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Antidepressant Effects of Noni Fruit and its Active Principals

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Abstract: The antidepressant effects of *Morinda citrifolia* (noni) fruit extracts were investigated *in vitro* with the Monoamine Oxidase (MAO) A and B bioassays. The ethyl acetate extract of freeze-dried noni fruit powder inhibited MAO-A and B enzymes 78 and 49%, respectively. A phytochemical study of the most active extract led to the isolation of nine compounds. Among these, three principles including two flavonoids, kaempferol and quercetin, as well as one lignan, (+)-3,4,3',4'-tetrahydro-9,7' α -epoxylignan-7 α ,9'-lactone, were found to be potent MAO-A and B inhibitors. These findings indicate that noni fruit is a natural MAO-A and MAO-B inhibitor, involving a synergistic effect from multiple active components.

Key words: Active compounds, antidepressant, MAO-A & B, *Morinda citrifolia*, noni

INTRODUCTION

Major depressive disorder, also known as clinical depression, remains a problem among developed and developing nations. Lifetime prevalence estimates range from about 3% of the population (Japan) to 17% (USA), with most nations between 8 and 12% (Andrade *et al.*, 2003). Within the United States, the 12-month prevalence has been estimated to be 6.6% (Kessler *et al.*, 2003). Clearly, depression remains an important public health issue. Treatment of depression involves many modalities, the majority of which are psychotherapy and pharmacological interventions. Among the antidepressant drugs are Monoamine Oxidase (MAO) inhibitors. Monoamine oxidase enzymes break down the monoamine neurotransmitters, such as dopamine, serotonin, epinephrine and norepinephrine (Spencer, 1977). The utility of MAO inhibitors lies in their ability to prevent the catalysis of the amine based neurotransmitters. MAO inhibitors have been found to be useful in the treatment of a wide variety of mental health disorders, but they also have a number of serious toxicities associate with their use, such as hypertensive reaction and other more common undesirable side effects, including weight gain and daytime sedation (Remick and Froese, 1990).

The scientific investigation of anti-depression and anti-anxiety botanicals is driven by the desire to find useful treatments which might be potentially safer and have more mild activities. Examples of antidepressive plants include *Hypericum perforatum*, *Ginkgo biloba*, *Apocynum venetum*, *Valeriana officinalis* and *Melissa*

officinalis (Shirai *et al.*, 2005; Weeks, 2009). *Morinda citrifolia*, commonly known as noni in indigenous tropical areas, has a long traditional history of use for the prevention and treatment of many diseases including cancer, colds, diabetes, flu, anxiety, hypertension, pain, and other health disorders (Wang *et al.*, 2002; McClatchey, 2002). Noni fruit may also be a useful natural remedy for the treatment of anxiety and depression. Noni fruit juice has been demonstrated to be well tolerated, even at high doses (West *et al.*, 2009). Among rural populations of the South Pacific, noni is thought to be useful for the treatment of anxiety and depression (Pande *et al.*, 2005). Consumption of noni juice was also associated with improvements in mood scores of postmenopausal women (Langford *et al.*, 2004). Therefore, the current investigation was conducted to examine the potential mechanisms responsible for the antidepressive activity of noni juice. As of today, the following classes of compounds have been isolated and identified from noni fruits: amino acids, anthraquinones, coumarins, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, sugars, sulfur-containing compounds, and terpenoids (Deng *et al.*, 2007; Pawlus and Kinghorn, 2007). In this study, noni fruit and its compounds were evaluated for their inhibitory effects on monoamine oxidase A and B *in vitro*.

MATERIALS AND METHODS

The experiments were conducted in 2007-2009 at the Research lab of Tahitian Noni International, USA.

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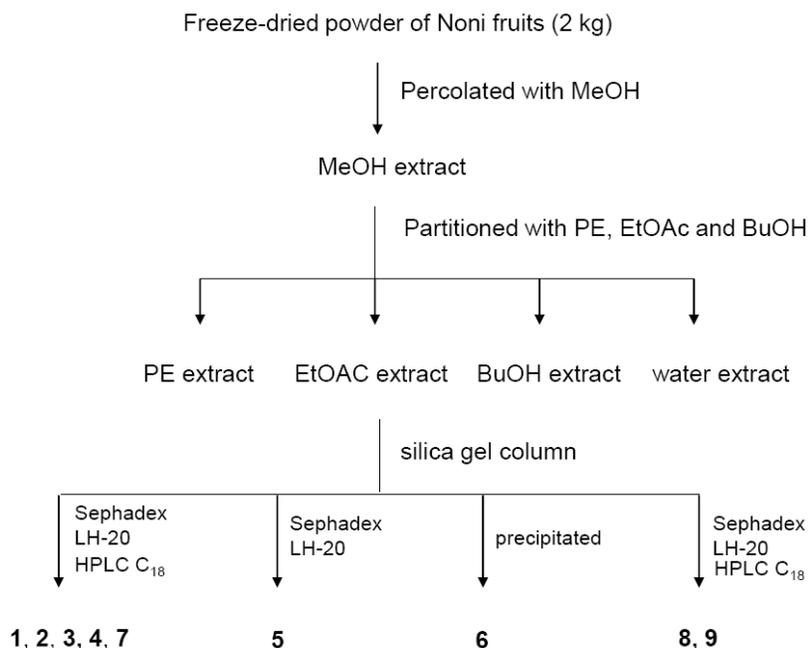


Fig. 1: Flow chart of the fractionation and isolation of MAO bioactive compounds from noni fruit using a series of chromatographic techniques. 1-9 represent pure compounds 3,4,3',4'-tetrahydroxy-9,7 α -epoxy lignano-7 α ,9'-lactone (1), 3,3'-bisdemethyltanegool (2), (-)-pinoresinol (3), (-)-3,3'-bisdemethylpinoresinol (4), quercetin (5), kaempferol (6), scopoletin (7), isoscapoletin (8), and vanillin (9)

Plant material: *Morinda citrifolia* fruits were collected from a farm in Mataiea, Tahiti during June 2004 and identified by the quality control department of Tahitian Noni International, Inc. (TNI). The fresh juice of *M. citrifolia* was dried using a lyophilizer. A reference sample of freeze-dried powder of fruits was deposited in the TNI research and development laboratory (lot # 52410).

Experimental: UV absorption data were recorded on a Varian Cary 1C UV/Vis spectrophotometer, and IR spectra were taken on a Thermo Nicolet Avatar 360 FT-IR spectrometer. All ^1H NMR and ^{13}C NMR data were recorded on a Varian INOVA-500 spectrometer using CDCl_3 or CD_3OD as solvents, and tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (HRMS) were obtained on an Agilent 1100 series liquid chromatograph/mass selective detector (LC/MSD) time-of-flight (TOF) mass spectrometer (Agilent Technologies, Inc., Palo Alto, CA), equipped with an electrospray ion source (ESI). Preparative HPLC was performed with a Waters AllianceTM 2690 separations module coupled with a Waters 2996 photodiode array (PDA) detector and utilizing a Waters XTerra[®]

preparative MS C_{18} OBD column (10 μm , 19 \times 300 mm, Wexford, Ireland).

Extraction, isolation and identification: Extraction and isolation was performed as described previously (Deng *et al.*, 2007). Briefly, freeze-dried *M. citrifolia* fruit powder (2 kg) was steeped in methanol for 24 h at room temperature, then percolated with 20 L of methanol. The methanol percolate was concentrated and diluted with H_2O , then partitioned with petroleum ether (PE), ethyl acetate (EtOAc), and butanol (BuOH) sequentially to yield corresponding partitions, as shown in Fig. 1. The resulting PE, EtOAc and BuOH extracts were dried *in vacuo* with a rotary evaporator. The aqueous mother liquid was lyophilized to produce a dried aqueous extract. Further, the EtOAc extract was subjected to flash column chromatography, Sephadex LH-20, and reversed-phase preparative HPLC chromatography to yield compounds 1-9. A flow chart of fractionation and isolation is summarized in Fig. 1. The chemical structures of 1-9 were elucidated by a series of spectroscopic techniques, including UV, IR, 1D and 2D NMR, as well as high resolution mass spectrometry. Compounds 1-9 were identified as 3,4,3',4'-tetrahydroxy-9,7 α -epoxy lignano-

7 α ,9'-lactone (1), 3,3'-bisdemethyltanegool (2), (-)-pinoresinol (3), (-)-3,3'-bisdemethylpinoresinol (4), quercetin (5), kaempferol (6), scopoletin (7), isoscapoletin (8), and vanillin (9).

Monoamine Oxidase (MAO) A and B inhibition assays:

Antidepressant effects of noni fruit extracts and isolated compounds were studied *in vitro* with the monoamine oxidase (MAO) A and B inhibition assays, according to a previously reported protocol (Urban *et al.*, 1991; Youdim and Finberg, 1991). Briefly, human recombinant MAO-A and MAO-B expressed in insect cells were used. Test extracts, compounds and/or vehicle were preincubated with 4.2 μ g MAO-A/mL or 13 μ g MAO-B/mL enzymes in phosphate buffer pH 7.4 for 15 min at 37°C. The reaction was initiated by addition of 50 μ M kynuramine for a 60 min incubation period and terminated by addition of 6 N NaOH. The amount of 4-hydroxyquinoline formed was determined spectrofluorimetrically by absorbance at 325 nm/465 nm. Extracts and compounds were screened at 100 μ g/mL, and active compounds (inhibition >50%) were tested for their 50% inhibition concentrations (IC₅₀). Reference standards were run as an integral part of each assay to ensure the validity of the result obtained. Tetrindole was used as a reference compound.

RESULTS AND DISCUSSION

Noni fruit was extracted with different solvents and prepared into different extracts and examined for their *in vitro* MAO-A and MAO-B inhibitory effects. The experimental results demonstrated that among PE, EtOAc, BuOH, and water extracts, the EtOAc extract

Table 1: The screening of MAO-A & B inhibitory activities of noni fruit extracts

Extracts	Inhibition (%)	
	MAO-A	MAO-B
Pet ether extract	33	36
Ethyl acetate extract	78	49
Butanol extract	23	26
Water extract	1	11

showed the most activity against MAO-A and MAO-B enzymes, with 78 and 49% inhibition at a concentration of 100 μ g/mL (Table 1 and Fig. 2). This finding suggests that noni may contain antidepressant components. As such, the active EtOAc extract was further subjected to phytochemical investigation for identification of potential active principle(s). The extensive screening led to isolation and identification of nine pure compounds which were further evaluated in *in vitro* assays.

The preliminary screening at a concentration of 100 μ g/mL suggested that three compounds, 3,4,3',4'-tetrahydroxy-9,7' α -epoxylignano-7 α ,9'-lactone (1), quercetin (5), and kaempferol (6), inhibited more than 50% of enzyme activity. Their structures are summarized in Fig. 3. The experimental results (Table 2) indicate that 3,4,3',4'-tetrahydroxy-9,7' α -epoxylignano-7 α ,9'-lactone exhibited similar inhibitory activities on MAO-A and MAO-B enzymes, with IC₅₀ values of 47.6 and 36.6 μ M, respectively. Quercetin and kaempferol, with IC₅₀ values of 3.15 μ M and 0.72 μ M for MAO-A, and 31.7 μ M and 20.4 μ M for MAO-B, respectively, displayed MAO-A selectivity indices of 10 and 28. These results indicate that both are more potent inhibitors of MAO-A than MAO-B enzyme.

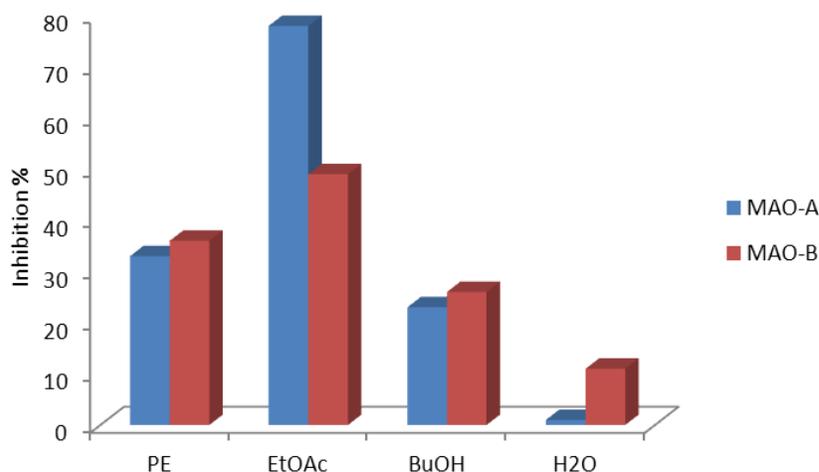
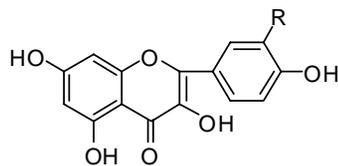
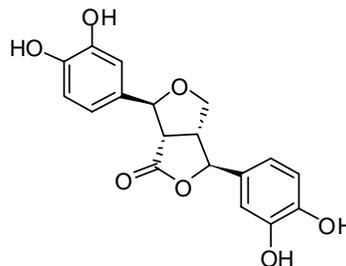


Fig. 2: MAO-A and B inhibitory activities of noni fruit extracts



Kaempferol R=H, Quercetin R=OH



(+)-3,4,3',4'-tetrahydro-9,7'α-epoxylygnan-7α,9'-lactone

Fig. 3: Structures of MAO bioactive compounds in noni fruit

Table 2: Determination of MAO-A & B inhibition of compounds isolated from noni fruit

Isolates	IC ₅₀ ^a (μM)		MAO-A Selectivity index ^b
	MAO-A	MAO-B	
(+)-3,4,3',4'-Tetrahydro-9,7'α-epoxylygnan-7α,9'-lactone (1)	47.6	36.6	0.77
3,3'-Bisdemethyltanegool (2)	-	-	-
(-)-Pinoresinol (3)	-	-	-
(-)-3,3'-Bisdemethylpinoresinol (4)	-	-	-
Quercetin (5)	3.15	31.7	10.06
Kaempferol (6)	0.72	20.4	28.33
Scopoletin (7)	-	-	-
Isoscapoletin (8)	-	-	-
Vanillin (9)	-	-	-
Tetrindole ^c	0.014	0.51	36.43

^a: concentrations of samples required to inhibit enzyme activities by 50%; ^b: Selectivity index = MAO-B IC₅₀ / MAO-A IC₅₀; ^c: Positive control, Compounds 2-4 and 7-9 were inactive in the preliminary screening (inhibition < 50% at a concentration of 100 μg/mL)

In conclusion, the experiments investigated the antidepressant effects of noni fruits and its bioactive principles in terms of the monoamine oxidase (MAO) A and B bioassays for the first time. The findings indicate that noni fruit is a natural MAO-A and MAO-B inhibitor, involving a synergistic effect from multiple active components. The results of this investigation provide an *in vitro* rationale for the traditional uses of noni fruits as a natural remedy for anti-depression and anti-anxiety, as well as improved sense of well-being. This study reports the possible *in vitro* mechanism responsible for noni antidepressant and anti-anxiety effects. Further animal and/or clinical investigation may be warranted.

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