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Anxiolytic and antidepressant properties of *Aegle marmelos*: An overview

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ABSTRACT

Aegle marmelos belongs to Rutaceae family, well known ancient ayurvedic medicinal tree commonly known as the Bael. It is medium sized tree growing throughout the forest of India of altitude 1200 meter. It is found all over India, from sub-Himalayan forest, Bengal, central and south India. The different parts of this plant contain number of coumarins, alkaloids, sterols and essential oils. Various parts of this plant such as leaves, roots, seed, bark and fruit, possess anti-microfilarial, antifungal, analgesic, anti-inflammatory, antipyretic, hypoglycaemic, anti dyslipidemic, immunomodulatory, antiproliferative, wound healing, anti-fertility, and insecticidal activity. Especially this study has been conducted to review the anxiolytic and antidepressant activity of *A. marmelos*. Among all the tissues leaf has been proved by the earlier researchers, which is potential for the treatment anxiolytic and antidepressant activity. Therefore the remaining tissue like fruits has not been proved to possess anxiolytic and antidepressant property. Therefore the study has confirmed that no reports are available to confirm the potentiality of fruit of *A. marmelos* against anxiolytic and antidepressant activity.

Keywords: Anxiolytic, Antidepressant, *Aegle marmelos*

1. Introduction

Over the past decades alternative medicine has increased and variety of studies has suggested that this use is greater in persons with symptoms or diagnoses of anxiety and depression. The effective support of some popular herbal remedies and dietary supplements; particularly kava, the potential for benefit seems greater than that for harm with short-term use in patients with mild to moderate anxiety. Hence, the evidence varies depending on the supplement and the anxiety disorder, physicians can collaborate with patients in developing dietary supplement strategies that minimize risks and maximize benefits [1]. India is well known for natural vegetation and herbals medicines. India's most fabulous ancient medicine is *Aegle marmelos*, which has been proved potential drug. *A. marmelos* Correa is a plant belonging to Rutaceae family. This plant grows widely in some areas of the Southeast and South Asia countries such as India, Sri Lanka, Indonesia, Malaysia and Vietnam. It is commonly called as Bael. It is slow-growing, medium sized tree, up to 12-15 m tall. It is armed tree to 8(15) m; branched pubescent; spines axillary, to 2(6) cm, Straight, single or paired. Leaves 3(5) foliate, to 5 cm. Fruit 2 1/2 to 3 1/4 inches in diameter, globular or ovoid in shape, colour greyish brown, outside surface hard and nearly smooth. Rind about 1/8 inch thick and adherent to a light red pulp, in which are ten to fifteen cells, each containing several woolly seeds. It has a faint aromatic odour and mucilaginous taste.



A. marmelos leaf



A. marmelos fruit



There are different types of *A. marmelos*, which is categorized by five different shape of fruit like oval, flat, spherical, oblong and pear, then in each category three sub categories in size like small, medium and big. It has long been used as an ancient and modern traditional medicine. Vernacular name of *A. marmelos* in Tamil is Aluvigam, Iyalbudi, Kuvilam, Mavilangai, Vilwam and Villuvam.

2. Phytochemicals

A. marmelos is reported to contain a number of coumarins, alkaloids, sterols and essential oils. Roots and fruits contain coumarins such as scoparone, scopoletin, umbelliferone, marmesin and skimmim. Fruits, in addition, contain xanthotoxol, imperatorin and alloimperatorin and alkaloids like aegeline and marmeline identified as N-2- hydroxy-2-[4-(3',3'-dimethyl allyloxy) phenyl] ethyl cinnamide, b- sitosterol and its glycoside. Roots and stem barks contain a coumarin - aegelinol. Roots also contain psoralen, xanthotoxin, 6,7- dimethoxy coumarin, tembamide, mermin and skimmianine. Leaves contain the alkaloids - O-(3,3- dimethyl allyl)-halfordinol, N-2-ethoxy-2 (4-methoxy phenyl) ethyl cinnamide, N-2-methoxy-2-(4-3',3'-dimethyl allyloxy) phenyl] ethyl cinnamide, N- 2- [4-(3',3'-dimethyl allyloxy) phenyl] ethyl cinnamide, N-2-hydroxy-2-[4-(3',3'- dimethyl allyloxy) phenyl] ethyl cinnamide, N-4-methoxy steryl cinnamide and N-2-hydroxy-2-(4- hydroxy phenyl) ethyl cinnamide, mermesinin, rutin and b-sitosterol - b-D-glucoside [2]. A series of phenylethylcinnamides, which included new compounds named anhydromarmeline [3], aegelinosides A and B were isolated from *A. marmelos* leaves as alfaglucoisidase inhibitors. A rare alkaloid, shahidine [3], having an unstable oxazoline core has been isolated as a major constituent from the fresh leaves of *A. marmelos*. It is moisture-sensitive, and found to be the parent compound of aegeline and other amides; however, it is stable in dimethyl sulfoxide. Shahidine [3], and showed activity against a few Gram-positive bacteria [4]. From dry leaves of *A. marmelos*, four new alkaloids, N- 2-[4-(3', 3'-dimethylallyloxy) phenyl] ethyl cinnamide, N-2- hydroxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethyl cinnamide, N-4-methoxystyryl cinnamide and N-2- hydroxy-2-(4-hydroxyphenyl) ethyl cinnamide were isolated and characterized. From the unripe fruits of *A. marmelos*, a new alkaloid named marmeline was isolated and identified as N-2-hydroxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethyl cinnamide. Aegline, imperatorin, alloimperatorin and xanthotoxol were also present [5]. The purified polysaccharide isolated from the cambium layer of a young *A. marmelos* tree contains galactose, arabinose, rhamnose, xylose, and glucose in the molar ratios of 10.0:9.8:1.4:1.9:1. A new compound 7- geranyloxy coumarin [7-(2,6-dihydroxy-7-methoxy-7- methyl-3-octaenyloxy) coumarin] named marmenol [3] has been isolated from the leaves of methanolic extract of *A. marmelos*. In addition to marmenol, several known compounds praealtin D, trans-cinnamic acid, valencic acid, 4-methoxy benzoic acid, betulinic acid, N-pcis- and trans-coumaroyltyramine, montanine, and rutaretin have also been obtained for the first time from the same source. Antifungal constituents, 2-isopropenyl-4-methyl-1-oxacyclopenta[b]anthracene-5,10-dione and (+)-4- (20- hydroxy-30-methylbut-30-enyloxy)-8H-[1,3]dioxolo[4,5- h]chromen-8-one in addition to known compounds imperatorin, b-sitosterol, plumbagin, 1-methyl-2-(30- methyl-but-20-enyloxy)-anthraquinone, b-sitosterol glucoside, stigmaterol, vanillin and salicin were isolated during phytochemical investigation on seeds of *A. marmelos* [6].

3. Pharmacological properties

A. marmelos possess various pharmacological activity, which has been reported and discussed many of the researchers. For our study purposes few has been depicted are as follows. The acute and sub-acute toxicity study was designed to elucidate the toxicity of the widely used plant metabolites in many biological systems. For example, the aqueous and organic extracts isolated from the leaves of *A. marmelos* was studied for their toxic effects by some of the earlier workers for acute, subacute and LD₅₀ levels. Following the chronic administration of *A. marmelos* for 14 days, the vital organs such as heart, liver, kidney, testis, spleen and brain were carefully evaluated by histopathological studies. There were no remarkable changes noticed in the histopathological studies after 50, 70, 90 and 100mg mg/kg body wt of the extracts of *A. marmelos* when administered intraperitoneally [7]. Pathologically, neither gross abnormalities nor histopathological changes were observed.

4. Contractile activity

The contractile activity of the alcoholic extract of the leaves of *A. marmelos* on guinea pig isolated ileum and tracheal chain was investigated, as this plant is used traditionally to treat asthma and related afflictions. After administration of alcoholic extracts, it showed complete relaxation of the guinea pig ileum and tracheal chain. The results were due to the presence of one or more antihistaminic constituents present in the alcoholic extract of this plant, therefore supporting to the traditional use of *A. marmelos* in asthmatic complaints [8].

5. Antifilarial activity

Methanolic extract of roots and leaves of *Vitex negundo* L. and leaves of *Ricinus communis* L. and *A. marmelos* were explored for possible anti filarial effect against *Brugia malayimicrofilariae*. It was observed that among the herbal extract, root extract of *vitex negundo* and leaves extract of *A. marmelos* showed complete loss of motility of microfilariae after 48 hrs of incubation. The presence of alkaloids, saponins and flavonoids in the roots of *V. negundo* and coumarin in the leaves of *A. marmelos is* responsible for anti-microfilarial activity [9].

6. Antifungal Activity

A new anthraquinone, 1-methyl-2-(3'- methyl-but-2'-enyloxy)-anthraquinone [3] has been isolated from seeds of *A. marmelos* was characterized exhibited significant antifungal activity against pathogenic strains of *Aspergillus* species and *Candida albicans* [6]. The antifungal activity of essential oil isolated from the leaves of *A. marmelos* has exhibited variable efficacy against different fungal isolates [10].

7. Analgesic activity

The methanol extract of leaves of *A. marmelos* at a dose level of 200 and 300 mg/kg showed significant analgesic activity on acetic acid-induced writhing and tail flick test in mice [11].

8. Anti-inflammatory activity

The serial extracts of the leaves of *A. marmelos* were investigated for anti-inflammatory property. The most of the extracts derived from the plant *A. marmelos* caused a significant inhibition of the carrageenan-induced paw oedema and cotton-pellet granuloma in rats. The extracts also produced marked analgesic activity by reduction the early and late phases of paw licking in mice. A significant reduction in hyperpyrexia in rats was also produced by the most of the extracts. This study was established anti-

inflammatory, antinociceptive and antipyretic activities of the leaves of *A. marmelos* [12].

9. Hypoglycemic activity

The hypoglycemic effect of the water extract of the fruits of *A. marmelos* was examined in streptozotocin-induced diabetic Wistar rats. Oral administration of the water extract (125 and 250 mg kg⁻¹) twice a day for 4 weeks resulted in significant reductions in blood glucose, plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin and α -tocopherol and a significant elevation in plasma reduced glutathione and Vitamin C in diabetic rats [13]. The investigations of clearly indicate that aqueous seed extract of *A. marmelos* possess antidiabetic and hypolipidemic effects in diabetic rats [14].

From the leaves of *A. marmelos* an alkaloidal-amide, Aegeline 2, was isolated and found to have antihyperglycemic activity as evidenced by lowering the blood glucose levels in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg body weight. Aegeline 2 has also significantly decreased the plasma triglyceride (Tg), total cholesterol (TC) and free fatty acids (FFA) in dyslipidemic hamster model at the dose of 50 mg/kg body weight [15].

10. Immunomodulatory activity

The immunomodulatory action of methanolic extract of *A. marmelos* fruit in experimental model of immunity Methods: Cellular immunity was carried out by neutrophil adhesion test and carbon clearance assay [16]. The findings concluded that the fruit extract of *A. marmelos* possesses potential for augmenting immune activity by cellular and humoral mediated mechanisms more at low dose than high dose.

11. Wound healing activity

Effect of topical and intraperitoneal administration of methanolic extract of *A. marmelos* ointment and injection was studied [17] on two types of wound models in rats, the excision and the incision wound model. Both the injection and the ointment of the methanolic extract of *A. marmelos* produced a significant response in both of the wound type tested. In the excision model the extract treated wounds were found to epithelialize faster and the rate of wound contraction was higher, as compared to control wounds. The extract facilitated the healing process as evidenced by increase in the tensile strength in the incision model. The results were also comparable to those of a standard drug nitrofurazone.

12. Antifertility activity

The leaf extract of *A. marmelos* suppresses fertility in male rats and complete recovery of fertility was observed following the withdrawal of drug. Absence of any deleterious effect on the vital organs points to the safe use of the extract [18].

13. Anti-proliferative activity

Hydroalcoholic extract of *A. marmelos* leaves has shown anticancer effect in the animal model of Ehrlich ascites carcinoma. Induction of apoptosis may be due to the presence of skimmianine in the leaf extract which may have killed the tumor cells [19]. The plant extract exhibits cytotoxicity against tumor cell lines in brine shrimp lethality assay and Methyl Thiazolyl Tetrazolium (MTT) based assay [20]. Extracts from *A. marmelos* are able to inhibit the in vitro proliferation of human tumor cell lines, including the leukemic

K562, T-lymphoid Jurkat, Blymphoid Raji, erythroleukemic HEL, melanoma Colo38, and breast cancer MCF7 and MDAMB- 231 cell lines due to the bioactivity of butyl p-tolyl sulfide, 6-methyl-4-chromanone and butylated hydroxyanisole [21].

14. Antioxidant activity

Oxidative stress is produced during normal metabolic process in the body as well as induced by a variety of environmental and chemical factors, which cause generation of various reactive free radicals and subsequent damage to macromolecules like DNA, protein and lipids. In artificially induced diabetic animals, the levels of lipid peroxidation, hydroperoxides (HP), conjugated diene, thiobarbituric acid reactive substances (TBARS), creatine kinase (CK) and lactate dehydrogenase (LDH) increased considerably, and then decreased after treatment with various extracts of *A. marmelos* leaves and fruits. Antioxidative parameter like reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD) and catalase have shown a dose dependent increase in their activity and a decrease in lipid peroxidation due to the treatment of *A. marmelos* leaf extracts [22-26]. The antioxidative phytochemicals such as flavonoids, alkaloids, sterols, tannins, phlobatannins and flavonoid glycosides present in the leaf extract possess free radical scavenging activity [26-32]. Glutathione (GSH) is reduced in erythrocyte whereas plasma glutathione-S-transferase (GST) and malondialdehyde (MDA) are increased in male albino rats with diabetes. However these alterations returned to normal level with *A. marmelos* leaf extract administration, suggesting antioxidant potential of *A. marmelos* leaves [33].

15. Anxiolytic and antidepressant activity

Kothari *et al.*, (2010) reported that methanol leaf extract of *Aegle marmelos* showed significant anxiolytic and antidepressant activities possibly by increasing monoamines level at post synaptic sites which has been confirmed by various methods like elevated plus maze, open field tests, Actometer and forced swim test (FST). Hence *Aegle marmelos* may be served as a potential resource for natural psychotherapeutic agent against stress related disorders such as anxiety and depression.

16. Conclusion

In conclusion, *A. marmelos* tissues are potential for the treatment of various disorders like anti-microfilarial, antifungal, analgesic, anti-inflammatory, antipyretic, hypoglycaemic, antidyslipidemic, immunomodulatory, antiproliferative, wound healing and anti-fertility. Now a days the herbal researchers are concentrating to identify the drugs from the natural resources, in order to stay away from the synthetic drugs and its adverse effect. Hence *A. marmelos* leaf has been reported as potential resources for treatment of anxiety and depression. It is quite evident from this review that *A. marmelos* an important medicinal herb and extensively used in Ayurveda, Siddha and other medicinal systems. *A. marmelos* contains a number of phytoconstituents, which are the key factors in the medicinal value of this plant. Almost all parts of this plant such as leaf, fruit, seed, bark and root are used to cure a variety of diseases. Based on the earlier report the fruit of *A. marmelos* has not been reported for the psychiatric disorders. As the pharmacologists are looking forward to develop new drugs from natural sources, development of modern drugs from *A. marmelos* can be emphasized for the control of various diseases. A systemic research and development work should be undertaken to identify

the efficacy of the different tissues of *A. marmelos*.

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