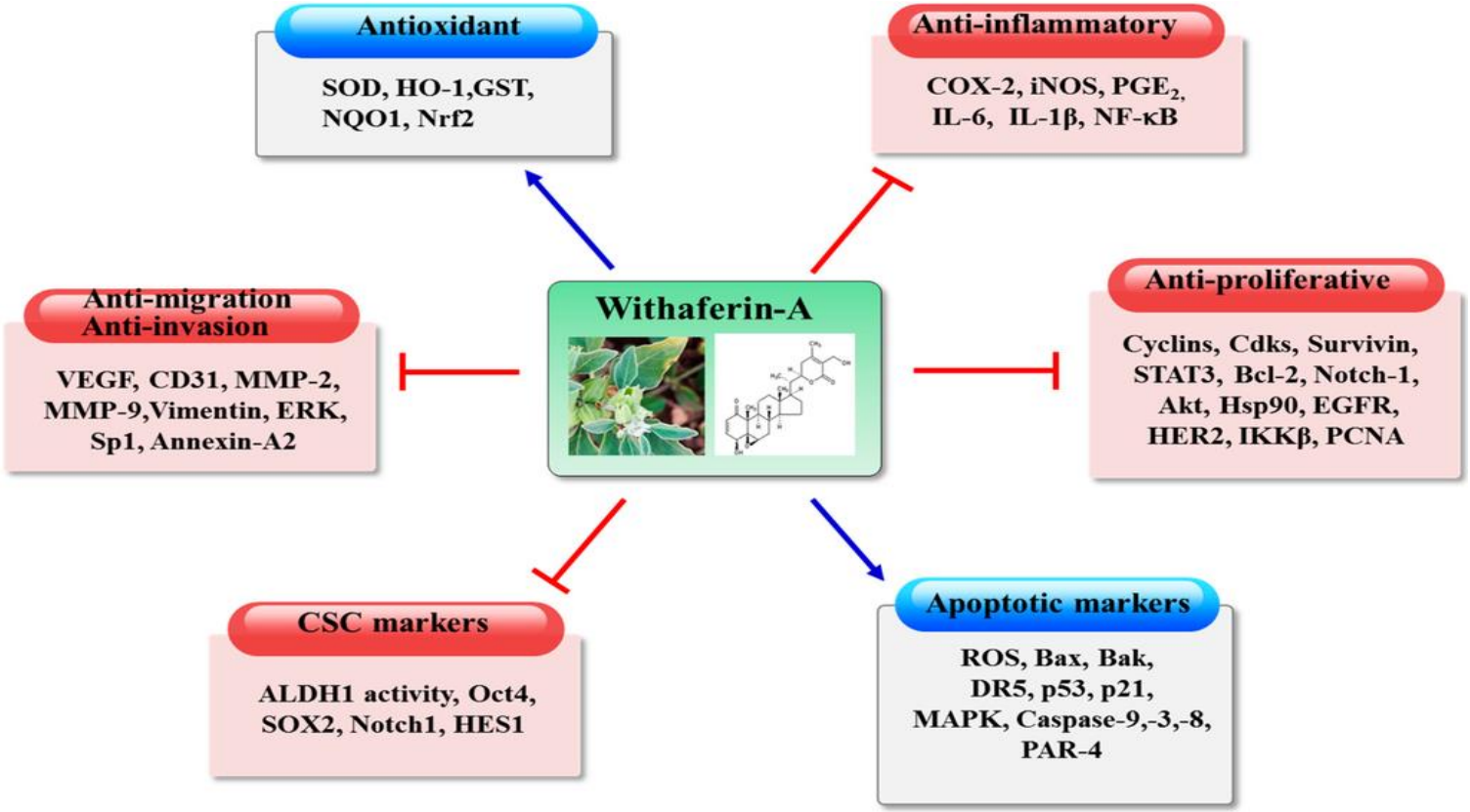
Withaferin A –A potential Phytochemical- with multiple indications as a drug



Dr. Sambasiva R Poreddy
Xenon Biosciences
www.xenonbio.com
www.withaferina.com

HISTORY

- Source: Withania somnifera (Ashwagandha)
- First isolated in 1956 by *Kurup et al 1*
- Structure elucidated in 1965 by *Lavie et al 2*
- First anti-tumor activity was reported in 1967 by *Shohat et al 3*
- Anti-angiogenesis activity was reported in 2004 *by Mohan et al 4*
- Anti-inflammatory activity was reported in 2008 *by Sabina et al 5*
- Chemo-preventive activity was reported in 2009 by *Manoharan et al 6*

1. Current Science 1956; 25: 57
2. J.Chem Soc 1965; 7517
3. Cancer chemotherapy reports 1967; 51; 271-276
4. Angiogenesis 2004; 7: 115-122
5. J. Pharm Pharm Sci 2008; 11: 46-55
6. Pharmacol Rep 2009; 61: 719-726

FUNDAMENTAL DETAILS

Source	Withania somnifera (Ashwagandha)
Alternative Name	5,6-Epoxy-4,27-dihydroxy-1-oxowitha-2,24-dienolide
Appearance	White to off white crystalline powder
Molecular Formula	$C_{28}H_{38}O_6$
Molecular weight	470.60
CAS No.	5119-48-2
Solubility	Soluble in DMSO(20 mg/ml), Methanol(10 mg/ml) (or) 100% Ethanol
Melting point	241-245^{o}C
λ Max	214, 335 nm (in ethanol)
Long term Storage	-20^{o}C
Product Stability	Stable for at least one year
Solution Stability	Stock solutions are stable for up to 3 months at -20^{o}C
MI	14:10048
RTECS	KE7288500

Indications

- **Withaferin A** has shown significant anti-cancer activity in animal studies
- **Withaferin A** has been extensively studied for
  - Anti-Inflammatory
  - Anti-angiogenesis
  - Chemo preventive
  - Radio-sensitizing activity and
  - Anti-tumor activity

➢ ANTI-INFLAMMATORY ACTIVITY

- Studied experimental mice model for gouty arthritis
- A cellular model of cystic fibrosis inflammation was established

J. Pharm Pharm Sci 2008; 11: 46-55

J. inflamm (London) 2009; 6 :15

➢ ANTI-ANGIOGENESIS ACTIVITY

- Withaferin A, revealed to inhibit HUVEC cell proliferation with IC 50 of 1.2 nm
- It exerts potent anti-angiogenesis activity in FGF-2 matrigel plug angiogenesis mice model at doses as low as 7µg/Kg/day
- It was 500 folders lower than the reported doses to exert anti-tumor activity in vivo
- Significantly inhibited neovascularization in injury-induced corneal neovascularization mouse model by about 70%

Angiogenesis 2004; 7: 115-122

Chem Biol 2007; 14: 623-634

➢ CHEMO PREVENTIVE ACTIVITY

- Exhibited excellent chemo preventive activity induced by DMBA in Syrian golden hamsters
- Oral administration of 20 mg/Kg withaferin A could completely prevent the tumor induction by DMBA

Pharmacol Rep 2009; 61: 719-726

Ind j Exp Biol 2009; 47: 16-23

➢ RADIO SENSITIZING ACTIVITY

- Radio sensitizing effect of withaferin A was demonstrated on ehrlich ascites implanted mice. An optimum dose of 30 mg/Kg of withaferin A in combination with 7.5 Gy gamma radiation is effective.
- Radio sensitizing effect of withaferin A on B6F1 mouse melanoma cells and mouse fibrosarcoma grown in C57B1 and swiss albino mice was evaluated.
- Withaferin A, Hyperthermia and irradiation acted synergistically against B16F1 melanoma
- Withaferin A served as a better radio sensitizer than hyperthermia

Cancer Lett 1995; 95: 189-193

Acta Oncol 1996; 35 : 95-100

Indian J Exp Biol 2000; 38: 432-437

Integr Cancer Ther 2010; 9: 370-377

➢ ANTI-TUMOR ACTIVITY

- First reported in 1967
- Confirmed the anti-tumor effect of withaferin A against mouse ehrlich ascites carcinoma cells by sharada et al
- Anti-tumor effect of withaferin A against human **prostate cancer** cell line was tested
- Withaferin A exhibited androgen receptor dependent cell killing against **Prostate cancer** cell lines
- Confirmed in PC-3 xenografts in nude mice
- Withaferin A was demonstrated to inhibit HSP 90 by directly binding to the C-terminaus. (**Pancreatic cancer**)
- Withaferin A in combination with myricetin enhanced anti-tumor efficacy in **pancreatic cancer** cells
- Withaferin A 6mg/kg inhibited tumor growth in pancreatic pan-1 xenograft

Cancer Res 2007; 67; 246-253

Yanke yu , Ph.D Thesis, 2011. Pharmaceutical sciences, The University of Michigan, USA.

➢ ANTI-TUMOR ACTIVITY

- Withaferin A inhibits proliferation of breast cancer cells with IC 50 s of 1.5 µm for MCF-7 and 2.0µm for MDA-MD-231 cancer cells
- Withaferin A exhibits anti-proliferation activity against human promyelocytic leukemia cells HL-60, U937, lymphoid origin human T (MOLT-4, Jurkat), B(REH)cells and myeloid origin K-562 leukemic cells.
- Withaferin A inhibited cell survival in three human colon cancer cell lines, SW-480, SW-620 and HCT-116 without affecting normal colon epithelial FHC cells
- Withaferin A exhibits anti-proliferative activity against human head and neck squamous cell carcinoma UM-SCC-2, MDA1986, JMAR and JHVO11

Cancer Res 2008; 68: 7661-7669

Apoptosis 2007; 12: 2115-2133

Apoptosis 2008; 13; 1494-1504

Mol Cancer Ther 2010; 9: 202-210

J. Nat Prod 2010; 73: 1476-1481

➢ NIH Small Business Innovation Research (*SBIR*) and Small Business Technology Transfer (*STTR*) Programs (USA).

- A project has been awarded worth of $ 300,000 under small business innovation research/ small business technology transfer (SBIR/STTR) for the treatment of Cervical cancer by using withaferin A

COMBINATION STUDIES

➢Withaferin A & Doxorubicin

- Treatment of various epithelial **ovarian cancer** cell lines (A2780, A2780/CP70 and CaOV3) with combination of withaferin A and doxorubicin showed a time and dose dependent synergistic effect on inhibition of cell proliferation and induction of cell death, thus reducing the dosage of requirement of doxorubicin which has severe side effects.
- By applying the withaferin A combination strategy, the ovarian and other cancers can be treated with no/minimum side effects.

PlosOne 2012;7:e42265

COMBINATION STUDIES

➢Withaferin A & Sorafenib

- Combination of withaferin A and sorafenib shows synergistic efficacy against **thyroid cancers.** This combination achieved potent anti cancer activity with lower overall doses of sorafenib with reduced toxicity.

  Am.J.Surg 2002: 204: 895-900

➢Withaferin A and Cisplatin

- Withaferin A alone and in combination with Cisplatin suppresses growth and metastasis of ovarian cancer by targeting putative cancer stem cells

  Plos One 2014; 9; e107596

  Biochem Biophys Res Commn 2012; 423; 819-25

CLINICAL STUDIES

•One of the withaferin A derivatives has been emerged as a preclinical lead for Amyotrophic Lateral Sclerosis (ALS) and Parkinson's diseases.

• Presently it is under phase-I clinical trial for ALS disease with ImStar Therapeutics, (IMS-088) http://imstartx.com/pipeline.html)

•Yumanity Therapeutics announces its first clinical candidate for Parkinson's disease (YTX-7739) https://businesswire.com/news/home/20180905005472/en/Yumanity-Therapeutics-Announces-Clinical-Candidate-Potential-Treatmentt

➢STRUCTURE ACTIVITY RELATIONSHIP

- The double bond at C_2-C_3 position in Ring A and 5β,6β epoxide ring is required for its cytotoxicity
- The conjugated ketonic carbon in the ring A is required for the proteosome inhibition
- C_{27} hydroxyl group and the α, β unsaturated delta lactone ring are not required for the cytotoxicity of withaferin A.

Neoplasma 1984; 31: 31-36

J.Nat Prod 2007; 70: 1146-1152

Chem Biol 2007; 14: 623-634

Chem Lett 2006; 16: 2603-2607

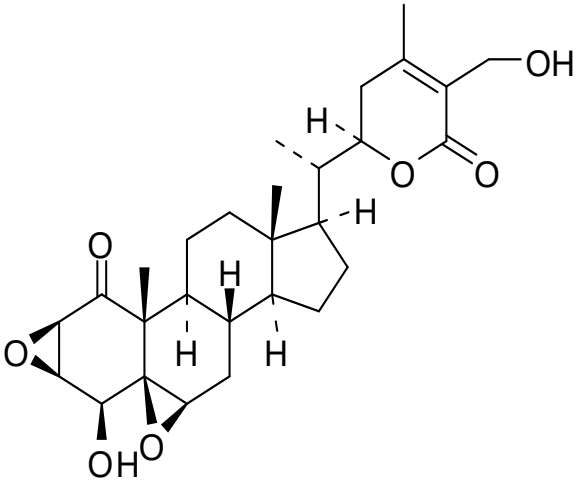
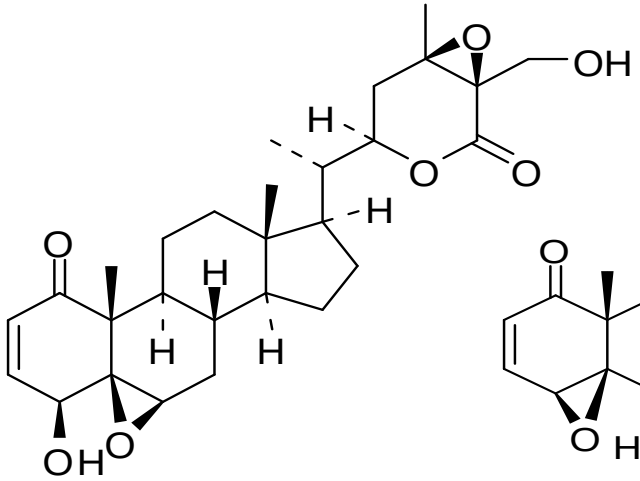
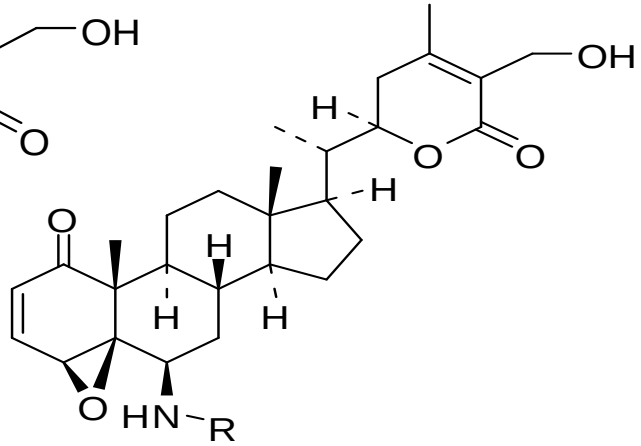
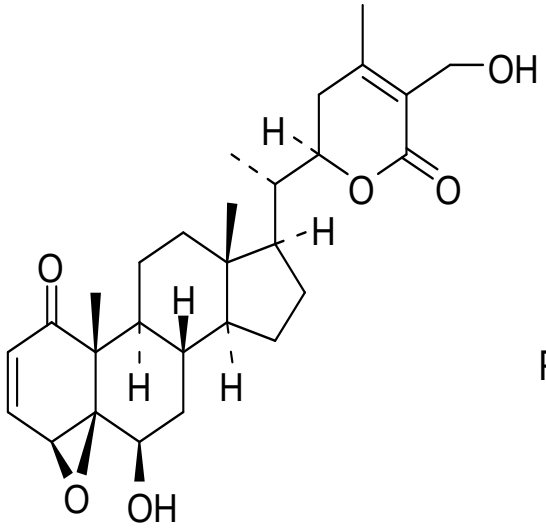
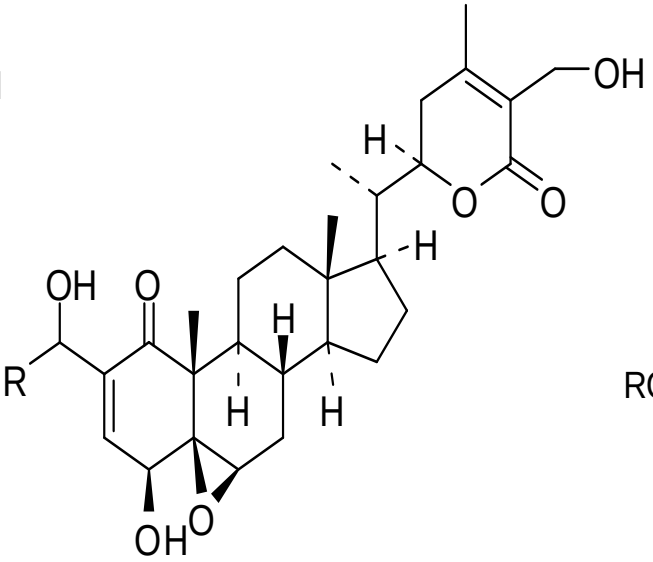
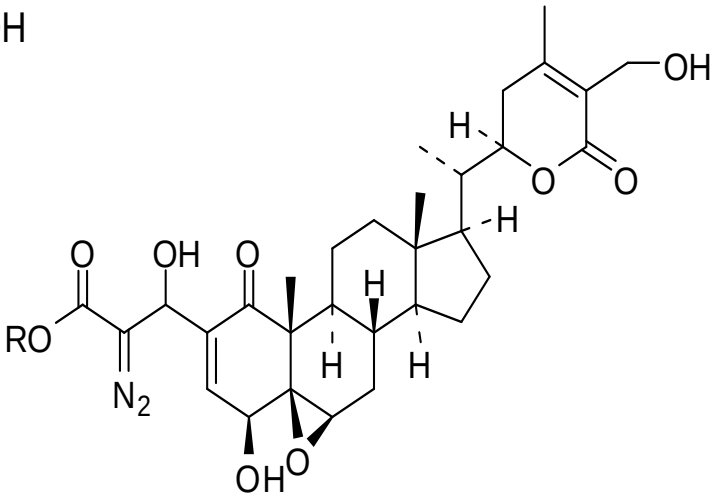
ANALOGUES OF WITHAFERIN-A

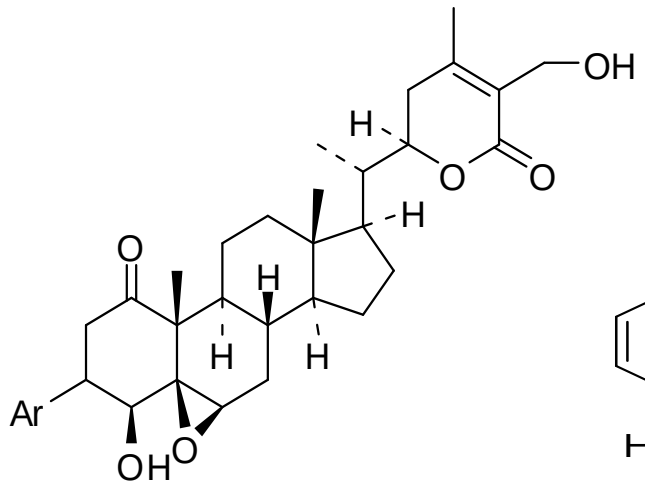
-DEVELOPED SO FOR

- Yokota developed a biotinylated affinity analogue for use as a probe to study angiogenesis (BMCL 2006, 16: 2603-2607)
- A library of 2,3 dihydro-3 β substituted withaferin A derivatives were prepared by IIIM, Jammu. 3-Azido analogue exhibited 35 fold increase in cytotoxicity against all cell lines compare to parent molecule (Steroids 2011, 76:1213-22)
- A series of withaferin A analogues were prepared and tested for its activity in proliferative diseases, neurodegenerative diseases, autoimmune and inflammatory diseases by Leslie Gunatilaka, University of Arizona, USA.
- 4-Epiwithaferin A and 4, 27-diacetyl-4-epi withaferin A were evaluated for anti-tumor activity in pancreatic cancer cells.
- (US Patent Publication Number: US2011/0230551 A1, Dt. Sep 22, 2011)

ANALOGUES PROPOSED

(Only frame works of the representative examples are given)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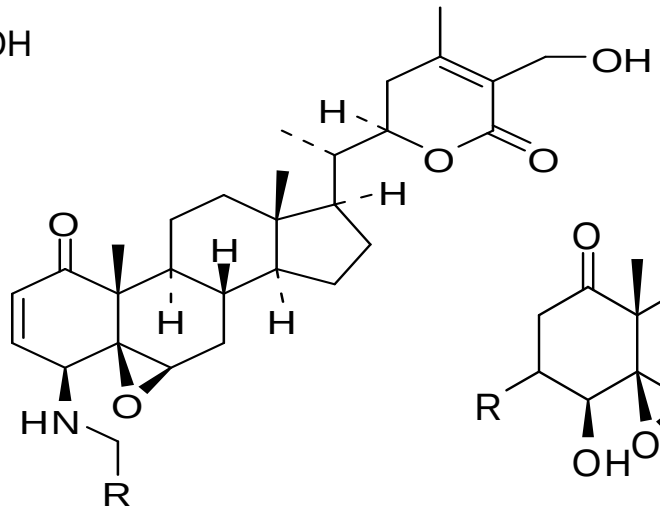
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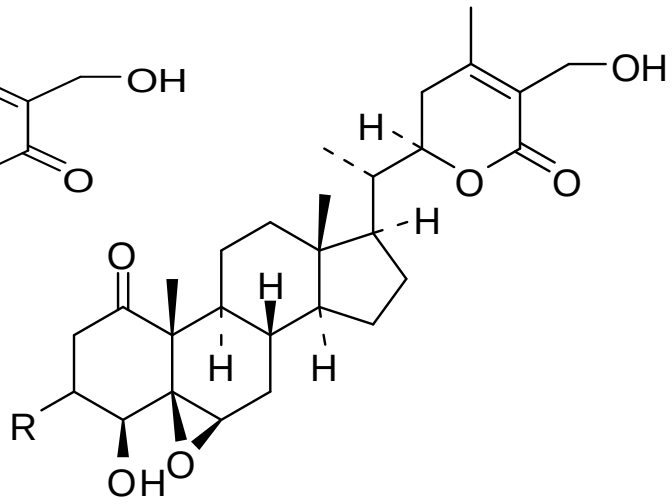
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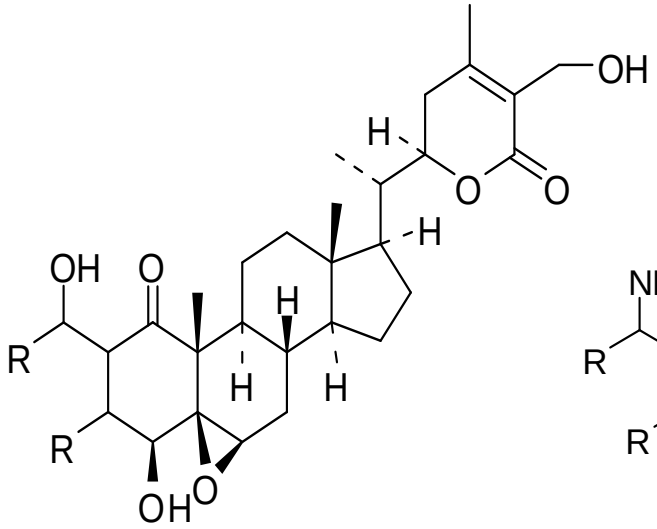
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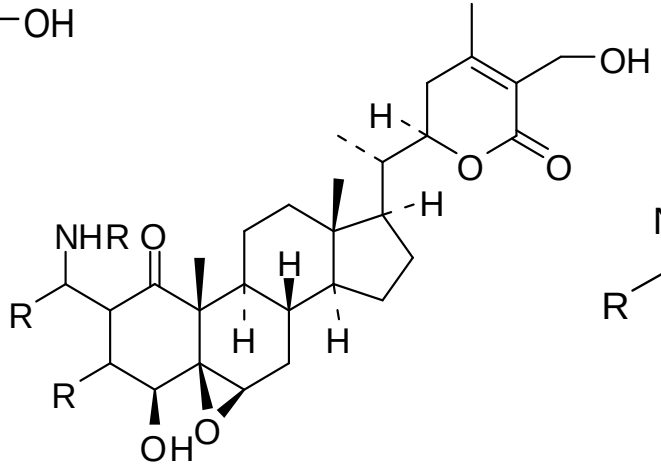
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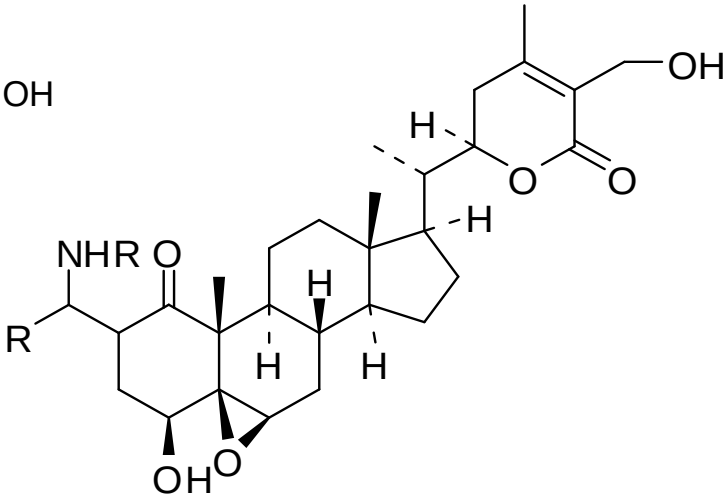
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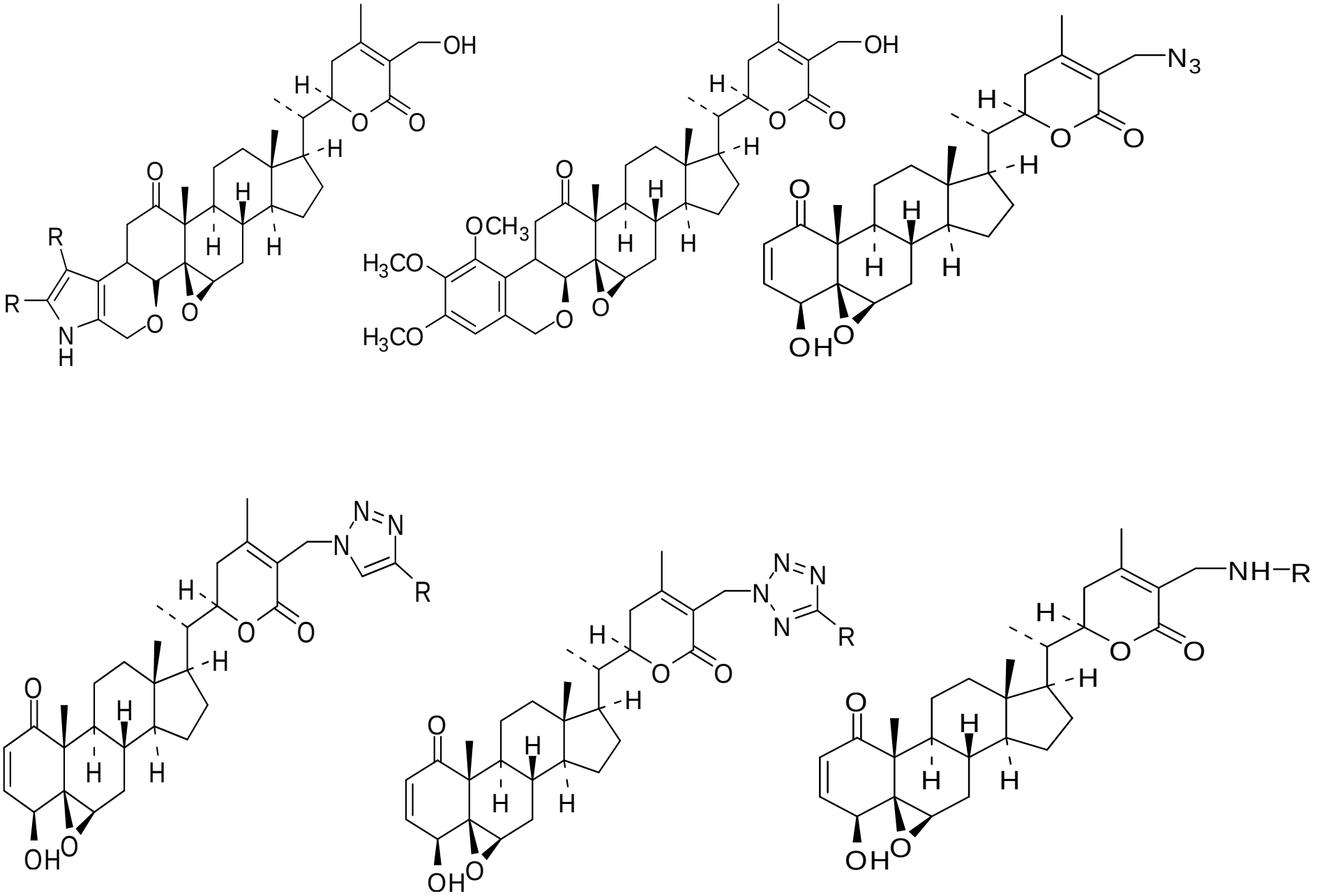

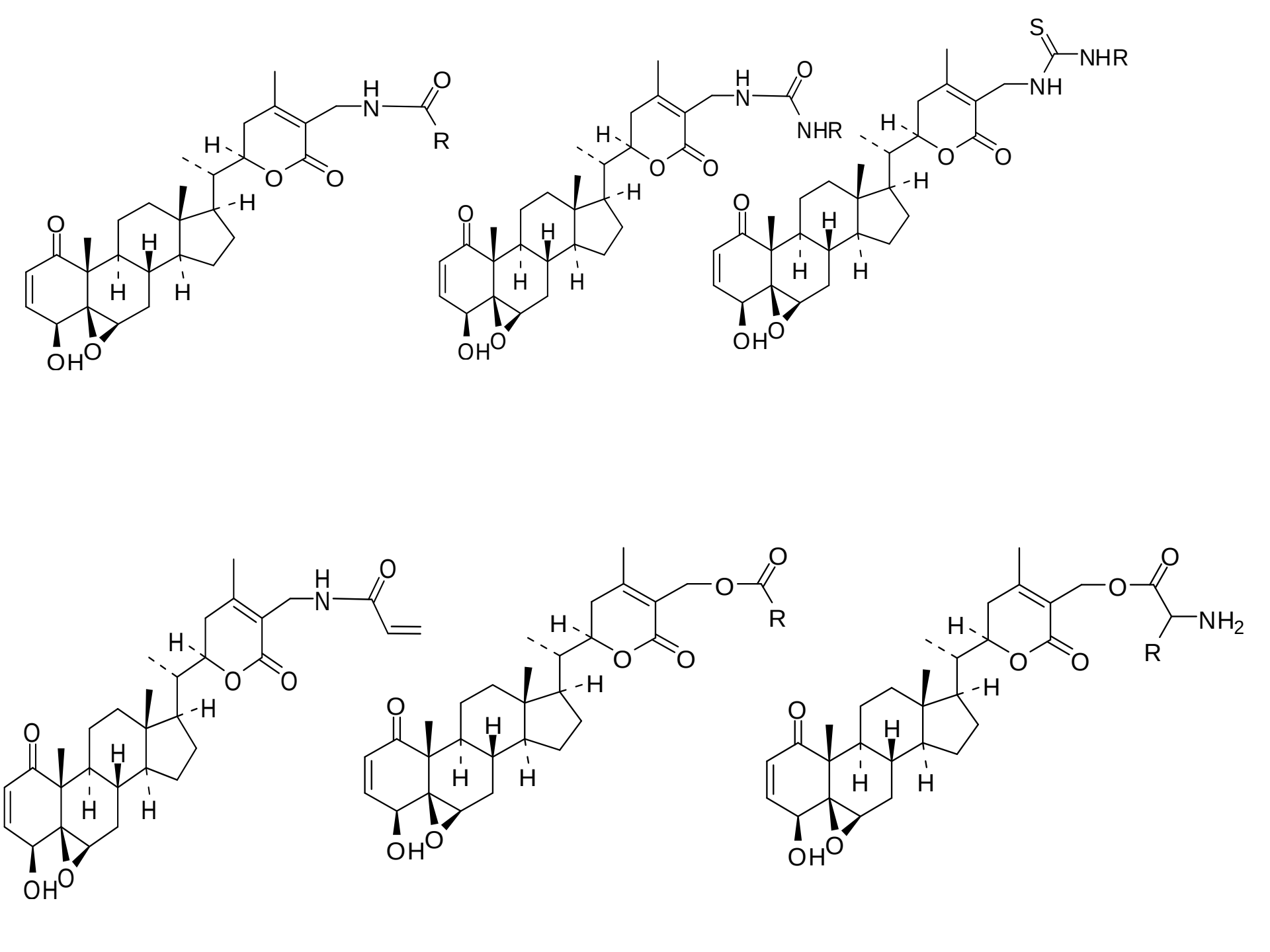

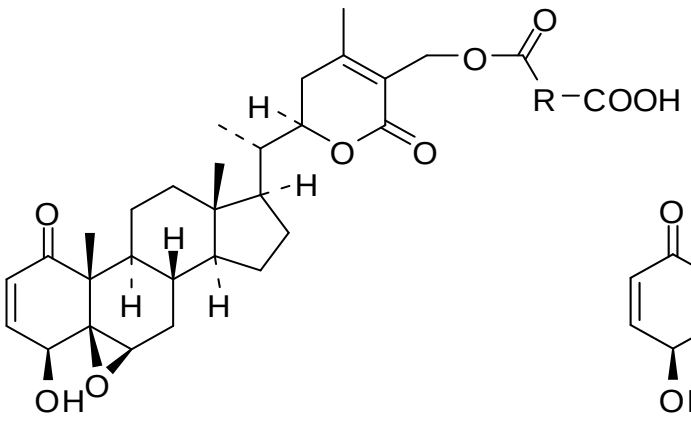
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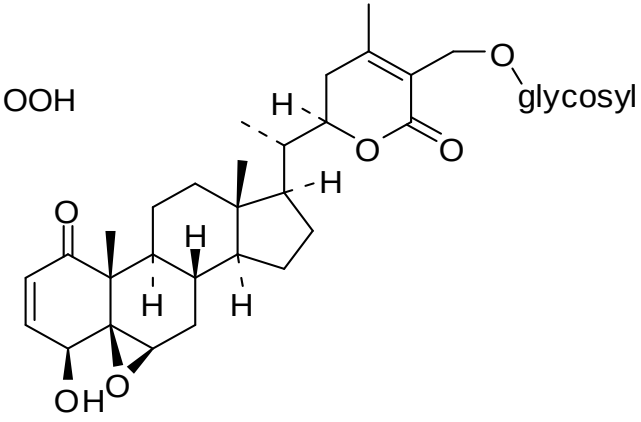
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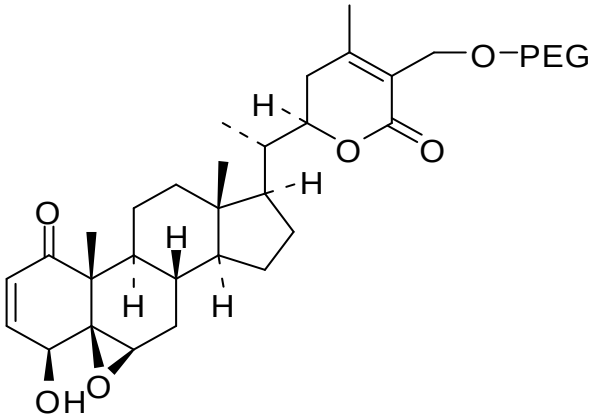
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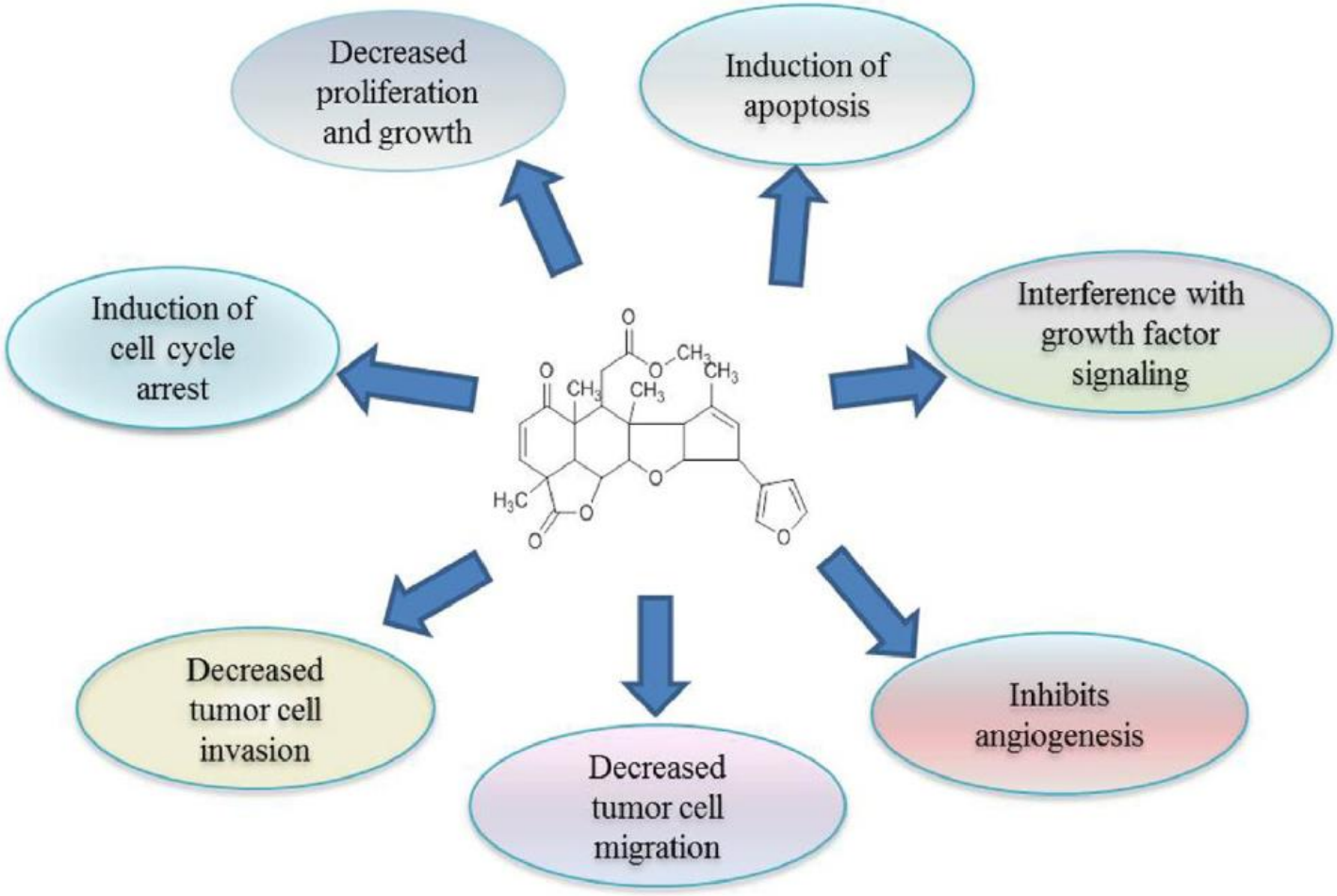
- 25-30 derivatives can be prepared on each frame work
- A minimum of 250-300 practically feasible derivatives can be prepared from withaferin A without affecting its basic activity by keeping the epoxide ring as it is
- A wide variety of derivatives can be prepared by introducing new epoxide rings
- **Lot of scope for making new derivatives and file patents**
- Sufficient quantity(**100g to1000 g**) of withaferin A is available for further research with very reasonable production cost.

- **DEVELOPED A PATENTED (Indian Pat. Appl. (2012), IN 2011CH00055 A 20121019) PROCESS TO ISOLATE BULK QUANTITIES OF WITHAFERIN A. WE CAN MEET ANY QUANTITIES OF INDUSTRIAL REQUIREMENTS WITH PURITIES >98% BY HPLC. FOR FURTHER DETAILS PLEASE FEEL FREE TO CONTACT xenonbiosciences@gmail.com / withaferina@gmail.com (OR) +91-9849601776**

- **Withaferin A supplied by us is for research use only. Not for human (or) drug use. Bulk quantities of API grade available ready in stock. GMP grade will be supplied upon request**

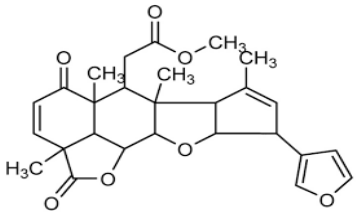
Other Lead Phytochemicals for Cancer and Neurodegenerative Disease Drug Development

NIMBOLIDE - A Lead Phytochemical- with Major Cancer Preventive Activity as a Drug Development Candidate



The major anticancer activities and cancer preventive effect of Nimbolide

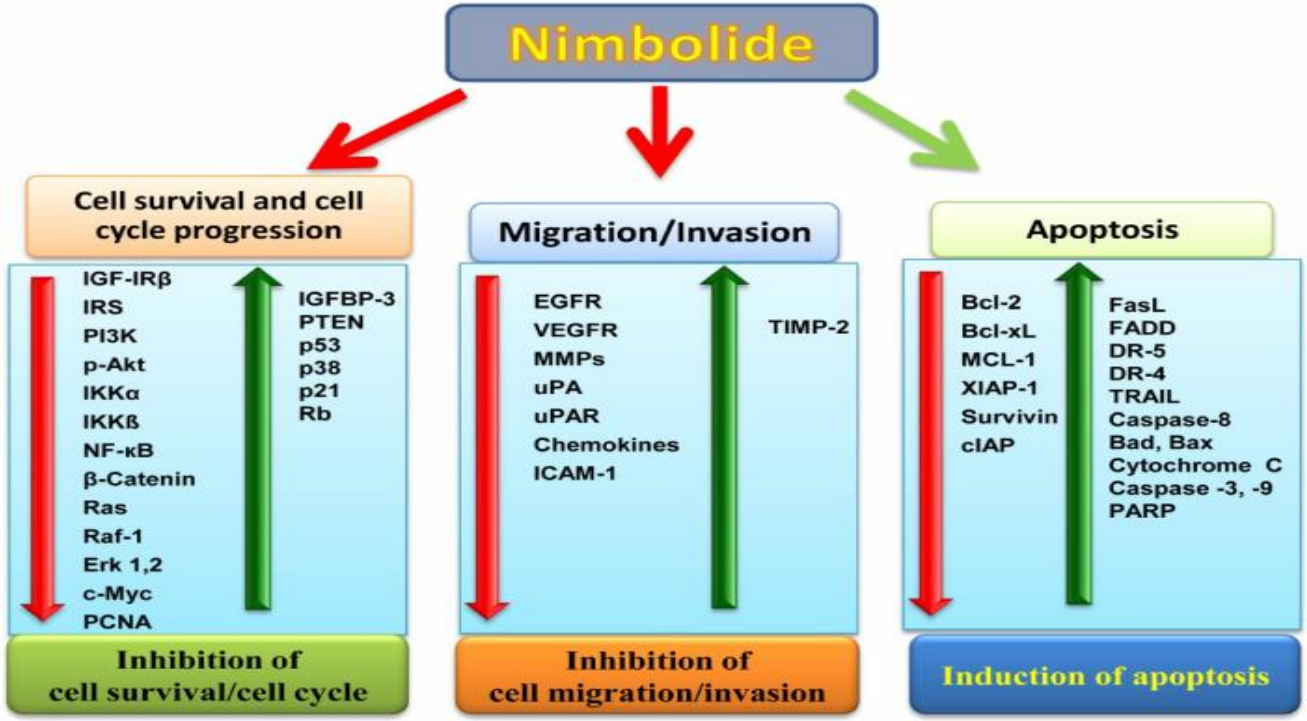
NIMBOLIDE



- CAS Number: 25990-37-8
- Source: Azadirachta indica leaf
- Availability: Multiple grams
- Supply Capability: Grams to Kg quantities

Functional activity:

Nimbolide exhibits anti-malarial, anti-bacterial, and anti-cancer activities



- **Key References:**

1. Anticancer properties of Nimbolide and pharmacokinetic considerations to accelerate its development

   Oncotarget 2016, 7, 44790-44802

2. Nimbolide targets BC12 and indices apoptosis in preclinical models of Waldenstroms macroglobulinemia

   www.nature.com-November 10, 2014

3. Anti-proliferative and apoptosis inducing effect of Nimbolide by altering molecules involved in apoptosis and IGF signalling via PI3K/Akt in prostate cancer (PC-3) cell line

   Cell Biochem Funct. 2014, 32, 217–228

4. Nimbolide –induced oxidative stress abrogates STAT3 signaling cascade and inhibits tumor growth in transgenic adenocarcinoma of mouse prostate model

   Antioxidants & Redox Signaling. 2016, 24, 575

5. Nimbolide, a Limonoid Triterpene, Inhibits Growth of Human Colorectal Cancer Xenografts by Suppressing the Proinflammatory Microenvironment

   Clinical Cancer Research, 2013, 19, 4465-4476

6. Nimbolide, a neem limonoid inhibits Phosphatidyl Inositol-3 Kinase to activate Glycogen Synthase Kinase-3β in a hamster model of oral oncogenesis

   Scientific Reports, 2016, 6:22192

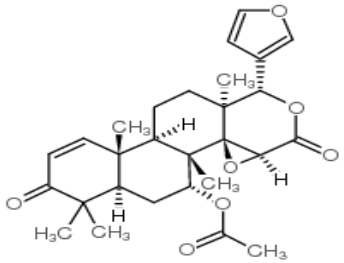
7. Neem compositions used for the treatment of cancer

   Mayo Foundation for Medical Education and Research, WO2015035199A1

8. Nimbolide epigenetically regulates autophagy and apoptosis in breast cancer

   Toxicol in Vitro 2018, 51, 114-128

GEDUNIN

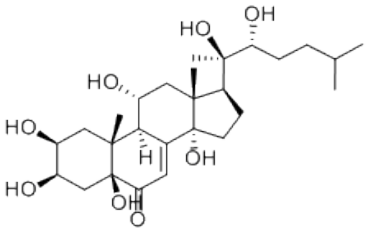


- CAS Number: 2753-30-2
- Source: Azadirachta indica fruit husk
- Availability: Multiple grams
- Supply Capability: Grams to Kg quantities
- **Functional activity:**
- Hsp90 inhibitor; exhibits anticancer and antimalarial activity
- Induces Hsp90-dependent client protein degradation and displays anti-proliferative activity *in vitro*
- IC_{50} values of SKBr3, MCF-7 and CaCo-2 cancer cell lines are3.22, 8.84 and 16.8 µM
- Decreases ovarian cancer cell proliferation *in vitro*
- Anti-malarial activity against P. falciparum (IC50 values are 0.14 and 3.1 µM in parasite development and [3H]-hypoxanthine uptake assays respectively

- **Key References:**

1. Gedunin for Treating Neurodegenerative Diseases
   http://emoryott.technologypublisher.com/tech/Gedunin_for_Treating_Neurodegenerative_Diseases
2. Celastrol, gedunin, and derivatives thereof as hsp90 inhibitors
   US20110263693A1, Dana-Farber Cancer Institute Inc, Massachusetts Institute of Technology
3. Chitosan Nano-encapsulation Enhances Gedunin Cytotoxicity A gainst Human Non-small-cell Lung Cancer (NCI-H292) Cell Line
   Drug Delivery Letters 2017, 7, 219-226
4. Gedunin inhibits pancreatic cancer by altering sonic hedgehog signalling pathway
   Oncotarget, 2017, 8, 10891-10904
5. Gedunin Inactivates the Co-chaperone p23 Protein Causing Cancer Cell Death by Apoptosis
   Journal of Biological Chemistry, 2013, 288, 7313–7325
6. Gedunin, a novel HSP-90 inhibitor, synergizes with cisplatin and paclitaxel to inhibit growth of chemoresistant ovarian cancer cell lines
   Cancer research 2014, 74, 4553
7. Effect of Gedunin on Acute Articular Inflammation and Hypernociception in Mice
   Molecules 2015, 20, 2636-2657
8. In Vitro Anticancer Effect of Gedunin on Human Teratocarcinomal (NTERA-2) Cancer Stem-Like Cells
   BioMed Research International 2017, 1–9
9. Gedunin Inactivates the Co-chaperone p23 Protein Causing Cancer Cell Death by Apoptosis
   J Biol Chem 2013, 288, 7313-7325
10. Gedunin, a Novel Hsp90 Inhibitor: Semisynthesis of Derivatives and Preliminary Structure–Activity Relationships
    J Med Chem 2008, 51, 6492-6502

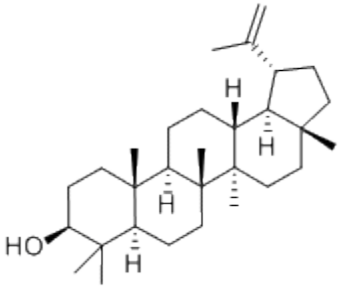
MURISTERONE A



- CAS Number: 38778-30-2
- Source: Ipomoea hederacea seed
- Availability: Multiple grams
- Supply Capability: Grams to Kg quantities
- **Functional activity:**
- Potent ecdysone-inducible gene expression inducer. Stimulates Bcl-XL mRNA transcription. Inhibits TRAIL- and hFasL-induced apoptosis. Induces NGF release from fibroblasts.
- The addition of Muristerone A causes a greater than 200 fold induction of expression of the target gene over basal levels in mammalian cells

- Since the discovery of Muristerone A in 1972, more than 1500 articles have been published on various aspects of its research

LUPEOL



- CAS Number: 545-47-1
- Source: Crataeva nurvala bark
- Availability: Multiple grams
- Supply Capability: Grams to Kg quantities
- **Functional activity:**
- potent anti-inflammatory, anti-carcinogenic, anti-mutagenic, and anti-malarial activity.
- an effective Androgen Receptor inhibitor, can be developed as a potential agent to treat human prostate cancer (CaP).
- It suppresses the growth of hepatocellular carcinoma cell lines SMMC7721 and HepG2 with IC_{50}values of 45 and 48.5 µM and melanoma cell lines Mel 928 and Mel 1241 with IC_{50} values of 75 and 72 µM.
- It has been tested for its therapeutic efficiency against conditions including wound healing, diabetes, cardiovascular disease, kidney disease, and arthritis

- Key References:

1. Non- surgical treatment of canine oral malignant melanoma. A case study of the application of complementory alternative medicine.

   Oncol Lett. 2014, 7, 1829-1830

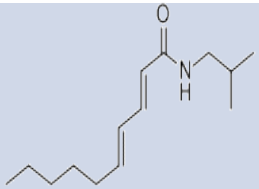
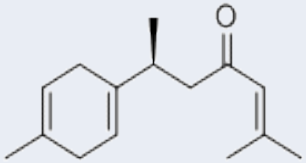
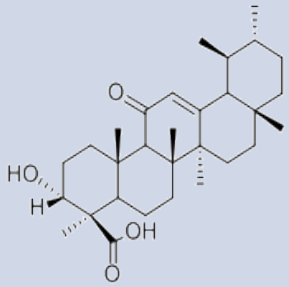
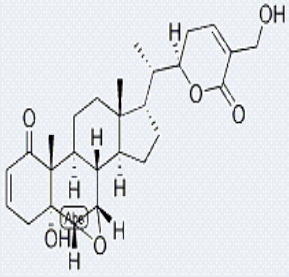
1. Clinical Trial of Lupeol for Mild-moderate Acne. **(https://clinicaltrials.gov/ct2/show/NCT02152865)**
3. Clinical Study for Topical Lupeol in Acne **(https://clinicaltrials.gov/ct2/show/NCT02205892)**
4. Clinical systemic lupeol administration for canine oral malignant melanoma

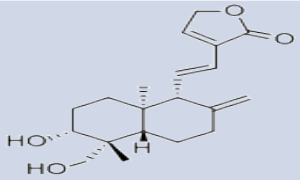
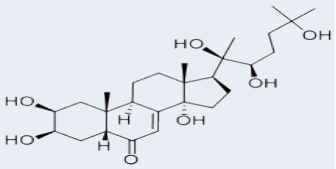
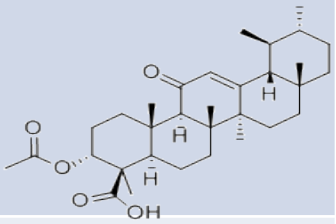
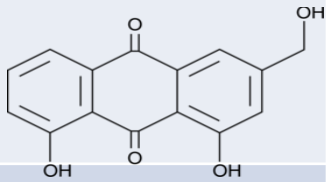
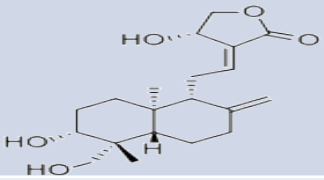
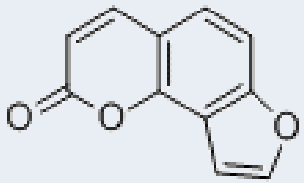
   Molecular and clinical oncology, 2015, 3, 89-92

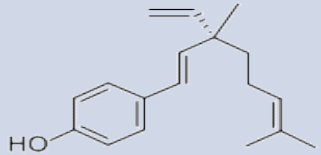
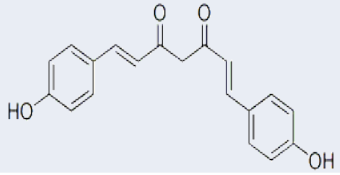
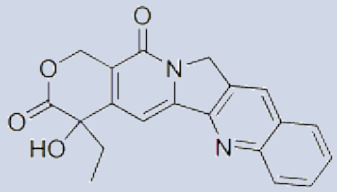
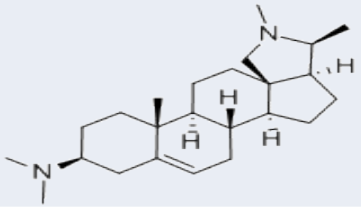
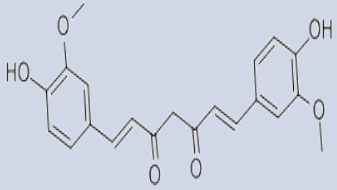
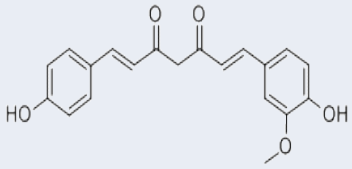
5. Lupeol, a novel androgen receptor inhibitor: implications in prostate cancer therapy

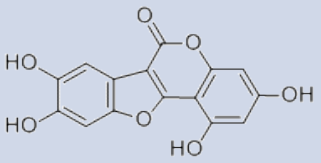
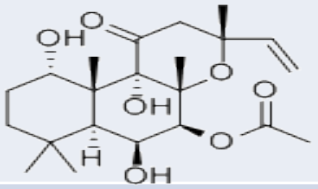
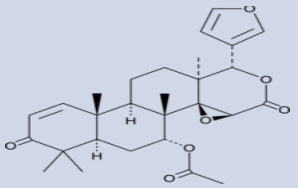
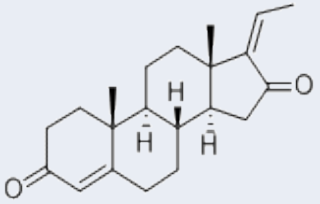
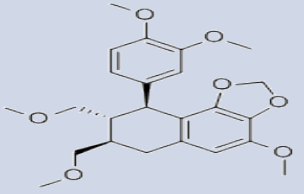
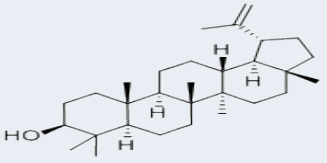
   Clin Cance Res. 2011, 17, 5379-5391

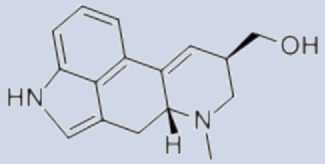
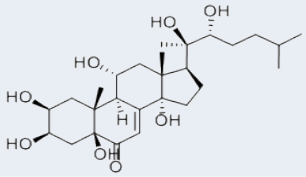
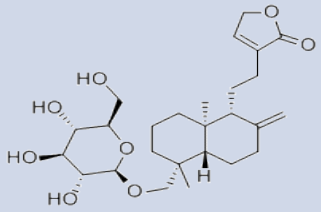
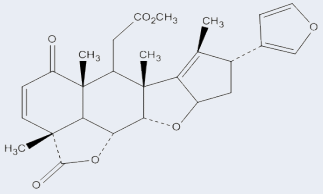
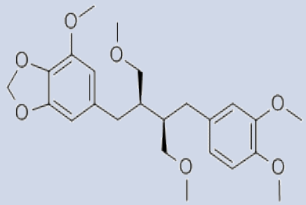
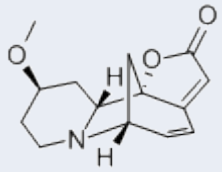
List of Available Phytochemicals with Functional Activity

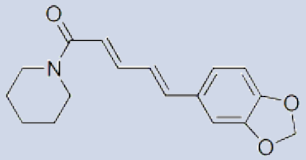
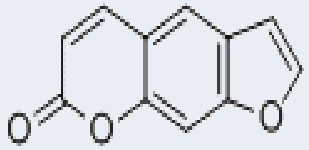
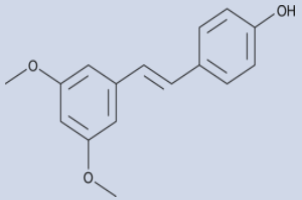
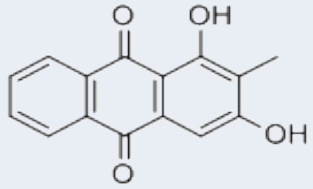
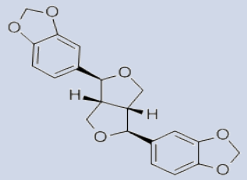
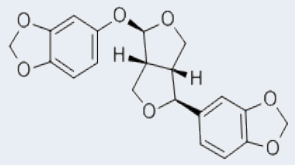
S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
1	(2E,4E)-N-Isobutyl Decadienamide (Pellitorin)	Piper longum		18836-52-7	Anti cancer
2	(S)-(+)-Turmerone,Ar (Ar-Turmerone)	Curcuma longa		532-65-0	Anti-inflammatory, Anti-microbial, Anti-acne, Anti-aging
3	11-Ketoβ boswellic acid (KBA)	Boswellia serrata		17019-92-0	Anti-inflammatory, Anti-cancer, COX-2 inhibitor
4	12-Deoxy withastramonolide (27-Hydroxywithanolide B)	Withania somnifera		60124-17-6	Neuro degenerative

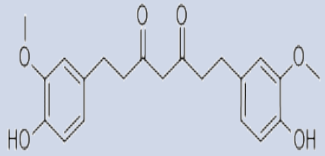
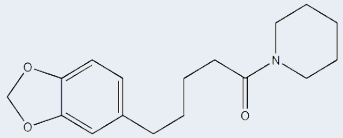
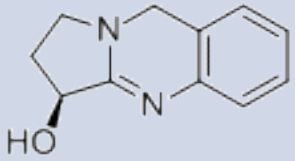
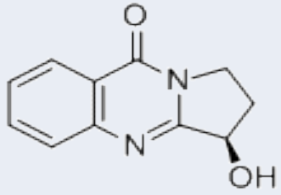
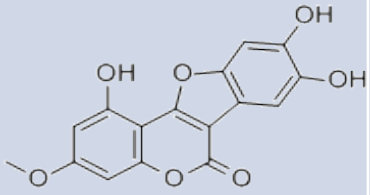
S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
5	14-Deoxy-11,12-didehydro andrographolide	Withania somnifera		42895-58-9	Hepatoprotective, Anti-viral
6	20-Hydroxy ecdysone	Ipomoea hederacea		5289-74-7	Gene expression
7	3-Acetyl-11-keto βboswellic acid(AKBA)	Boswellia serrata		67416-61-9	Anti-inflammatory, Anti-cancer, COX-2 inhibitor
8	Aloe emodin	Aloe barbadensis		481-72-1	Anti-cancer, Anti-viral (HSV)
9	Andrographolide	Andrographis paniculata		5508-58-7	Hepatoprotective, Anti-viral
10	Bakuchicin (Angelicine)	Psoralea corylifolia		523-50-2	Antimicrobial, Anti-fungal and Anti-cancer

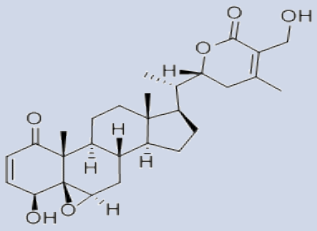
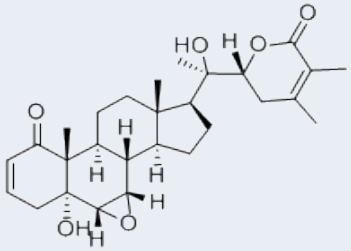
S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
11	Bakuchiol	Psoralea corylifolia		10309-37-2	Anti-acne, Skin whitening
12	Bisdemethoxycurcumin	Curcuma longa		33171-05-0	Anti-oxidant, Anti-inflammatory
13	Camptothecine	Mappia foetida		7689-03-4	Anti-cancer
14	Conessine	Holarrhena antidyssentrica		546-06-5	Anti-histamine
15	Curcumin	Curcuma longa		458-37-7	Anti-oxidant, Anti-inflammatory
16	Demethoxycurcumin	Curcuma longa		22608-11-3	Anti-oxidant, Anti-inflammatory

S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No:	Functional Activity
17	Demethylwedelolactone	Eclipta alba		6468-55-9	Hepatoprotective, Anti-cancer
18	Forskolin	Coleus forskohlii		66575-29-9	Skin conditioning, Anti-aging
19	Gedunin	Azadirachta indica		2753-30-2	Anti-cancer
20	Guggulsterone-Z	Commiphora mukul		39025-23-5	Cholesterol lowering
21	Hypophyllanthin	Phyllanthus amarus		33676-00-5	Hepatoprotective
22	Lupeol	Crataeva nurvala		545-47-1	Anti-cancer

S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
23	Lysergol	Ipomoea hederacea		602-85-7	Serotonin receptor activity
24	Muristerone A	Ipomoea hederacea		38778-30-2	Gene expression
25	Neoandrographolide	Andrographis paniculata		27215-14-1	Hepatoprotective
26	Nimbolide	Azadirachta indica		25990-37-8	Anti-cancer
27	Niranthin	Phyllanthus amarus		50656-77-4	Hepatoprotective
28	Phyllanthin	Phyllanthus amarus		10351-88-9	Hepatoprotective

S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
29	Piperine	Piper nigrum		94-62-2	Bio availability
30	Psoralen	Psoralea corylifolia		66-97-7	Vitiligo, psoriasis
31	Pterostilbene	Pterocarpus marsupium		537-42-8	Anti-oxidant
32	Rubiadin	Rubia cordifolia		117-02-2	Hepatoprotective
33	Sesamin	Sesamum indicum		607-80-7	Anti-oxidant, Anti-inflamma tory, holesterol lowering
34	Sesamolin	Sesamum indicum		526-07-8	Anti-oxidant, Anti-inflamma tory, holesterol lowering

S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
35	Tetrahydrocurcumin	Curcuma longa		36062-04-1	Skin whitening, Anti-oxidant, Anti-aging, UV-B protectant
36	Tetrahydropiperin	Piper nigrum		23434-88-0	Permeation enhancer
37	Vasicine	Adhatoda vascica		50591-64-5	Bronchodilator activity, Anti-tubercular, Cytotoxic activity
38	Vasicinone	Adhatoda vascica		486-64-6	Bronchodilator activity, Anti-tubercular, Cytotoxic activity
39	Wedelolactone	Eclipta alba		524-12-9	Hepatoprotective, Anti-cancer

S. No	Name of the Phytochemical	Source/Host	Chemical Structure	CAS No.	Functional Activity
40	Withaferin A	Withania somnifera		5119-48-2	Anti-cancer, Neuro degenerative
41	Withanolide A	Withania somnifera		25990-37-8	Neuro degenerative

THANK YOU