf juice is used in combination with other
natural products as a vermifuge. Extracts of the plant
are applied topically for lice, but the toxic nature of the
components (in particular picrotoxin) make this a dan-
gerous use, especially when the skin is abraded or irri-
tated. Although picrotoxin had been considered an
official remedy for epilepsy at the turn of the century
in the United States, It had found use as a stimulant for
the management of morphine poisoning (Morton JF,
1977). In Traditional African Medicine a drug like mole-
cule picrotoxin obtained from a poisonous plant Ana-
mirta Cocculus (Fam. Menispermaceae) has a historical
background of being a fish poison (David T Okpako,
1999). An herbal supplement Fish berry (Anamirta coc-
culus) is used to treat eye disease (Nystagmus) (Frede-
rick W and Fraunfelder MD, 2004). It is also used by
traditional siddha healers in treating ailments of wom-
en and hemorrhoids (S Mutheeswaran et al., 2011).
Experiments based on ethnobotanical practices has
shown that the plant itself to be effective in treating
ringworm. Its crushed seeds are an effective pediculi-
cide (anti-lice) and are also traditionally used to stun or
kill fish or as a pesticide (James A Duke, 1983).

PHYTOCHEMICAL

The fruit contains the nontoxic alkaloids menispermine
and paramenispermine (Morton JF, 1977). Four qua-
ternary alkaloids berberin, palmatin, magnoflorin, co-
lumbamine and one tertiary alkaloid (-) – 8 – oxotetra-
hydropalmatine have been isolated from the stem and
root of the plant. Oxypalmatin and stepharine have
been isolated in addition to (-) – 8 – oxotetrahydro-
palmatine in an investigation of the non quaternary
alkaloidal fraction of Anamirta Cocculus (U L B Jaya
singhe et al., 1992). The husk of cocculus grains also
contains two isomeric, non-poisonous, non-bitter, crys-
tallizable alkaloids—menispermine and para-
menispermine (C_{34}H_{32}N_{2}O_{5}, Pelletier and Couerbe,
1834). The former is soluble in ether, the latter inso-
luble. Both are insoluble in water, but soluble in warm
alcohol. Menispermine is also soluble in diluted acids,
forming well-crystallizable salts; it melts at 120°C (248°
F). The husk also contains a yellow resin, fat, wax, chlo-
rophyll, and the hyp-picrotoxic acid, insoluble in boil-
ing water and ether, readily soluble in alkanes with
brown color. The seeds, or nuclei, of cocculus contain
resin, gum, starch, and large amounts of fat (23.6 per
cent), free fatty acid, principally stearic acid. The seeds
also contain the very poisonous, bitter principle, picro-
toxin (C_{39}H_{52}O_{13}) and picrotoxic acid. It is accompani-
ied by the crystallizable, tasteless cocculin or anamirtin

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(C₁₅H₁₅O₁₆), crystallizable from hot water, insoluble in alcohol and ether. The chemical composition of picrotoxin was reported to be of formula C₂₃H₃₄O₁₃. Barth and Kretschy (1884) asserted that it is not a uniform body, being a mixture of the poisonous picrotoxin (C₁₅H₁₅O₆) and the bitter, non-poisonous picrotin, separation being effected by boiling with benzol, in which picrotoxin is soluble, picrotin very little soluble. Schmidt and Loewenhardt, reported that that picrotoxin is a definite body, gets decomposed by boiling in benzol into the constituents named, as follows: C₂₃H₃₄O₁₃ (picrotoxin) = C₁₅H₁₅O₆ (picrotoxinin) + C₇H₇O₇ (picrotin). Quite recently, Richard Joseph Meyer succeeded in obtaining picrotoxin, with all its characteristics synthetically, by the mere crystallization of a mixture of 2 molecules of picrotoxinin and 1 molecule of picrotin, and concludes that picrotoxin is a mixture of picrotoxinin (C₁₅H₁₅O₆+H₂O) and picrotin (C₁₅H₁₅O₇) in the approximate proportion of 2 molecules of the former and 1 molecule of the latter. He has also shown that the molecular weight of picrotoxin, as determined by the kryoscopic method, is only one-third of that represented by the formula C₃₀H₃₄O₁₃; that the above decomposition is not equimolecular, but picrotin invariably forms only one-third of the picrotoxin employed.

Three known sesquiterpene lactones\ picrotoxinin, methyl picrotoxate, and picrotin as well as two new sesquiterpene lactones\ dihydroxy picrotoxinin and picrotoxic acid were isolated and characterized from the seeds of A. cocculus (Santosh K Agarwal et al., 1999).

One new triterpenoid, 2α, 3β, 23 - trihydroxy-11α, 12α- epoxyolean-28, 13β - olide and two new triterpenoid glycosides, β- d- glucopyranosyl -2β, 3β, 23 - trihydroxyolean- 12- en- 28- oate and 2α, 3α, 3β - dihydroxy- 23- β- d- glucopiranoyloxylolan- 12- en- 28- oic acid, are reported from the stem of Anamirta Cocculus (Jayasinghe et al., 1983). Isolation of 2α, 3β, 23- trihydroxyolean- 12- en- 28- oic acid (arjunolic acid) and its 28-O-β- d-glucopyranoside are also reported (J.E. Jablonski and L.S. Jackson, 2008). Phenolic compounds identified in Anamirta Cocculus (L.) Wight and Arn. are Phenolic terpenoids and phenolic acids. The representative components are Sesquiterpenes (picrotoxin derivatives), triterpenoids, alkaloids (berberine, magnoflorine) (Siddharthan Surveswaran et al., 2007). Based on computer models, similarities in the three-dimensional shape and charge distribution of active convulsant derivatives of the anisatin and picrotoxinin type are shown which results in the proposal of a common pharmacophore structure for these two structurally different classes of sesquiterpenes (Thomas J Schmidta et al., 1999).

**Description and Tests.** —Picrotoxin is officially described as forming "colorless, flexible, shining, prismatic crystals, or a micro-crystalline powder; odorless, and having a very bitter taste; permanent in the air. Soluble, at 15° C. (59° F.), in 240 parts of water, and in 9 parts of alcohol; in 25 parts of boiling water, and in 3 parts of boiling alcohol; also soluble in solutions of the alkalies, and in acids. Very slightly soluble in ether or chloroform"—(U.S.P.). It is also soluble in amyl alcohol and glacial acetic acid. "Picrotoxin is neutral to litmus paper. When heated to 200°C. (392° F.), picrotoxin melts, forming a yellow liquid, and upon ignition it is consumed, leaving no residue. Concentrated sulphuric acid dissolves picrotoxin with a golden-yellow color, very gradually changing to reddish-brown, and showing a brown fluorescence. On mixing about 0.2 gm. of powdered sodium nitrate with 3 or 4 drops of sulphuric acid, in a small, flat-bottomed capsule, sprinkling a minute quantity of picrotoxin over it, and then adding, from a pipette, concentrated solution (1 in 4) of sodium hydrate, drop by drop, until it is in excess, the particles of picrotoxin will acquire a brick-red to deep-red color, which fades after some hours. On diluting 2 Cc. of alkaline cupric tartrate V.S. with 10 Cc. of water, and adding a small portion of picrotoxin, red cuprous oxide will be separated within half an hour at ordinary

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**Figure 1:** Sesquiterpene lactones isolated from the seeds of A. Cocculus: Picrotoxinin (1), methyl picrotoxate (2), picrotin (3), dihydroxy picrotoxinin (4), picrotoxic acid (5)

**Figure 2:** Molecular models of anisatin (top) and picrotoxinin (bottom) showing the arrangement of the molecular skeletons. Yellow ellipsoids mark areas of high similarity that are likely to determine binding to a common receptor site.
temperatures, and much more rapidly upon the application of heat. The aqueous solution of picrotoxin should remain unaffected by mercuric or platinic chloride T.S., tannic acid T.S., mercuric potassium iodide T.S., or other reagents for alkaloids (absence of alkaloids)—(U S. P.) (Harvey Wickes, 1989).

PHARMACOLOGICAL

Picrotoxin when applied on visual cortex neurons was reported to block the inhibitory effect of 5-HT on it. Picrotoxin continues to find use in experimental models of central nervous system stimulation, but its use in medicine has largely been abandoned in the United States and Europe. Stepharin alkaloid was reported to possess moderate spermicidal activity. Picrotoxin isolated from Anamirta Cocculus was reported to inhibit GABA actions. The agent, picrotoxin, was used to test whether or not the deeper neurons are spared the effects of topical convulsants simply because of their location. Picrotoxin, injected intravenously, produced enhancement of the corticofugal reflex discharge evoked by stimulation of any of the four paws and by auditory stimulation. The surface-recorded primary evoked response was also enhanced but only slightly, far less than with topical application. The evoked response in the medial lemniscus was not altered by picrotoxin, but that in the thalamic radiations was enhanced. Single-cell recordings in other laboratories have shown that intravenous picrotoxin converts small-field cells to wide-field cells (M D Mann, 1987). Pharmacophore of picrotoxin was reported using Anisatin which has been demonstrated to possess a mechanism of action identical with that of picrotoxinin, a similarly toxic (LD50 at 3 mg/kg, mouse, i.p.) convulsant sesquiterpene lactone of a different skeletal class isolated from seeds of Anamirta Cocculus (Fish berry plant) and further related Menispermaceae. The mechanism of action by which picrotoxin exerts its convulsant activity has been studied in detail. It was shown to be a non-competitive allosteric inhibitor at GABA-receptor coupled chloride ionophores that mediate postsynaptic inhibition in the CNS of many different classes of organisms. It was found to bind to a specific site which is distinct from the GABA-receptor itself and from the benzodiazepine binding site, which is located inside the chloride channel pore. Here, binding of picrotoxin leads to a decrease in GABA-induced CI⁻ influx that normally causes a hyperpolarization at the postsynaptic neuron thus modulating the intensity of excitatory impulses. Repression of this inhibitory mechanism by picrotoxin results in an overflow of excitatory neuronal impulses and, consequently, in lethal convulsions. Anisatin, has been demonstrated to act by the same mechanism of action as picrotoxinin and experimental evidence indicates that it may bind to the same site at the channel protein (Thomas J Schmidt, 1999). Picrotoxin is reported to be a proconvulsant drug, acting as an antagonist on the GABA-benzodiazepine receptor complex (B Skeie, 1992). Pharmacology of a chemiconvulsant picrotoxin is investigated in a model of planaria (Latha Ramakrishnana et al., 2011). Picrotoxin in doses of 0.3 to 0.6 mg has been used to manage epilepsy and in slightly higher doses to manage night sweating. The effects of picrotoxin, have been studied in conscious chicks and on the flexor, crossed extensor, and patellar reflexes of anaesthetised and spinal chicks. The results obtained were similar to those obtained in mammalian species and show that the chick provides a useful preparation for studying the effects of centrally-acting drugs (Gabriel Osuide, 1968). Picrotoxin was reported to cause myoclonic jerking of the opposite forelimb when applied to the striatum and the cortical surface of rat brain. Intrastraiatal microinjection increased [3H]2-deoxyglucose uptake by the ipsilateral frontal cortex, thalamus and subthalamic nucleus (S Patel and P Slatera, 1987). Injections of small doses of picrotoxin into the lateral cerebral ventricles of rabbits was reported to induce a rise in blood pressure and cardiac arrhythmias (bradycardia, tachycardia, extrasystoles, ventricular fibrillation) (D R Varma, 1962). Intravitreal administration of picrotoxin into the closed eye was reported to abolish the directional asymmetry of head and eye OKN, indicating the involvement of GABAergic mechanisms in the inhibition of the N-T component of the monocular eye and head OKN (Y H Yücel et al., 1990). The unilateral injection of picrotoxin into the subpallidal region was reported to produce a significant increase in locomotor activity (S M Brudzynski et al., 1996). Picrotoxin microinjections into the dorsal motor nucleus of the vagus nerve was reported to produce increase in gastric circular muscle activity, gastric motility, gastric secretion (Robert J Washabau et al., 1995). Picrotoxin was reported to be a powerful CNS stimulant, the DE50 for the convulsant effect of PIC in mice was found to be near 5.5 mg/kg. After administering picrotoxin (PIC) (0.3 mg/kg) animals exposed to open space produced fear-induced anxiety during memory retrieval, whereas the exposition to enclosed ones develop fear-induced avoidance behavior (Mariano G Blake et al., 2008). The DE50 and 2B2 proteins in the liver microsomes (hepatic drug metabolizing enzymes) were reported to be increased by picrotoxin. Picrotoxinin and picrotin, (components of the picrotoxin molecule) had the same ability to induce the hepatic activity of benzphetamine N-demethylation (Yamada Hydeyuki et al., 1983). Picrotoxin was reported to reduced the depolarizing effects of L-glutamic acid and GABA on dorsal roots, and depressed dorsal root reflexes (A K Tébecica et al., 1969). The aq. extract of Anamirta Cocculus plant has been reported to posses Heinz body inhibition and antioxidant activity (Attakorn Palasuwan et al., 2005). Picrotoxin was reported to be used as a prophylactic measure to protect the respiratory center from
untoward or undue assault by the barbiturate. (A H Maloney, 1936).

CONCLUSION
From the foregoing accounts it is evident that the plant *Anamirta Cocculus L.* has been Ethno-medicinally used as a valuable therapeutic agent for a variety of diseases, as we have illustrated in this article. Moreover, numerous research works have proven its uses beyond the ethno-medicinal ones in experimental animals. Various compounds which were isolated from this plant may be responsible for its pharmacological activities. Being useful and of immense medicinal values it require more exploration in every pharmaceutical aspect. So it needs further research towards the development of safe and suitable medications. The road ahead is to establish specific bioactive molecules, which might be responsible for these pharmacological action.

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