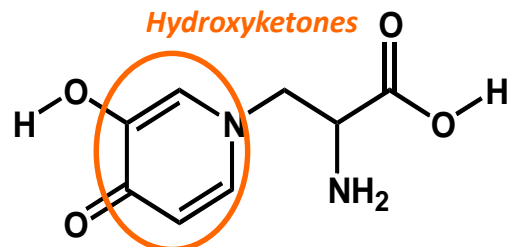


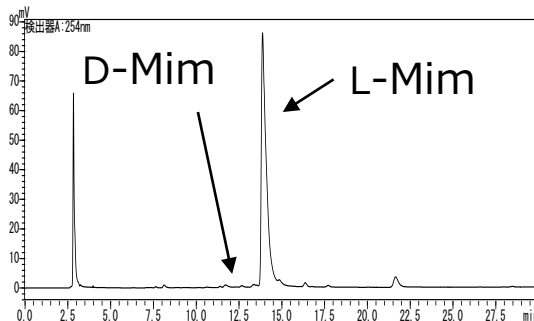
Mimosine, a non-proteinogenic amino acid, Mimosine-derivatives for Mimosyl-peptides

Mimosine, useful functional ingredients for development of pharmaceuticals/ cosmeceuticals:

Derivatives containing hydroxyketone, which is involved in Mimosine (Mim) are attracted by their anti-tumor effects and apoptosis inducing effects. Mim has the tyrosinase, cyclooxygenase and lipoxygenase inhibitory activities and thus for whitening big in the cosmetic field is one of the big interests. Mim exhibits no significant cytotoxicity nor acute dermal toxicity. A large scale extraction, purification, physico-chemical characterization of high quality Mimosine from plant *Leucaena leucocephala* de Wit has been established by HiPep Laboratories as a sustainable starting material for development of drugs or cosmetics, without causing environmental damages. Optical purity has been assessed by the novel method (*A part of those work was funded by the Regional Resource Utilization R&D Programs: Ministry of Economy, Trade and Industry, Okinawa General Bureau 2007-8. HiPep Laboratories has also established production of Mimosyl-peptides for functional cosmetics or active pharmaceutical ingredients. Reagent for peptide syntheses are commercialized.



2-amino-3-(3-hydroxy-4-oxo-4H-pyridin-1-yl)-propionic acid



Products from HiPep Laboratories

Mimosine (Mim) with high optical purity) is a plant-derived non-proteinogenic amino acid; further Fmoc-Mim, Mim-resin (for SPPS), Mim-CTCResin are available for the syntheses of Mimosyl-peptides. Mim-Peptides have antioxidant, whitening activities.

History of the Okinawa Project

2004-2006 Okinawa Bio Project was started and HiPep-Okinawa Lab was founded. Fundamental technologies for molecular design, library construction, highly efficient library construction, synthesis and purification have been carried out in Okinawa.

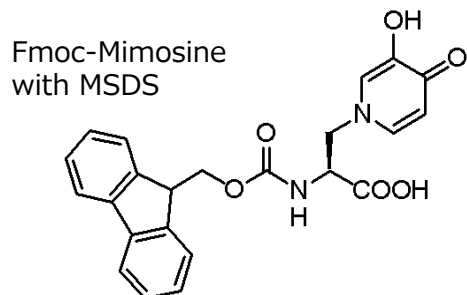
2007-2008 Manufacturing unnatural amino acid Mimosine as an unique resource of Okinawa as started. Efficient production method has been established, that is purification of industrial scale of high quality Mimosine from natural (plant) *Leucaena leucocephala*, was succeeded.

2011 After 3 years of "Innovation R&D Project" focusing on diagnostics and therapeutics, HiPep Okinawa Laboratory was closed, although HiPep continues looking for business partners not only domestic but also world wide market.

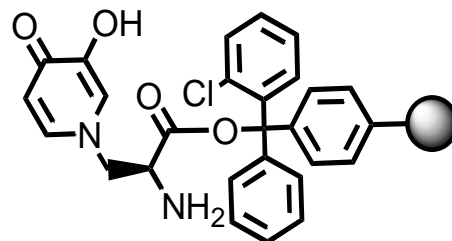
References

Nokihara, K, et.al., *Amino Acids* (2012) 54, 27-36.

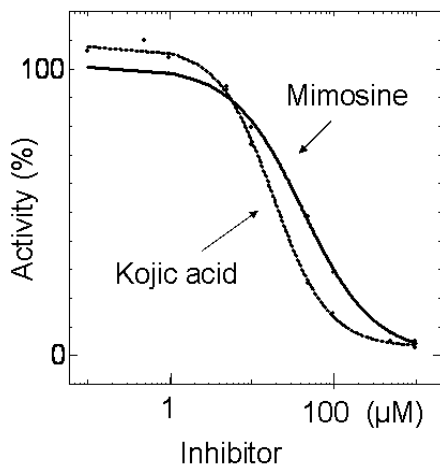
Nokihara, K, et.al., *Peptide Science 2010, Japanese. Peptide Society*, (2011) p 282.



Mimosyl Chlorotriyl Chloride-Resin (Mim-CTCResin) with MSDS



Mimosine, a non-proteinogenic amino acid, Mimosine-derivatives for Mimosyl-peptides



Melanocyte

Tyrosine

Tyrosinase

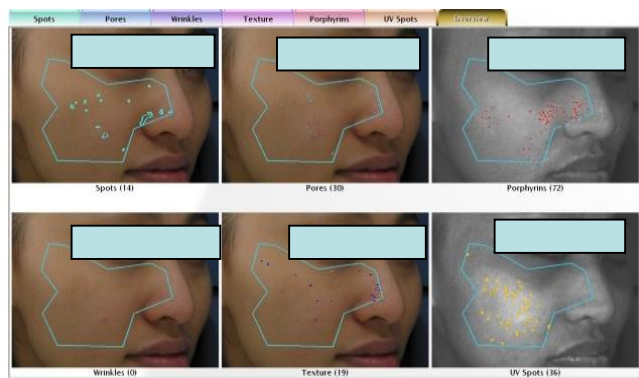
Melanine

List of Safety test	Patch test 5 volunteers)
Itch	0/5
Erythema	0/5
Eczema	0/5
Scaliness	0/5
Acne	0/5

Mim showed no-toxicities,

Evaluation Skin irritation showed SAFE

(Patch test + Usage Test) = Itch, Erythema, Eczema, Scaliness, Acne (*all Negative*)



Efficacy of Mimosyl-peptides		Cosme.	Drug	Sani-tary	Food
1	Anti-oxidant	○	○	○	○
2	αMSH antagonist	○	○		
3	Whitening	○			
4	Anti-viral	○	○	○	
5	Anti-tumor		○		
6	Anti-bacterial	○	○	○	
7	Anti-angiogenesis		○		
8	Anti-inflammatory		○		
9	Treatment of alopecia	○			
10	Fat suppression				○

Topic: Immunopotentiality by "L-Mimosine" and prevention of invasive Candida infection

UT Southwestern Medical Center group (Texas, USA) found that immunomodulation by administration of "L-Mimosine (Mim)" and Mim could be useful for treatment for invasive cancer infections.

Candida is a type of mold normally inhabiting human skin and intestines, usually occurring in the skin, mouth, in the woman's vagina, half of those who have internal Candida. Normally it is harmless but Candida increases too much and if it leaks from the internal organs to the blood, it becomes "invasive Candida infection" and the mortality rate is about 30%. There are antibiotics against serious invasive Candida infections, but it is not always effective. Even those with durability in medicine are also occurring in the first place. The research group noticed that bacteria (especially intestinal bacteria) present in the internal organs constrained the proliferation of Candida and administered "Mim" to Candida infected rats and verified it.

"Mim" is known to enhance the activity of the transcription factor HIF-1α. As a result of the experiment, it was found that "HIF-1α" made LL-37, a natural antibiotic, built in the internal organs and suppressed Candida to 1/100. The approach of boosting the immune system of the bowel and reducing Candida may be a novel treatment to prevent invasive infections.

References

Boosting gut bacteria defense system may lead to better treatments for bloodstream infections, study shows
 Fan D et al. Activation of HIF-1α and LL-37 by commensal bacteria inhibits Candida albicans colonization. Nat Med. 2015 Jun 8.
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 title="Activation of HIF-1α and LL-37 by commensal bacteria inhibits Candida albicans colonization. – PubMed – NCBI Nat Med. 2015 Jul;21(7):808-14.