

Natural Agents Affecting Excitatory and Inhibitory Neurotransmission:

Adenosine receptor antagonism:

- Caffeine (*Coffea* spp/Coffee)

Primary GABA inhibition:

- Anisatin (Japanese star anise/*Illicium anisatum*)
 - non-competitive GABA (channel) inhibition^{1,2}
- Bicuculline (*Dicentra cucullaria*/Dutchman's breeches)
 - competitive inhibition GABA site
 - (and probably non-competitive via allosteric change)³
- *Cicuta maculata* (Water Hemlock) & *Cicuta Virosa* (*Cowbane* or Northern Water Hemlock)
 - Cicutoxin- GABA +/- ***inhibition potassium channels***^{4,5}
 - Virol A: non-competitive with GABA binding site, but does produce competitive GABA channel (chloride) inhibition
 - structurally similar to cicutoxin⁶
- Colchicine (*Colchicum autumnale*/autumn crocus)
 - competitive antagonist⁷
- *Oenanthe fistulosa* (Water Dropwort) [Toxin]
 - probably competitive inhibition of GABA Chloride channel (dose dependent blockade)
 - **structure similar to cicutoxin**
 - from island of Sardinia; ? glycine antagonism- risus sardonicus⁸
- Picrotoxin (*Anamirta cocculus*/Fishberries)
 - non-competitive inhibition⁹

¹ Rietjens IM, Martena MJ, Boersma MG, et al. Molecular mechanisms of toxicity of important food-borne phytotoxins. *Molecular mechanisms of toxicity of important food-borne phytotoxins. Mol Nutr Food Res.* 2005 Feb;49(2):131-58. PMID: 15635687

² Perret C, Tabin R, Marcoz JP et al. [Apparent life-threatening event in infants: think about star anise intoxication!]. [Article in French] *Arch Pediatr.* 2011 Jul;18(7):750-3. doi: 10.1016/j.arcped.2011.03.024.

³ Ueno S, Bracamontes J, Zorumski C, et al. Bicuculline and gabazine are allosteric inhibitors of channel opening of the GABAA receptor. *J Neurosci.* 1997 Jan 15;17(2):625-34. PMID: 8987785

⁴ Schep LJ, Slaughter RJ, Becket G, Beasley DM. Poisoning due to water hemlock. *Clin Toxicol (Phila).* 2009 Apr;47(4):270-8. doi: 10.1080/15563650902904332.

⁵ Strauss U, Wittstock U, Schubert R et al. Cicutoxin from *Cicuta virosa*--a new and potent potassium channel blocker in T lymphocytes. *Biochem Biophys Res Commun.* 1996 Feb 15;219(2):332-6.

⁶ Uwai K, Ohashi K, Takaya Y, et al. Virol A, a toxic trans-polyacetylenic alcohol of *Cicuta virosa*, selectively inhibits the GABA-induced Cl(-) current in acutely dissociated rat hippocampal CA1 neurons. *Brain Res.* 2001 Jan 19;889(1-2):174-80. PMID: 11166701

⁷ Weiner JL, Buhler AV, Whatley VJ, Harris RA, Dunwiddie TV. Colchicine is a competitive antagonist at human recombinant gamma-aminobutyric acidA receptors. *J Pharmacol Exp Ther.* 1998 Jan;284(1):95-102. PMID: 9435166

⁸ Appendino G, Pollastro F, Verotta L et al. Polyacetylenes from sardinian *Oenanthe fistulosa*: a molecular clue to risus sardonius. *J Nat Prod.* 2009 May 22;72(5):962-5. doi: 10.1021/np8007717. PMID: 19245244

- ? Also affects glycine receptors
- Thujone (*Artemisia absinthium*/Wormwood)¹⁰
 - non-competitive- see Olsen 2006
- PCN/Quinolone Abx*

Glutamate agonism:

- β -N-oxalylamino-L-alanine (BOAA) (*Lathyrus Sativa*/Chickling Pea)
- Domoic Acid (*Pseudo-nitzschia australis* [Amnestic Shellfish Poisoning])¹¹
 - Kainic/glumatic acid analog
 - Amnestic Shellfish Poisoning¹²
 - Due to contaminated mussels Eastern Rivers PEI, 1987
 - Deaths of > 400 Sea Lions off CA coast 1998¹³
 - Linked to bloom *Pseudo-nitzschia australis* (diatom) Monterey Bay
- Ibotenic Acid (*Amanita Muscaria*/Fly Agaric)
- Kainic Acid (*Digenea simplex* [seaweed only found in South China Sea])
 - Glutamate analog¹⁴
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Glutamic Acid Decarboxylase Inhibition:

- Cyanide (Various spp. containing cyanogenic glycosides)¹⁵
- Domoic Acid/*Pseudo-nitzschia australis* [Amnestic Shellfish Poisoning]
 - see section on Glutamate Agonism
- Gyromitrin (*Gyromitra Esculenta*/False Morel)
 - Also inhibits pyridoxine kinase
- Kainic Acid (*Digenea simplex* [seaweed only found in South China Sea])
 - Glutamate analog

Glycine receptor antagonism

- Strychnine (*Strychnos Nux Vomica*)*
- *Oenanthe fistulosa*/Water Dropwort [Toxin]

⁹ Olsen RW. Picrotoxin-like channel blockers of GABAA receptors. Proc Natl Acad Sci U S A. 2006 Apr 18;103(16):6081-2. PMID: 16606858

¹⁰ Rietjens IM, Martena MJ, Boersma MG, et al. Molecular mechanisms of toxicity of important food-borne phytotoxins. Molecular mechanisms of toxicity of important food-borne phytotoxins. Mol Nutr Food Res. 2005 Feb;49(2):131-58. PMID: 15635687

¹¹ Stewart GR, Zorumski CF, Price MT, Olney JW. Domoic acid: a dementia-inducing excitotoxic food poison with kainic acid receptor specificity. Exp Neurol. 1990 Oct;110(1):127-38. PMID: 2170163

¹² Teitelbaum JS, Zatorre RJ, Carpenter S et al. Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. N Engl J Med. 1990 Jun 21;322(25):1781-7. PMID: 1971710

¹³ Scholin CA, Gulland F, Doucette GJ et al. Mortality of sea lions along the central California coast linked to a toxic diatom bloom. Nature. 2000 Jan 6;403(6765):80-4. PMID: 10638756

¹⁴ Ding R, Asada H, Obata K. Changes in extracellular glutamate and GABA levels in the hippocampal CA3 and CA1 areas and the induction of glutamic acid decarboxylase-67 in dentate granule cells of rats treated with kainic acid. Brain Res. 1998 Jul 27;800(1):105-13.

¹⁵ Cassel G, Karlsson L, Sellström A. On the inhibition of glutamic acid decarboxylase and gamma-aminobutyric acid transaminase by sodium cyanide. Pharmacol Toxicol. 1991 Oct;69(4):238-41. PMID: 1956876

- similar mechanism to strychnine- from island of Sardinia¹⁶
- Tranexamic acid (not natural)¹⁷

Nicotinic:

- Nicotine/Coniine/ conium maculatum/Nicotiana spp./etc

Serotonergic:

- Hypericum perforatum/St. John's Wort

Sodium-channel agents:

- Aconitine/Aconitum spp (Monkshood/Wolfsbane)
- Taxine/Taxus (Yew)

Sympathomimetic:

- Cathinones (Khat/Qat)
- Cocaine (Coca)
- Ephedra/ (Ephedra spp./ Ma Huang)
- Synanceia/Stonefish [toxin]

Unknown mechanism:

- Camphor
 - Approximately 8500 pediatric exposures/year¹⁸
 - 33 cases “life-threatening” toxicity from 1985-1989 AAPCC reports
 - Approx 7/year, or < 1:1000 chance of “life-threatening” toxicity per exposure
 - Few case reports of death in literature
 - Only one pediatric death noted in (recent) AAPCC data - 1994

¹⁶ Appendino G, Pollastro F, Verotta L et al. Polyacetylenes from sardinian *Oenanthe fistulosa*: a molecular clue to risus sardonicus. *J Nat Prod.* 2009 May 22;72(5):962-5. doi: 10.1021/np8007717. PMID: 19245244

¹⁷ Lecker I, Wang DS, Romaschin AD et al. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest.* 2012 Dec 3;122(12):4654-66. doi: 10.1172/JCI63375. PMID: 23187124

¹⁸ Love JN, Sammon M, Smereck J. Are one or two dangerous? Camphor exposure in toddlers. *J Emerg Med.* 2004 Jul;27(1):49-54. PMID: 15219304