



Review Article

Therapeutic Applications of *Morinda citrifolia* in Dental Sciences: A Review of Its Endodontic and Periodontal Benefits

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Around the world, herbal medicine is becoming a more often used alternative type of treatment. As a result, the field of dentists and its arsenal is finding a growing number of users for herbal medications. The medicinal benefits of *Morinda citrifolia* (*M. citrifolia*) and its components will be covered in the article in a number of different ways. There were many diverse types of properties found, which were categorized into anti-inflammatory, analgesic, antioxidant, wound-healing, anti-tumor, anti-diabetic, antibacterial and anti-septic, fungal, antiviral, anti-fungal, anti-wrinkle, anticaries agent, periodontal tissue regeneration activities, endodontic irrigant, and intracanal medicament. Using both in vitro and in vivo models, as well as clinical trials, it was determined that *M. citrifolia* should only be ingested cautiously and after extensive examinations into its chemical components and methods of action. Although *M. citrifolia* is commonly and effectively used in dentistry and medicine for the treatment or prevention of a number of ailments, this is the case.

Introduction

Folk medicines made of natural and herbal ingredients have been utilized for generations in every culture on earth. As more people become aware of the genuine health advantages of these treatments, medical experts and scientists have expressed a growing interest in this area. Hippocrates, considered the founder of medicine, once said, "Let food be your medicine and let medicine be your nourishment" [1]. Food concepts in the developed world have evolved over the past few decades from a focus on survival, satiety, and malnutrition to a promising use of foods to promote better health and wellbeing and reduce the risk of a number of diseases, including certain types of cancers, cardiovascular diseases, and obesity. Functional meals are a key component of this new "Healthy Eating Concept." One such superfood that has recently gained popularity is noni. Noni, also known by its scientific name *Morinda citrifolia* (MC), is a medicinal plant that has been used for centuries all over the world. On the Indian subcontinent, it goes by the names Indian mulberry, nuna, noni, cheese plant, or Mannanatti [2]. It is crucial to stress that the biochemical makeup of these substances varies drastically depending on the plant's structure, as well as on where they were grown and when they were harvested [3]. Its fruit juice is highly sought after in alternative medicine to cure various dis-

eases [4]. Heinicke (2005) made one of the more well-known assertions, claiming that the MC fruit contains the active "alkaloid" xeronine, which is thought to be generated from the precursor compound perxeronine. MC juice may be used to treat a variety of ailments, including menstrual cramps, hypertension, gastric ulcers, sprains, injuries, mental depression, atherosclerosis, blood vessel issues, drug abuse, pain alleviation, and several more conditions are among them. It has been demonstrated in numerous papers that it can be utilized to treat a variety of disorders. Some substances, including alkaloids, scopoletin, damnacanthal, and many other known chemicals, may be the cause of the observed positive effects. Despite the genuine prospects, there hasn't been much scientific investigation into the functional aspects of MC products. Concurrently, research on biological activity and phytochemical components has increased as a result of this [2]. It has lost favor over time due to the smell of the full fruit. People frequently favor taking MC in the form of capsules that include berries that have been dried or in the form of fruit juice [5]. Aside from describing MC's therapeutic applications and the most recent advancements in dentistry made possible by its various components, this review also strives to compile vast and up-to-date information on MC [3].

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Nourishment Value

The fruit's complete physio-chemical makeup has not yet been documented. The fruit's dry matter is believed to be primarily made up of proteins, dietary fibers, and soluble solids, with the remaining 90% being water. Isoleucine, glutamic acid, and aspartic acid are the three main amino acids found in fruit, and there is a significant amount of fruit protein, according to Chunhieng (2003), making up 11.3% of the juice dry matter. A 100 g sample of fruit powder contains about 71% carbs, 36% fiber, and 5.2% protein, according to Dar et al. The quantities presented differ obviously as a result of the fruit's postharvest handling procedures and environmental conditions [3].

Chemical Composition

The medicinal power of any medicinal plant is mainly depending on the presence of phytochemical constituents that impart a great pharmacological significance [4]. A total of more than 200 phytochemicals have been extracted and identified from various plant sections yet. Each component has a unique chemical makeup. The primary phenolic chemicals that have been discovered and isolated from various MC sections are anthraquinones [2]. There have also been reports of minor bioactive such as alcohols, acids, caretonoids, phenols, esters, saccharides, anthraquinones, triterpenes, flavonoids, glycosides, lactones, iridoids, nucleosides, ketones, lignans and sterols among other classes of biochemically active compounds. In the juice extract of the noni fruit, Ali et al. (2016) found 51 volatile chemicals, including linalool oxide, acetaldehyde, and methanethiol, that belonged to the class of aldehydes, ketones, terpenes, and sulfur-containing compounds. The authors claim that the flavor characteristics in noni juice are caused by the presence of sulfur [3]. MC fruit with physicochemical, phytochemical, and antibacterial properties was gathered at various stages of maturation while that was being researched. According to the findings, the mature MC fruit's ethanolic extract has the most antibacterial activity against *K. pneumonia* and its methanolic extract has the greatest antifungal activity against *A. flavous*. MC fruit juice is a nutritious beverage that also offers a number of pharmacological benefits. Juice from the MC plant can be utilized to induce postischemic glucose intolerance, which is a cerebral defense mechanism [6].

Biological Activity

The widespread assertions of therapeutic efficacy have prompted researchers all across the world to look at some of these possibilities more closely.

Antibacterial effect: Studies have shown that MC has antibacterial activity against a variety of pathogenic bacterial strains, including *Salmonella*, *Escherichia coli*, *Proteus morgaii*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Shigella*. This is attributed to the presence of phenolic compounds in the fruit, such as acubin, alizarin, and L-asperuloside [2]. When compared to levofloxacin, Selvam et al. (2009)'s investigation of the antibacterial properties of MC revealed that its extracts had only modest *E. coli*, *staphylococcus aureus*, and *Proteus vulgaris*'s antimicrobial activity [7].

Anticancer and antiviral: Cyclooxygenase2 (COX2) suppression, a crucial inflammatory marker, and the upregulation of the tumor (cancer) suppressor gene are two ways that the ethanol extract of Noni fruit and leaves affects tumor cells and the pathways involved in an immune response [6]. Regarding anthraquinone's role in its anti-cancer and anti-HIV action, damnacanthal among the reported anthraquinones appears to be rather distinctive. 2-methoxy-1, 3, 6-trihydroxyanthraquinone is a very powerful quinone reductase inducer that was discovered and isolated by Pawlus et al. in 2005. Despite its low concentration, the described compound has a protective effect against chemical carcinogenesis via quinone reductase activation to halt the cancer start phase. Sung-Woo et al. (2005) discovered the anthraquinone 4-dihydroxy-2-methoxy-7-methylanthraquinone from fruits and determined that this substance a powerful inducer of the biosynthetic activity of extracellular matrix constituents, making it a promising option for an anti-wrinkle drug [2].

However, it was discovered that the individual noni compounds were examined for anticancer efficacy in earlier pharmacological trials. Carotene and polysaccharides, which have been shown to have anticancer action, are abundant in the MC fruit juice. Because tumor necrotizing factor-alpha, an endogenous tumor promoter, is inhibited by these antioxidants' interactions with tumor cells, tumor cells are destroyed. The anticancer properties of MC juice include 6-D-glucopyranose pentaacetate, anthraquinones, alizarin, epigallocatechin gallate, monoterpenes, and terpenoid compounds, including beta-carotene and ursolic acid. In order to suppress the expression of tumors that express activated ras, it was found that damnacanthal and alizarin, an anthraquinone isolated from the roots of noni using chloroform extract, are new RAS inhibitor [8]. A study by Lim et al. (2016) showed that the ethanolic extract of MC fruit or leaves had an impact on tumor cells as well as immune system pathways by suppressing the inflammatory marker cyclooxygenase 2 (COX2) and promoting the expression of concentrated fruit and tumor(cancer) suppressor genes. The 10% noni juice injection in lab animals also helps to prevent gene changes since carcinogenic substances attach covalently to DNA and form structures called diffract that, if broken, lead to mutations. The use of MC may prevent the development of these structures [6,7].

Immunomodulation: MC has been proven to influence the immune system to prevent the development or spread of cancer cells. Nitric oxide, IL-1 beta, TNF-alpha, IL-12, IFN-gamma, IL-10, were among the mediators from murine effector cells that MC precipitate was observed to induce. Furthermore, it was found that MC juice appeared to indirectly prevent tumor growth by boosting the immune system. Adoptogenesis is the mechanism by which MC can perform these functions. Nitric oxide (NO), which is produced by active macrophages, aids in the host's defense against pathogens and cancerous tumors. The biosynthesis of NO by the body is increased by MC [10].

Wound healing: MC leaves are applied topically as a traditional remedy claimed to speed up wound healing. Topical treatment of *M. pubescens* fruit extract at concentrations of 20 mg/mL and 10 mg/mL dramatically sped up the healing of wounds in rats compared to controls in research by Smith et al. Animals treated with the 20 mg/ml chloroform fruit extract of *M. pubescens* experienced complete wound contraction and new hair began to grow in the entire damaged area within 15 days, in contrast, to control rats, which only displayed a 60% wound contraction without hair regrowth. Numerous investigations led to the conclusion that the MC aqueous leaves have antioxidant activity and improve wound healing [11].

Antidiabetic: Numerous investigations have been sparked by the rising number of diabetes patients who embrace integrative or functional treatment. The anti-diabetic properties of MC in mice with a high-fat diet were studied by Nerurkar et al. (2012). Through phosphorylation of the transcription factor FOXO1, an improvement in glucose metabolism was seen. Similar results were seen when MC juice was used to treat rats with induced diabetes, which resulted in lower blood glucose levels. When administered in combination with insulin, noni has a synergistic effect [6]. In a study by Kamiya et al. (2008), the hypoglycemic and hepatoprotective effects in rats with diabetes were examined. Streptozotocin-administered diabetes is caused. Diabetes-related experimental mice were assessed and treated for 20 days orally with the reference hypoglycemic medication glibenclamide and MC juice (2 ml/kg, twice daily) in diabetic standard. Blood glucose levels significantly decreased in both groups [12,13].

Antifungal: The aqueous extract of the MC fruit has been shown to inhibit serum-induced changes in *Candida albicans*' morphology from a cellular yeast to a filamentous form, indicating that it may have significant therapeutic benefits against all *Candida* infections [14]. According to studies, MC extract inhibits *C. albicans* growth in different ways depending on the concentration. It has been demonstrated that the inhibitory impact grows as the extract's concentration grows. According to the findings of a double-blinded controlled trial to ascertain the toxicity of fruit, humans may tolerate up to 750 ml of fruit juice per day without experiencing any hazardous consequences. According to some accounts, the fruit has been routinely consumed for many years without any known negative consequences throughout the world. Therefore, stronger MC

fruit extract concentrations can be used to create oral therapeutic antifungal preparations to treat oral candidiasis, which can affect people using long-term medications, immune-compromised hosts, and chemotherapy patients. Jankittivong et al. examined the antifungal efficacy of MC juice. At varying concentrations and contact periods, the fruit juice from MC was evaluated for its ability to kill *Candida albicans*. This was performed utilizing cultures and broth dilution studies. The minimum fungicidal concentration of the extract against *Candida albicans* was 40 mg/ml at a 90-minute contact period or 50 mg/ml at a 15-minute contact time. This demonstrates that MC fruit extract inhibited *C. albicans* growth, with the inhibitory impact changing with concentration and contact duration [15]. Furthermore, a comparable work conducted by Barani et al. demonstrated that the concentration-dependent inhibitory action of MC fruit extract on *C. albicans* was antifungal [8].

Analgesic: According to Joseph Betz, MC fruits contain calming and analgesic properties. A French research team under the direction of Younos has examined the analgesic and sedative properties of MC extracts. The results confirmed its dose-related central conventional analgesic properties in the treated mice. The analgesic effectiveness of MC extract is 75% more than morphine's, but it has no addictive properties and no adverse effects. Hypotensive technique Vietnam's Dang Van Ho established the hypotensive properties of a complete extract of MC roots. According to Moorthy and colleagues, Young ken's research team found that a hot water extract of MC roots lowered the blood pressure of an anesthetized dog by using an ethanol extract of the MC roots. A Hawaiian doctor validated that noni fruit juice has a diuretic effect since MC induces sedatives. Since opioids are known to have a sedative effect and lower behavioral characteristics. *Citrifolia* could be used to ink its primary analgesic action [4,16].

Antitubercular effect: MC leaf extracts killed 89 percent of the germs in a test tube, which is nearly as effective as the well-known anti-TB drug Rifampicin, which has an inhibition rate of 97 percent at the same dose. To confirm this knowledge, pharmaceutical companies must conduct additional research.

Analgesic activity: According to Joseph Betz, noni fruits have calming and analgesic properties. Younos led the research team in France and examined the sedative and analgesic properties of MC plant extracts. The extract did demonstrate a significant, dose-related, central analgesic activity in the treated mice. The MC extract is non-addictive and has no side effects, however, it has analgesic efficacy that is 75% as strong as morphine [1].

Periodontology: In an animal model, noni leaf extract proved effective at accelerating wound healing. Additionally, noni leaf crude extract has been traditionally utilized to stimulate tissue regeneration and reduce inflammation in patients with bone fractures or dislocations. It is widely known that growth factors are necessary for bone and periodontal tissue repair or regeneration to encourage precursor/progenitor cells to differentiate and produce matrix mineralization [17]. According to a 2013 study by Glang et al, noni juice is a promising treatment for gingivitis and periodontitis when used in conjunction with proper oral hygiene and other local and systemic treatments [18]. Boonanantanasarn et al. study's from 2014 tested MC leaf extract for its effectiveness in encouraging protein synthesis, matrix mineralization, alkaline phosphatase activity, and cell proliferation in vitro. MC leaves are a promising osteoinductive agent for bone and periodontal tissue regeneration, it was concluded as a result [19].

Prosthodontics: The effectiveness of MC as an antibacterial agent and its impact on dental impressions when combined with irreversible hydrocolloids were both examined by Shafath A. et al. (2015). He came to the conclusion that while MC and irreversible hydrocolloids reduced the number of microorganisms when compared to water, they had no impact on the casts' surface quality or dimensional stability. In contrast to immersion in distilled water, Duggal et al. study demonstrated that immersion in MC considerably increased the flexural strength of the heat-cured denture base resin. A bigger shift in the material's strength suggests that the majority of the material was intact in the solutions since the bulk of the material controls the flexural strength. Denture storage can be done frequently without concern because the flexural strength of the denture base resin increased as a result of immersion in

MC [7].

Anticaries agent: Aciduric and acidogenic Gram-positive bacteria, including *Streptococcus mutans*, *Lactobacilli*, and *actinomyces*, are in charge of halting the progression of dental caries. These microorganisms break down sucrose into lactic acid and other organic acids, which dissolve the calcium phosphate found in teeth and eventually lead to decalcification and tooth decay. Enamel and dentin are adhered to by *Streptococcus mutans*, which results in an acidic environment that causes cavitation. Using a disc diffusion bioassay to determine the lowest inhibitory concentration, the inhibitory activity against caries-causing bacteria was studied in ripe MC fruit juice. At 125 and 62.5 g, respectively, MC fruit juice exhibited zones of inhibition and minimum inhibitory concentrations against the two main caries-causing bacteria, *S. mutans* and *Streptococcus mitis*. MC was therefore shown to have an inhibiting effect on organisms that cause cavities [8].

Restorative Dentistry: Dikmen et al. evaluated the effects of several antioxidant solutions on the resin dentin bond strength of adhesive systems after adding MC juice to NaOCl. In a self-etching adhesive system, they compared the usage of 5.25% NaOCl, pure water, NaOCl mixed with water, NaOCl mixed with proanthocyanidin (PA), and NaOCl mixed with MC juice (Single Bond Universal Adhesive). According to the authors, the "NaOCl with MC juice" group considerably outperformed the "NaOCl without MC juice" group in terms of resin-dentin bond strength. They came to the conclusion that the binding strength of the dentin pretreatment solution was enhanced greatly with the addition of MC juice to NaOCl [20].

Intracanal medication: Following their inoculation in removed teeth for a period of 21 days, MC gel, CHX gels, and herbal agents were tested as an intracanal medication against *E. faecalis* by microbiological testing. The outcomes demonstrated that MC gel exhibited superior antibacterial activity and second-best *E. faecalis* suppression after CHX gel. When colony-forming units (CFUs) were assessed on days 1, 3, and 5, MC gel showed good suppression up to the fifth day of treatment in a different investigation. This demonstrates that MC gel's potent antibacterial characteristics, which can be improved with enough contact time with the bacteria, make it an effective intracanal medication. The antibacterial effects of 2% CHX gel propolis, MC juice, and $\text{Ca}(\text{OH})_2$ have been examined on *E. faecalis*-contaminated root canal dentin at two distinct depths and three intervals. It was discovered that propolis and MC may be able to get rid of *E. faecalis* from the dentin of extracted teeth [8,21].

Endodontic irrigant: As an alternative to sodium hypochlorite (NaOCl) as an intracanal irrigant, this fruit juice seems to be the first to be mentioned [22]. The use of MC juice as an endodontic irrigant may be of interest to patients and endodontic specialists as part of the growing trend to incorporate natural treatments as part of dental care because it is a biocompatible antioxidant and is less likely to cause severe patient injuries than NaOCl accidents. In an in vitro experiment, the effectiveness of MC juice, NaOCl, and CHX in eliminating the smear layer from the root canal walls of teeth with instrumentation was compared. It was shown that MC performed similarly to NaOCl and EDTA when used as an intracanal irrigant [21]. According to a study by Bhardwaj et al., the gel of MC consistently showed good inhibition up to day 5, followed by the aloe and papain [23]. MC, when administered as an intracanal irrigant, exhibited a substantial antibacterial effect against *E. faecalis*, according to Balakrishnan et al. and Kandaswamy et al [24]. According to a study by Teja et al. (2022) the ethanolic extract of MC showed nearly the same inflammatory response and systemic toxicity at the 7th and 14th days as 3% sodium hypochlorite. Therefore, MC fresh fruit juice may be favored as a natural root canal irrigant because it has fewer potential cytotoxic effects than ethanolic extract [25].

Conclusion and Future Prospects

The main benefits of utilizing herbal substitutes are their accessibility, low toxicity, longer shelf life, affordability, and absence of microbial resistance as of yet [21]. For a variety of dental illnesses, new substances with significant levels of pharmacological activity are currently needed. Numerous scientific studies have revealed that this plant includes a vari-

ety of useful and nutritive substances, but our understanding of these compounds is still far from complete. Damnacanthal and a few other phenolic compounds have been identified as the most significant chemicals. Academic institutions and pharmaceutical companies have launched a number of projects in an effort to reap the rewards of these extracts [2].

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