

**BIOACTIVE COMPOUNDS PRESENT IN *AEGLE MARMELLOS* AND THEIR ROLE IN MEDICINAL PROPERTIES: A REVIEW****NIDHI SHARMA AND WIDHI DUBEY\****School of Sciences, JECRC University, Jaipur, Rajasthan, 303905***ABSTRACT**

Plants used by ethnic groups are proved to be a rich source of novel drugs that form the ingredients in traditional and modern systems of medicines. Pharmacological studies have acknowledged the value of ethnomedicinal plants as prospective source of bioactive principles. *Aegle marmelos* (L.) Corr. Serr. of family Rutaceae, commonly known as wood apple plant, is one of the important plants with medicinal and nutraceutical properties. It can tolerate a wide range of climatic conditions and used as a panacea for various ailments by tribal people throughout the world. This review has been done to find out the role of various bioactive compounds present in the plant parts of *A. marmelos* in medicinal properties.

**KEY WORDS:** Ethnomedicinal plant, *Aegle marmelos*, Bioactive principles, Rutaceae**WIDHI DUBEY***School of Sciences, JECRC University, Jaipur, Rajasthan, 303905***\*Corresponding Author**

## INTRODUCTION

From the time immemorial plants have been the major source of food and medicines for mankind. Traditional medicines, predominantly acquired from plants have played a critical role in perpetuating disease free human survival on this planet. In recent years, plant pathogenic microorganisms and human being have developed multiple drug resistance due to the haphazard use of synthetic drugs. So traditional medicines designed as herbal drugs have retained their place in therapy. The efficacy, affordability and comparative freedom from toxic effects of these medicines make them more favoured. These plants are used in traditional Chinese, Ayurvedic, Siddha, Unani and Tibetan medicines. Ancient literature such as Charak Samhita, Rigveda, Yajurveda, Atharvaveda and Sushrut Samhita also describes the use of plants for the treatment of various ailments.<sup>1</sup> Bioactive compounds in the plants can be defined as 'secondary metabolites', eliciting pharmacological or toxicological effects in men and animals. Plants synthesize a variety of secondary metabolites which provide protection against the harmful and infectious agents. This drives the need to screen medicinal plants for novel bioactive compounds due to their biodegradability and fewer side effects.<sup>2</sup> *Aegle marmelos* (L.) Corr. Serr. belongs to family Rutaceae, the family of flowering plants. *Aegle marmelos* is commonly known as wood apple plant and other vernacular names are as - English (Bael Fruit, Indian Bael, Holy Fruit, Golden Apple, Elephant Apple, Bengal Quince, Indian Quince, Stone Apple); Hindi (baelputri, bela, sirphal, siri-phal, kooralam); Gujarati (bili); Burmese (Opesheet, Ohshit); German (Belbaum, Schleimapfelbaum, Baelbaum); Indonesian (maja batuh, maja); Javanese (modjo); Khmer (bnau); Lao (Sino-Tibetan) (toum); Malay (bilak, bel, bila, maja pahit); Portuguese (marmelos); Thai (matum, mapin, tum); Vietnamese (traï mam, mbau nau). *Aegle marmelos* is a subtropical plant which can grow up to an altitude of 1200 m from the sea level where a wide range of temperature occurs throughout the year. It grows well in the dry forests of hilly and plain areas and fruiting of this tree requires sufficient dry season. If there is no long, dry season as in southern Malaysia, fruiting will not occur. Though *A. marmelos* is native to India and has its

origin from Eastern Ghats and central India but it can revamp in a wide range of habitat and can be cultivated worldwide. It thrives well on rich, well-drained soil, but it also grows well in swampy, alkaline or stony soils having pH range from 5 to 8. So, it is well known for thriving in the harsh climatic conditions, where other fruit trees cannot survive.<sup>3</sup> It is one of the important plants with several medicinal and nutraceutical properties.<sup>4</sup> Variety of bioactive compounds has been isolated from different parts of the plant and were analysed pharmacologically for their medicinal properties. In last few decades, extensive study by the use of advanced scientific techniques have reported various medicinal properties of *Aegle marmelos* viz., antimicrobial activity, antidiabetic activity, antioxidant activity, hepatoprotective activity, haemolytic activity and anti-inflammatory activity.<sup>5</sup>

Almost all of the plant parts such as leaves, roots, stem, bark, fruits and seeds possess medicinal properties as proven by various researchers. Looking upon wide prospects and potential of *A. marmelos* (bael) for various purposes, it is fruitful to grow this plant on large scale especially on barren and wasteland. Besides providing base for the research and development of low-cost and more potent drugs it will also lead to economic revival of the poor farmers.

## A SURVEY OF AGRICULTURAL FIELDS FROM SEMI-ARID AREA OF RAJASTHAN, INDIA

Rajasthan is a state with dry and hot climatic conditions but in spite of the harsh climatic conditions bael plant thrives well in this area. It is not only beneficial from the medicinal point of view but also helps in reducing desertification and provides shade, fruits and foliage for cattle. A survey was done at 'Chaumon' agricultural lands in Jaipur district of Rajasthan which is a semi-arid area. The bael plants were grown on large areas without any specific cultivation conditions. Fruit juice of *A. marmelos* is very well marketed in summer season due to its cooling and digestive properties. It was found to be a major source of livelihood for farmers and tribes of this area.



**Figure 1**  
**A survey of local fields at Jaipur (semi-arid) Region in Rajasthan**

## SECONDARY COMPOUNDS IN *AEGLE MARMELLOS*

The flow chart given below is prepared to give an idea of classification of the secondary metabolites present in *Aegle marmelos*<sup>6,7</sup>

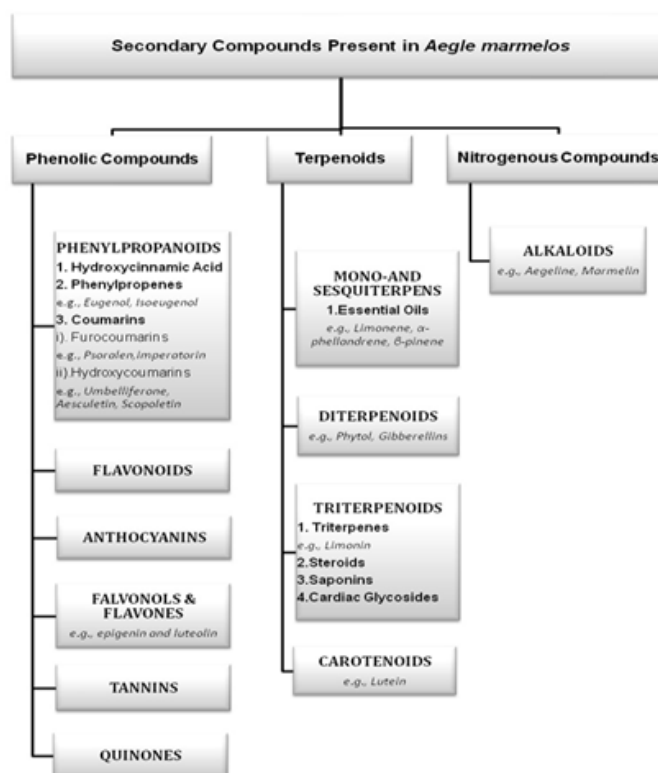


Figure 2

Flow Chart showing the classification of secondary metabolites in *Aegle marmelos* plant

## PHARMACOLOGICAL FINDINGS

Many Indian workers have isolated and characterized various compounds. The main compounds found are tannins (20%), saccharides, starch, fatty oil, furocoumarins, furoquinoline and alkaloids. Fruits contain luvangetin, aurapten, psoralen, marmelide and tannin. Fruits in addition contain coumarins, steroids, essential oils, xanthotoxol, imperatorin and alloimperatorin and alkaloids like aegeline and marmeline. Marmelosin, skimmianine and umbelliferone are the therapeutically active principles of bael fruit. Minor constituents like ascorbic acid, sitosterol, crude fibres, tannins,  $\alpha$ -amyrin, carotenoids and crude proteins are also present. It also contains polysaccharides like galactose, arabinose, uronic acid and L-rahamnose, which can be obtained after hydrolysis. Different organic extracts of the leaves of *A. marmelos* have been reported to possess alkaloids, cardiac glycosides, terpenoids, and various phenolics compounds such as, saponins, tannins, flavonoids and steroids.<sup>8</sup>

B.R. Sharma and co workers isolated a new alkaloid named marmeline from unripe fruits of *Aegle marmelos* in 1981, which was identified as *N*-2-hydroxy-2-[4-(3', 3'-dimethylallyloxy)phenyl]ethyl cinnamides. Other compounds, such as Aegeline, imperatorin, alloimperatorin and xanthotoxol were also present.<sup>9</sup> Govindachari and Premila in 1983 reported four alkaloids, *N*-2-[4-(3', 3'-dimethylallyloxy)phenyl]

ethylcinnamide, *N*-2-hydroxy-2-[4-(3', 3'-dimethylallyloxy) phenyl] ethylcinnamide or marmelin, *N*-4-methoxystyryl cinnamides and *N*-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide and Aegeline in the dry leaves of *A. marmelos*.<sup>10</sup> Aegeline was initially identified as a sterol but after a critical study it was found to be a neutral nitrogenous alkaloid compound.<sup>11</sup> Radhika Samarasekera and co-workers in 2004 afforded a new compound named skimmiarepin C and A from ethyl acetate extracts of stem bark of *Aegle marmelos* by using bioassay-directed fractionation. skimmiarepin A is a known compound but isolation from *A. marmelos* was new. The new compound skimmiarepin C is a senecioate ester analogue of skimmiarepin A. Spectroscopic methods on the separated mono-acetate derivatives were used for complete identification of the new compound. Protolimonoids, Skimmiarepins A and C both exhibited moderate insecticidal activity against *Phaedon cochleariae* and *Musca domestica* in comparison with natural pyrethrum extract.<sup>12</sup> In 2004, Ali and Parvez isolated marmenol from the methanolic extract of the *Aegle marmelos* leaves which was also identified as 7-geranyloxy coumarin [7-(2,6-dihydroxy-7-methoxy-7-methyl-3 octaenyloxy) coumarin]. Other Known compounds including praealtin D, *trans*-cinnamic acid, valencic acid, 4-methoxy benzoic acid, betulinic acid, *N*-*p*-*cis*- and *trans*-coumaroyltyramine, montanine, and rutaretin were also obtained. NMR Spectroscopy was used to establish the structure of marmenol and other known constituents.<sup>13</sup> Umadevi and co-workers

from Bharathi Women's College, Chennai (Tamil Nadu) in 2011 determined forty seven compounds in ethyl acetate fraction of *Aegle marmelos* leaves extract by GC-MS analysis. The prevailing compounds were Benzo [b] -1, 4-diazabicyclo [2.2.2] octane, 3, 4-Dimethoxybenzoic anhydride, Cinnamic acid, Palmitic acid, 1 Phenylpyrrole, Cinnamamide, 4-Methoxybenzaldehyde,  $\gamma$ -Sitosterol, Caryophyllene oxide,  $\alpha$ -amyrin and Loliolide.<sup>14</sup> Skimmianine is a quinoline alkaloid, also known as 4, 7, 8-trimethoxyfuroquinoline isolated from the roots and leaves of *Aegle marmelos*. New alkaloids from the leaves of *A. marmelos* were reported viz., O-3, 3-(dimethylallyl) halfordinol, N-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide, N-2-methoxy-2-[4-(3', 3'-dimethylallyloxy) phenyl] ethylcinnamamide, N-2-

methoxy-2-(4-methoxyphenyl) ethylcinnamamide and marmelin. Recently, series of phenylethyl cinnamides, which included new compounds named anhydromarmeline, aeglinosides A and B were isolated from *Aegle marmelos* leaves as  $\alpha$ -glucosidase inhibitors. Besides these, there are more than 100 compounds which have been isolated from *Aegle marmelos*.<sup>15, 16</sup> In 2014, Farina Mujeeb with her co-workers studied leaf extracts of 18 varieties of *Aegle marmelos* and through GC/MS analysis it was found that the plant extracts are rich source of bioactive compounds. 33 compounds were identified and found responsible for various activities, predominantly play a role in antimicrobial activity of the plant.<sup>17</sup> Following table gives an account on bioactive compounds present in the various plant parts.<sup>18,19,20</sup>

**Table 1**  
**Bioactive compounds identified in *Aegle marmelos* plant parts**

Sr. No.	Plant Part	Bioactive Compounds
1.	Roots	coumarins such as scoparone, scopoletin, umbelliferone, marmesin and skimmianine, alkaloids, halopine and terpenes
2.	Bark	Umbelliferone, skimmianine, marmin, $\beta$ -sitosterol, lupeol, and $\gamma$ -sitosterol. Stem bark contain fagarine, furoquinoline and alkaloids. marmenol, a new 7-geranyloxy coumarin [7-(2, 6-dihydroxy-7-methoxy-7-methyl-3-octaenyloxy) coumarin], rutacine, $\gamma$ -sitosterol, aegeline, aegeline, marmeline, fragrine, dictamine, cinnamide and different derivatives of cinnamides. lupeol, rutin, marmesin, $\beta$ -sitosterol, flavone, glycoside, O-isopentenyl halfordiol, cuminaldehyde, eugenol, cineol, citral, citronellal and phenylethyl cinnamides
3.	Leaves	
4.	Leaf Oil	$\alpha$ -Phellandrene, p-cymene, p-Menth-1-en-3; 5-diol, Limonene
5.	Fruit Rind	umbelliferone, dictamine, xanthotoxol, xanthotoxin, scaparone, isopimpinellin, isoimperatorin, N-2 methoxy-2-[4 methoxyphenyl] ethylenamide
6.	Fruit Pulp	steroids, terpenoids, phenolics compounds, mucilage, pectin, lignin, fat and volatile oil, insulin, proteins, carbohydrates, alkaloids, cardiac glycosides and bitter principle
7.	Seed oil	Seeds have essential oil which is bitter in taste and contains D- limonene, $\alpha$ -D-phellandrene, cineol, citronellal, citral, P-cymene, cuminaldehyde palmitic acid, stearic acid, linoleic and linolenic acid while seed residue contains about 70% protein.

## ROLE OF BIOACTIVE PRINCIPLES OF *AEGLE MARMELLOS* IN MEDICINAL PROPERTIES

In 2002, Badam and his co-workers evaluated the *A. marmelos* extracts for their efficacy against human coxsackieviruses B1-B6 and it was suggested by the study that marmelide was most effective as a virucidal agent.<sup>21</sup> In 2003 Dhuley, verified the antidiarrhoeal and gastroprotective effects of raw fruit extracts of *Aegle marmelos* Corr. in rats against gastric damage of mucosal membrane. It was demonstrated that pre-treatment of animals with unripe fruit extract produces a significant inhibition of gastric lesion and point out a possible antidiarrhoeal effect of unripe fruit extract of *A. marmelos* Corr.<sup>22</sup> Panda and Kar in 2006, isolated, Scopoletin (7-hydroxy-6-methoxy coumarin) from *Aegle marmelos* leaves and evaluated its efficacy to control hyperthyroidism. Results indicated that Scopoletin given to levo-thyroxin treated animals decreased the level of serum thyroid hormones. The study proved the superiority of Scopoletin over the standard anti-thyroid drug, propylthiouracil.<sup>23</sup> In 2007, Shankarananth and his colleagues evaluated that methanolic extracts of *A. marmelos* leaves show significant analgesic activity on acetic acid-induced writhing and tail flick test in mice.<sup>24</sup> In 2007, Narender and his co-workers isolated an alkaloidal-amide Aegeline from the leaves of the plant *Aegle marmelos*. It was evidenced that this compound found to have antihyperglycemic activity as it lowered the blood glucose levels in sucrose challenged streptozotocin

induced diabetic rats. Aegeline also significantly decreased the plasma triglyceride levels, total cholesterol and free fatty acids accompanied with increase in HDL-C and HDL-C/TC ratio in dyslipidemic hamster model.<sup>25</sup> Rajamanickam and co-workers in 2007 studied and concluded that the therapeutic administrations of fine powder of *Aegle* leaves greatly change the biochemical parameters in the ethanol intoxicated rats and maintained well to the normal level. Results of the study suggested the value of *Aegle marmelos* in hepatoprotective activity and created possibility of using the extracts of the plant as precursor in new drug discovery.<sup>26</sup> In 2009, Khan and Sultana evaluated antioxidant property and hepatoprotective potential of *A. marmelos* against CCl<sub>4</sub> – induced oxidative stress and early events of tumour formation and It was found by the study that *A. marmelos* play significant role.<sup>27</sup> In 2008, Dhalwal and his co-workers presented the work on antioxidant profile and high performance thin layer chromatography-densitometric analysis of Umbelliferone and Psoralen in methanolic extract of *A. marmelos* fruit. It was found by the study that *A. marmelos* fruit is a potential source of natural antioxidant.<sup>28</sup> Rana in 1997 evaluated the antifungal activity of essential oils isolated from Bael leaves using "Spore Germination Assay" and showed the activity of oil against the fungal strains used in the study. They proposed that essential oil from bael leaves may interfere with the Ca<sup>2+</sup>-dipicolinic acid metabolism pathway and possibly inhibit the spore formation.<sup>29</sup> In 2007, S.K. Gond and co-workers from Banaras Hindu University studied the endophytic fungal community from

different parts of *Aegle marmelos* from Varanasi, India. They selected the host plant due its medicinal value and to isolate and identify the endophytic microflora which is responsible for production of secondary metabolites. They isolated total of 79 isolates representing 21 genera of endophytic fungi.<sup>30</sup> Nowadays, endophytes are viewed as prominent source of novel bioactive compounds because many of the fungi occupy millions of plants as their niches growing in many unusual environments.<sup>31</sup> Based upon the previous literature they considered it possible that some endophytes of this plant could produce bioactive compounds as in case of fungal Taxol, a potent anti-breast cancer drug, discovered from the *Taxus brevifolia* and also by its endophytic fungus *Taxomyces andreanae*. In 2008, Gangadevi and Muthumary isolated an endophytic fungus *Bartalinia robillardoides* (strain AMB-9) Tassi from *Aegle marmelos* Correa ex Roxb., which produces Taxol. The fungal taxol isolated from the organic extract of this fungal culture shown strong cytotoxic activity towards human cancer cells in vitro.<sup>32</sup> Unsaponifiable portion and fixed oil of the *Aegle* seeds actively suppressed the growth of various Gram positive and Gram-negative bacteria and also proved effective as antifungal agent. Balakumar and co-workers in 2011 studied the antifungal activity of *Aegle marmelos* leaves and found that leaf extract significantly inhibited the growth of all the dermatophytic fungi used for study. So they concluded that if this activity is also found in in-vivo study then it can be used as a potential remedy for dermatophytosis.<sup>33</sup> Essential oil from the leaves of *Aegle marmelos* was effective on the insect infestation of stored gram from *Callosobruchus chinensis* and wheat from *Sitophilus oryzae*, *Rhyzopertha dominica*, and *Tribolium castaneum*. In the study, grains were infected with test insects, and were fumigated with essential oil of *A. marmelos*. Results showed that extracted leaf oil notably mitigated the damage of grain and weight reduction in disinfected gram and wheat samples infested with all insects except *T. castaneum*. Different doses of essential oil sufficiently reduced oviposition and adult emergence of *C. chinensis* in treated cowpea seeds.<sup>34</sup> Limonene was found to be the major component in the oil through GC-MS analysis.<sup>35</sup> Function of various bioactive compounds isolated from *Aegle marmelos* were described by Umadevi and co-workers in 2011. One of the important compounds isolated was Cinnamic acid and its derivatives including esters and carboxylic functional derivatives which are important components in pharmaceuticals. Cinnamate are used as sunscreen agents to reduce skin damage by blocking UV-A and B. N-heterocyclic aromatic compounds 1-phenylpyrazole and 1-phenylpyrrole are attractive precursors for synthesis of pharmaceuticals and agrochemicals, including fipronil and ethiprole insecticides.<sup>36</sup> Cinnamates and cinnamamides inhibit fungal 17 $\beta$ -hydroxysteroid dehydrogenase, whose dysfunctions have been associated with reproductive and neuronal disorders as well as the development of

hormone-dependent cancer forms.<sup>37</sup> 2-Hydroxy-4-methoxy benzaldehyde has been used as a flavouring agent for the preparation of soft drinks and bakery products, also contribute to its best role towards antimicrobial and antioxidant property.  $\gamma$ -sitosterol is C-24 isomer of  $\beta$ -sitosterol, which is androgenic in nature.<sup>38</sup> These compounds have Anti-adenomic, Anticancer (Cervical), Antiemetic, Antifeedant, Antigonadotrophic, Antihyperlipoproteinaemic, Anti-inflammatory, Antimutagenic, Antiophidic, Antioxidant, Antiprosthetic, Artemicide, Candidicide, Estrogenic, Hepatoprotective, Spermicide and Ulcerogenic activities as per Duke's ethnobotanical and phytochemical database.  $\alpha$ -amyrin is found to have antiedemic, anticancer, cytotoxic, antipyretic, hepatoprotective, insecticidal, anti-hyperglycaemic activity, germination inhibitory and anti-repellent activities.  $\beta$  - caryophyllene oxide, if given in a dose-dependent and time-dependent manner then show significant cytotoxic activity against HepG2, AGS, HeLa, SNU-1, and SNU-16 cells. A monoterpene lactone loliolide can protect the cells against H<sub>2</sub>O<sub>2</sub>-induced apoptosis and also known to have immunosuppressive activity.<sup>14</sup> A quinoline alkaloid, Skimmianine isolated from the roots of *Aegle marmelos* was studied and its effects on the histamine release from rat mast cells were tested. It was found that skimmianine markedly inhibited the histamine release from the cells under study.<sup>11</sup> Tamilselvi and co-workers in 2012 prepared an Anti infertility syrup using dried plant powders of *Aegle marmelos*, *Tinospora cordifolia*, *Withania somnifera*, *Ficus religiosa* and many other plants to prevent the infertility in females. This syrup contained the nutrients and antioxidants to induce and balance the immune system and hence increase the chances of fertility.<sup>39</sup> Bhattacharjee and his co-workers, in April 2013, determined Marmelosin and Psoralen in Bael by fruit using high performance liquid chromatography. These two bioactive coumarins present in bael fruit are reported to have antibacterial, antihelminthic, analgesic and cytotoxic activities. Marmelosin is responsible for the laxative and diuretic character of the bael fruit pulp. High doses of marmelosin lowers the rate of respiration, depresses heart functioning and causes sleepiness.<sup>40</sup> In 2014, Victoria and co-workers showed the antibacterial activity of *Aegle marmelos* plant parts and found out the compounds responsible by using GC/MS technique, from the fraction of plant used for antibacterial activity. Pharmacologically active compounds which are responsible for antimicrobial activity were identified such as; Di-n-octyl phthalate, 1,2-benzenedicarboxylic acid, Alpha-pinene (mono terpene) and Squalene (triterpene). Other antimicrobial compounds like, tetradecanoic acid, octa decanoic acid, D-limonene were found in trace amount.<sup>41</sup> Following table is prepared to summarise the research work of various researchers on therapeutic potential of *Aegle marmelos* and the possible bioactive principles responsible for the activity.

Table 2

**Pharmacological properties and bioactive compounds responsible in *Aegle marmelos* plant parts**

Sr. No.	Property	Plant Part	Compound/s Responsible
1.	Antidiarrhoeal activity	Root and Unripe Fruit	Tannins, Flavanoids, and phytosterols
2.	Antimicrobial and antiviral activity	Root, Fruit and Leaves	Essential oil, Cuminaldehyde eugenol and Marmelide (antiviral)
3.	Antimalarial activity	Leaves and Seeds	Schizontocidal compounds
4.	Radioprotective effects	Leaves and fruit	Phenolics, Flavonoids and all Possible Free Radical Scavenging compounds
5.	Antioxidant activity	Leaves and Fruit	Phenolic compounds and Flavonoids
6.	Anticancer activity	Leaves and Fruit	lupeol, eugenol, citral, and Marmelin
7.	Chemopreventive action	Fruit	lupeol, eugenol, limonene, citral, rutin, and anthocyanin
8.	Antipyretic potential	Leaves and Root Bark	Lupeol and skimmianine
9.	Ulcer healing potential	Seeds and Fruit Pulp	Flavonoids, such as quercetin
10.	Antigenotoxic activity	Fruit	Polyphenolic compounds
11.	Diuretic activity	Fruit	Marmelosin
12.	Antifertility activity	Leaves, seed, fruit, bark	Marmin, Fagarine
13.	Anti-inflammatory activity	Leaves	Lupeol, Skimmianine

**CONCLUSION**

This review study concludes that almost all the plant parts of *Aegle marmelos* are of immense importance both ethnobotanically and medicinally. It has become of more interest to researchers because the bioactive compounds isolated from the different parts of the plant represent it as a valuable source of medicinal compounds. It was observed in various studies that it has antidiabetic, antibacterial, antifungal, antibiotic and anti-diarrhoeal properties. After reviewing various research papers this study indicates that every part of *Aegle marmelos* plant contains bioactive compounds

which are responsible for pharmacological properties of the plant.

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**CONFLICT OF INTEREST**

There is no conflict of interest.

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