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The noni fruit (*Morinda citrifolia* L.): A systematic review on anticancer potential and other health beneficial pharmacological activities

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Abstract

Morinda citrifolia has been reported as a traditional Polynesian medicine for over 2000 years. This review investigated the relationship of fruit juice or its extract to anticancer or other therapeutic properties. More than 160 phytochemicals have been extracted from the plant *Morinda citrifolia* making it an herbal remedy in curing bacterial, tumorous, anthelmintic, analgesic, viral, fungal, cardiovascular, hypotensive disorders. It even demonstrates beneficial consequences in the conditions like skin diseases, respiratory infections, gastritis, menstrual, diabetes and venereal diseases. All recent studies have shown that noni fruit has antioxidant and antibiotic properties *in vitro* but we still do not have any scientific evidence which supports its nutritional and medicinal values in humans. However, both the fruit and damnacanthal, an anthraquinone compound extracted from noni roots, are currently being studied in the order of anti-cancer research. In this paper, we deliberate on various phytoconstituents present, ethnobotanical use, pharmacological effects and various biological activities and therapeutic potential of *Morinda citrifolia*

Keywords: *Morinda citrifolia*, phyto-constituents, therapeutic properties anti-cancer, anti-oxidant.

Introduction

India is abounding with herbs and medicinal plants and a large number of plant extracts have been reported to be having high utility against various tropical diseases and physiological disorders like cancers and tumors. The natural medicines are gaining much popularity due to their low toxic effects and costs, availability and great usefulness as complementary medicines^[1, 2]. In present era, Cancer is one of the main challenges in human health care which reported as a world's second largest cause of death. The most commonly used medicinal plants include *Ocimum sanctum* (tulsi), *Piper longum* (pipali), *Withania somnifera* (ashwagandha), *Aloe vera*, *Azadirachta* (neem), *Zingiber officinale* (ginger), *Curcuma longa* (turmeric) etc.,^[1-5]. We must remember that before the emanation of current medical sciences we have been very close to nature and have divulge the plants having medicinal importance, leading to cure of many human ailments. *Morinda citrifolia* is one such plant- having eminent medicinal value. *Morinda citrifolia* is one of the most important fruit which was widely used for its health restorative properties, over the years of its popularity diminished due to unpleasant smell from the ripened fruit. The common name of the *Morinda citrifolia* is also Indian Mulberry. The scientific name of Noni is *Morinda citrifolia*. There are broad range of health benefits of *Morinda citrifolia* fruit like for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain. The *Morinda citrifolia* fruit is primarily used to fight against the fungal, viral, bacterial infections^[6]. The roots, stems, leaves, barks and fruits of *Morinda citrifolia* plant are involved in various combinations with more than 40 recorded and known herbal remedies^[7]. Mostly *Morinda citrifolia* is consumed in the form of juice. Sometimes people are also preferred to take *Morinda citrifolia* in the form of capsules which contains dehydrated *Morinda citrifolia* fruit. The *Morinda citrifolia* plant flowers throughout the year. The color of the flower is white. *Morinda citrifolia* plant is evergreen plant. Medical studies have reported that by consuming the *Morinda citrifolia* the chances of having arthritis and diabetes fall down^[8]. According to the demand, the countries like Costa Rica and Cambodia, has increased the yield of *Morinda citrifolia*. The *Morinda citrifolia* juice is also consumed by mixing with the other juices like grapes or mulberry. There is lot of researches going on *Morinda citrifolia* fruit and many patents have been also registered *Morinda citrifolia* fruit is also capable of wrenching

out flavoured compounds^[9]. Many hydrophilic compounds like carbohydrates, proteins, minerals, vitamins and small amount of fat are present in this fruit. The European Union has established *Morinda citrifolia* fruit as a noble food^[10]. Due to its high therapeutic and safety profile it's very famous as a health enhancer and a food supplement worldwide^[11]. In afflictions like burns, headaches, arthritis, wounds and many more skin infections *Morinda citrifolia* fruit is proved very beneficial^[12]. This review effort has been made to provide ethnobotanical use, Phytochemistry and scientific evidence for the therapeutic potential, discussing the pharmacology at a molecular level and the challenges confronted towards clinical validation of herbal medicines.

Scientific classification

Botanical name: *Morinda citrifolia*

Domain: Eukarya

Kingdom: Plantae

Phylum: Magnoliophyta

Class: Magnoliopsida (dicot)

Order: Rubiales

Family: Rubiaceae (coffee family)

Genus: *Morinda*

Species: *Morinda citrifolia*

Morphology and physiology

There are 80 distinctive species of Genus *Morinda* distributed in south – East Asian countries, Australia and Pacific islands. *Morinda citrifolia* is a short evergreen tree growing up to 3-10 m in height until it reaches maturity. The arrangement of leaves is pinnately, glossy, opposite to one another having 5-17 cm of length and 10-40 cm width. It's attributable by its straight trunk, bright green and elliptical leaves, its peculiar ovoid, grenade like yellowish fruit- fruit growth seen is up to 12 cm consisting of a surface which is lumpy whereas topped with polygonal shaped sections. Fruit when gets matured it delivers a foul taste and odour^[13]. Flowers are grouped together to insert on a peduncle. The peduncles are 5 lobed corollas and the calyx with taunted rim and length up to 10-30 cm^[8]. Root systems are extensively lateral compromising of a tap root. The major characteristic feature of the species is yellowish wood and roots yielding yellow coloured dye^[14].

Phytochemistry

There are around 160 phytochemicals compounds already recognized in *Morinda citrifolia* plant; the major micronutrients which have been identified are phenolic acid, organic acid and alkaloids^[15]. It has been reported that out of 160 phyto-constituents of *Morinda citrifolia* plant 120 constituents have nutraceutical attribute with evince biological activity^[16]. Micronutrients, non-volatile and volatile components, ketones, lactones, beta-carotenoids, terpenoids, pro-xeronine occur in fermented fruit extract^[17]. The organic acids present are cupric and caprylicacids^[18]. The protein in the fruit is comparatively high representing 11.3 of the juice dry matter. Aspartic acid, glutamic acid and isoleucine are main amino acids^[19] and pro vitamin A^[20]. According to Hawaiian teams there is the report of presence of novel component pro xeronine in the *Morinda citrifolia* that is the precursor of xeronine an alkaloid which improve the functionality of human proteins when combines with human proteins^[21]. There are 51 volatile compounds in the ripe fruit are reported^[22] which contain organic acids (octatonic and hexanoic acid) alcohols (3-methyl-3-buten-1-ol), Ketones (2-heptanone), esters (methyl octanoate, methyl

decanoate), and lactones [(E)-6-dodeceno-glactone]^[23].

Ethnobotanical use

It has been recognized that *Morinda citrifolia* has lot of therapeutic uses in ailment such as burns, headache, arthritis, skin infection and wounds^[7]. *Morinda citrifolia* has been cultured from more than 1000 years back by Polynesian where it is used as medicine, food and coloring agent. As root of the *Morinda citrifolia* plant has been used as dyeing agents by Australians and Indians for different gloom of red, yellow, and purple^[24]. It has been also reported that various parts of *Morinda citrifolia* plants such as bark, root, stem, leaf, fruits are used by Hawaiians and Tahitians in a traditional way as medicinal use for the treatment of various disease like cold, cough, pain, liver diseases, blood pressure, malaria, hypertension, tuberculosis, diabetes, loss of appetite, urinary tract infection, cancer menstrual disorders, hernias, cardiovascular diseases, arthritis etc. It also has been reported that the seeds and its oil if applied topically on the scalp as insecticide and also used as the treatment for arthritis. The flowers of *Morinda citrifolia* plants are applicable in the case of insect stings. It has been proclaimed for topical use in conditions like sprains, wounds, swellings, bruises^[25]. Whole of the *Morinda citrifolia* plant utilized in various combinations for herbal remedies by Polynesians. Scientific evidence of the beneficial features of the *Morinda citrifolia* plant is limited but some anecdotal evidence for successful treatment of cold and influenza is present^[26]. Former botanical chemist at the University of Hawaii, Isabel Abbott articulated that "everybody is crazy for this plant" and using it for treating many ailments like cancer, blood pressure, diabetes and many more^[27].

Anticancer phyto-constituents

Polysaccharides

It was consummated that *Morinda citrifolia*-ppt contained some polysaccharides which suppressed tumor growth whereas stimulating immune system^[12]. Galactose, arabinose, rhamnose, glucuronic acid, glycosides and trisaccharide fatty acid ester showed immune- modulatory, anti-cancer and anti-tumor activity^[28].

Xeronine

Pre cursor of xeronine, pro-xeronine is present in *Morinda citrifolia* fruit which coalesce with pro-xeroninase, an enzyme of the body which reacts to form xeronine initiates the enlargement of pore size of tumor cells consenting anticancer drugs to enter the cells easily. Potassium ions permeability is also enhanced by Xeronine^[17].

Monoterpene

Monoterpene, a limonene stimulates thymus gland to secrete large number of T-cells which have a detrimental effect on carcinoma cells. Limonene present in the *Morinda citrifolia* juice have preventive effects on mammary, liver and lung and other cancers^[29]. Carcinogenic process at the beginning and advancement levels of cancer with nil toxic effects on body is preventable by monoterpenes. The treatment of leukaemia is reported by *in vitro* studies^[30].

Ursolic acid

Anti-cancerous effects are shown both externally and internally repressing the growth of cancerous cells and induce apoptosis by modulating immune process^[31].

Alizarin and limonene

Inhibit the formation of blood vessels over the tumor by antiangiogenesis property. Growth and mutations of malignant cells is inhibited by *Morinda citrifolia* juice or apoptosis/ programmed cell death^[32].

Quercetin

Quercetin notably reduces the apoptosis in ACC cells by dependent pathway of mitochondria which showed close relation with down regulation of PI3K/ IKK- alpha/NF-kappa-b pathways. Decreased cells viability was reported for both low metastatic cell line and high metastatic cell line in time dependent manner by quercetin treatment. Quercetin is emerging as a hopeful chemotherapeutic agent against ACC by functioning of down regulation of certain signalling

pathways^[33].

Anthraquinone

Morindone, damnacanthal and morindin are vital anthraquinone compounds possessing various biological activities which include anti-oxidant, antibacterial, anti-inflammatory, anthelmintic effects. There is prevention of formation of tumor by impeding ras gene activation. It has formidable inhibitory proceedings on tyrosine kinases including Lyn, src, EGF, Ickreceptors^[34]. Antiangiogenic outcome is shown by another anthraquinone admixture-Alizarin. Restriction of blood circulation of malignant cancers leads to repercussion in arrest of growth of tumor cells. Cytochrome-C, a cancer producing agent- activity is also impeded by alizarin without production of free radicals^[35].

Table 1: Important chemical constituents of *Morinda citrifolia* along with their reported effects of compounds.

Noni Plant Organ(s)	Compound(s)	Proposed or Reported effects of compounds
Roots	Damnacanthal(Anthraquinone)	Obstructs development of Lung Carcinoma in mice.
	Morindin and Morindone	Dyes, Yellow colorants and Red colorants required for tapa cloth; anti-bacterial.
Fruit and Fruit Juice	xeronine (Alkaloids)	xeronine supplements the enzyme action and protein structure
	trisaccharide fatty acid ester(Polysaccharides)	Immuno-stimulatory, immuno-modulatory, anti-bacterial, anti-tumour, anti-cancer.
	Scopoletin	Dilates vasculature & reduces blood pressure, anti-inflammatory analgesic, histamine-impeding, arthritic conditions, allergies, sleeping disorders, migraine headache, and depression.
	Vitamins and Minerals; Magnesium, iron, potassium, selenium, zinc, copper, sulphur, ascorbic acid	The positive medical effects of the vitamins and minerals in Noni juice are observed and documented.
Foliage & Cell Suspension	Damnacanthal(Anthraquinone)	Antiseptic & antibacterial effects in digestive tract (Staphylococcus, Shingela, Salmonella).
	Glycosides-Flavanol glycoside; iridoid glycoside.	Anti-cancer effects: (DPPH free radical scavenging activity; inhibition of UVB-induced Activator Protein-1 activity in cell cultures.

Pharmacological Effects

Effect on lung and colon cells

In recent studies it has been noticed that there are six known chemical compounds and two new compounds which have been isolated from the roots of the plant that demonstrated remarkable restrictive effects on the development of human lung and colon cancer cells^[36].

Effect on breast cancer

The results of Tahitian *Morinda citrifolia* Juice (TNJ) were tested on mammary carcinogenesis in MMTV neutransgenic mice. It has been reported that TNJ treatment did not affect mammary tumor potency, multiplicity and metastatic frequency. But TNJ demonstrated significant decrease in the tumor size, weight and longer tumor repetition times in mice. So it was observed that a mouse equivalent of dose for humans remarkably repressed the growth of mammary gland cancer^[37]. It was examined that the effect on *Morinda citrifolia* juice on Ehrlich ascites tumor bearing Balb-c mice, concluded that for the treatment of breast cancer *Morinda citrifolia* juice may be useful either on its own or with complexation with doxorubicin. This is because the effect of *Morinda citrifolia* juice Ehrlich ascites tumor bearing Balb-c mice, which creates significantly short, small and long diameters of the tumor tissues in each treated group analyze to those in control group either alone or with doxorubicin^[38].

In one hundred and sixty female Sprague-Dawley rats the anti-growth of TNJ has been reported. It was reported that TNJ has a significant role in reducing the multiplicity and malignancy of lesions, and the endurance rate of animals

when compared with positive control rates at different time points^[39].

Effect on colorectal cancer

Damnacanthal has capacity to control cancer in colorectal tumor beginning findings that Damnacanthal demonstrated cell growth stoppage as well as caspase activity induction. It also has been reported that Damnacanthal has the effective anti-tumorigenic activity in human colorectal cancer cells^[40].

Effect on cervical cancer

Morinda citrifolia juice and cisplatin, either in combination with each other or alone has the capacity to stimulate apoptosis through the mitochondrial pathway on HeLa and Siha cells. Even so, cisplatin somewhat higher cell killing when it was compared with *Morinda citrifolia* juice while both of their combination showed adjuvant effects. So, the results suggested that *Morinda citrifolia* juice can be used as chemo adjuvant in the treatment of cervical cancer^[41].

Effect on cardiovascular system

Morinda citrifolia fruit has a capability to inhibit arteriosclerosis is related to the oxidation of low density lipoproteins (LDLs). They described that this beneficial effect could be due to the presence of lignans^[42].

In vitro anti-cancer effects of *Morinda citrifolia*

Damnacanthal- extracted from chloroform amasses of *Morinda citrifolia*, an anthraquinone associate. Ras oncogene activity is impeded which is associated with signal

transduction in leukemia, colon, lung and pancreatic cancer. Normal morphology and cytoskeletal structure was demonstrated by damnacanthol in K-ras-NRK cells without altering the amount and localization of ras. Reversible impact was performed having no effect on NRK cells; expressing src oncogene^[43]. The anti-tumor activity was showing against sarcoma 180 cells in mice by *Morinda citrifolia*^[44]. Polysaccharide-rich substance present in *Morinda citrifolia* fruit juice consisting of anti-tumor role shows increment in production of cytokine INF-gamma from thymocytes. It consist of ethanol precipitate, a soluble fraction resulting in zero anti tumor activity, although it has anti tumor activity against Lewis lung peritoneal carcinomatosis (LLC) by inducing the immune system through discharge of tumor necrosis factor-alpha and various interleukins (IL-10, IL-12) and nitric oxide and decreased impacts on IL-4 and no impact on IL-2^[45].

Two atypical glycosidase NB10 (6-O-(β-D-glucopyranosyl)-1-O-octanoyl-β-D-glucopyranose) and NB11 (asperulosidic acid) depict anti-cancerous activity. There extraction occurred from the soluble fraction of n-butyl alcohol of *Morinda citrifolia* fruit. They lead to suppression of 12-O-tetradecanoylphorbol-13-acetate (TPA) and epidermal growth factor (EGF) instigating cell transformation and associated AP-1 activation in the mouse epidermal JB6 cell line. AP-1 trans activation is instigated by TPA and UV radiation resulting in tumor genesis. These compounds also intercept the phosphorylation of JNKs substrate, suggesting that JNKs are prime targets in mediating the AP-1 functioning and cell transformation.^[46] *Morinda citrifolia* juice in minute amount was unproductive in obstructing initiation of angiogenesis. Explants of the human breast tumor showed 10% *Morinda Citrifolia* juice in growth media impedes capillary initiation, apoptosis, and vessel degeneration in wells within 2-3 days^[47]. From *Morinda citrifolia* fruit a methanol fruit extract was isolated which included presence of new saccharide- fatty acid ester (2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-glucopyranose), flavanol glycosidase, and four saccharide fatty acid ester. Inhibitory activity has been shown by these compounds in contrast to TPA potentiated inflammation reported in mice ear whereas fatty acid- saccharide demonstrated robust anti-inflammatory activity. Moderate inflammatory effects were illustrated against Epstein barr virus early antigen (EBV-EA) induced by TPA^[48]. *Morinda citrifolia* fruit methanolic extract exhibits tumor cell suspension pubescent on Hep2 cells i.e. human laryngeal epithiloma. Hexane extract failed to show any Cytotoxicity on Hep 2 cells^[49].

In vivo* anticancer effect of *Morinda citrifolia

Alcohol-precipitate of *Morinda citrifolia* fruit juice demonstrated antitumor activity intraperitoneally injected Lewis lung carcinoma (LLC) in C57BL/6 mice. The therapeutic effect of *Morinda citrifolia* juice has also been observed from 3-20mg mouse⁻¹ and there was observation of anti-cancerous activity at the doses of between 6-15mg mouse⁻¹. *Morinda citrifolia* juice also extended the life span of mice for more than 75%^[50]. The antitumor activity of ethanol precipitated fractions of *Morinda citrifolia* juice can be easily observed against intraperitoneally implanted LLC in syngeneic C57BL/6 mice. 4 out of 13 mice were cured with intraperitoneally injected *Morinda citrifolia* ppt and life span was increased to 119%. It has been reported that there is no antitumor activity of Ethanol soluble fraction of *Morinda citrifolia* fruit juice^[45]. The ascites in mice can be prevented with *Morinda citrifolia* –precipitate, but untreated mice

develop ascites^[12] Tahitian *Morinda Citrifolia* juice which is made from *Morinda citrifolia* inhibit the DMBA induced mammary gland carcinogenesis in female Sprague-Dawley at the early stage of multiple step carcinogenesis. It prevents DMBA-DNA adduct development in mammary tissue. DMBA-DNA adduct formation was noticed by^[32] p post labeling assay and it is necessary marker for “DNA damage” to determine the preventive effect on *Morinda citrifolia* juice in DMBA induced mammary glands carcinogenesis model. The DMBA-DNA adduct levels were decreased to 30% in heart, 41% in lung, 80% in kidney and 42% in liver of female SD rats. Impressive reduction of DMBA-DNA adduc5 formation was observed in male C57 BL-6 by 60% in heart, 90% in kidney, 50% in the lung and 70% in liver. This protective effect of TNJ was due to the Antioxidant activity by dose- dependent inhabitation of both Superoxide Anion Radicals (SAR) and Lipid Hydro peroxide (LPO).

Biological activity

Antimicrobial properties

The first observed property of *Morinda citrifolia* was antimicrobial property. Indeed, the fruits contain relatively large amounts of sugars that are not fermented when fruits are stored in closed containers at ambient temperature. It has been reported that *Morinda citrifolia* inhibits the growth of certain bacteria- such as Staph, pseudomonas aeruginosa, Proteus morgaii, Bacillus subtilis and *E. coli*^[51]. Antimicrobial effects observed may be due to the presence of phenolic compounds. Dried fruits acetonitrile extract inhibits the growth of Bacillus subtilis, *E. coli*, Pseudomonas aeruginosa^[52]. Evidence even shows that ethanol and hexane extracts of *Morinda citrifolia* have been showing ant tubercular effects. Mycobacterium tuberculosis growth is inhibited up to 89-95%^[53]. Additionally they arrived to the conclusion that antimicrobial properties increases with the degree of ripeness and when ripe fruit it becomes greater. The capacity to amplify the immune system properties of *Morinda citrifolia* juice have recently been studied by Japanese research team^[12]. *Morinda citrifolia* seems to stimulate the production of T-cells, thymocytes and macrophages that produces cytokines which are chief mediators of tumor cytostatic and Cytotoxicity. Murine effectors' cells such as cytokines, slows down the cell cycle in tumor cells and speeds up the response of immunized cell which fight tumor growth due to *Morinda citrifolia* precipitate^[28].

Anti – Cancerous activity

The *Morinda citrifolia* juice has the capacity to enhance the host immune system which has been recently studied by Japanese research team^[54]. The *Morinda citrifolia* juice has ethanol perceptible fraction which corresponds to the polysaccharide-rich substance which is composed of galactose, arabinose, glucuronic acid and rhamnose which have immuno modulatory and anti-tumors effects which works against Lewis lung carcinoma (LLC). Cell model describes, *Morinda citrifolia* triggers the production of T-lymphocytes cells, thymocytes and macrophages as these cells produces cytokines which alters the Cytotoxicity and cytostatic. *Morinda citrifolia*-precipitate also helps to stimulates the release of mediators from murine effectors cells such as cytokines that work on the cell cycle of the tumors and slow down the cell cycle, that signals the other immunized cells that fight with the tumor growth and it also contains potent macrophage activator activity, which plays the role in the death of tumor^[54].

Anti-oxidant properties

As a result of metabolic activity in our body, free radicals are produced which are engaged in the pathogenesis of many human diseases such as cancer, aging and may other degenerative diseases. Free radicals cause lipid per oxidation and consequently oxidative damage to cell components and DNA which will finally result in cell damage. Fruits and vegetables are sources of natural antioxidants, which inhibit free radical-induced oxidative damage [55]. The radical scavenging activity was calculated *in vitro* by the tetrazolium nitro blue TNB, by assessing the potential ability of the juice to protect cells or lipids from oxidative alteration promoted by superoxide anion radicals SAR. The SAR scavenging activity of *Morinda citrifolia* juice was shown to be 2.8 times higher than that of vitamin C and almost of the same order as the grape seed powder [15]. Ethanol and ethyl acetate extracts of *Morinda citrifolia* fruit was obtained and anti-oxidant effects have been assessed using thiobarbituric acid test (TBA) and ferric thiocyanate method (FTC). Results prove that ethyl acetate extracts demonstrated potent inhibition of lipid per oxidation comparable to α -tocopherol and butylated hydroxyl toluene (BHT) [56].

Anti- Inflammatory Activity

COX enzymes inhibit selectively *in-vitro* due to *Morinda citrifolia* juice and comparatively strong anti-inflammatory activity to that of celebrex without any aftermath [57]. Commercialized *Morinda citrifolia* juice has selective inhibition cyclo oxygenase enzymes (COX) and even anti-inflammatory activity. In an acute liver injury model of female rats anti-inflammatory activity was observed which was induced by carbon tetrachloride. 6 hours post carbon tetrachloride administration in animals pre-treated with 10% *Morinda citrifolia* juice for twelve days in drinking water observed a reduction in inflammatory foci and lymphocytes surrounding central vein areas [58]. distinct polyphenols with proximity to coumarin, phenolic compounds, iridoid, flavonoids, and ascorbic acid found in *Morinda citrifolia* juice have free radical scavenging activity. *Morinda citrifolia* anti-inflammatory properties are subjected to be due to NO and PGE2 pathways [59]. A new fatty acid ester 2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-glucopyranose, extracted from *Morinda citrifolia* juice is a new polysaccharide which exhibits anti-inflammatory activity against 2-O-tetradecanoylphorbol-13-acetate resulting inflammation in mice [48]. *Morinda citrifolia* seed oil (NSO) have prospective anti-inflammatory activity by impedance of enzymes COX-2 and 5-LOX enzymes in concentration dependent manner. The impact by COX-2 is more pronounced than 5- LOX. Hence for skin care usage of *Morinda citrifolia* seed oil is advisable and is non-comedogenic [60]. Quercetin isolated from *Morinda citrifolia* exhibits mild/weak inhibitory activity towards COX-2 [61].

Anti-depressant activity

Many scientists have inspected the potential action of some plants i.e., Ginkgo biloba, Apocynumvenetum, Hypericum perforatum, Valeriana officinalis, Melissa officinalis and *Morinda citrifolia* for the treatment of anxiety and depression [62]. Recent studies showed that *Morinda citrifolia* act as an inhibitor of MAO-A and MAO-B [63].

Lesion alleviating activity

1,6-dihydroxy-5-methoxy-2-methoxymethylanthraquinone (1) and 1,5,7-trihydroxy-6-methoxy-2-

methoxymethylanthraquinone were obtained from *Morinda citrifolia* fruit along with 11 compounds including new lignanisoamercanoic acid A [64]. Antidyslipidemic effects are shown by voltage dependent calcium channels of *Morinda citrifolia* fruit's root extract having vasodilatory and antispasmodic activities that have been reported. For further clinical settings more studies and research on *Morinda citrifolia* is needed which will prove its efficiency and safety also [65]. Crucially improved biological synthesis of glycosaminoglycans and type-1 C terminal peptide was manifested by the compound anthraquinone which was isolated from the extracts of *Morinda citrifolia* fruit juice. In a very adequate dose dependent manner reduction of collagenase matrix metalloproteinase-1 from human dermal fibroblasts occurred using the compound. Anthraquinone is a potential compound which is derived from *Morinda citrifolia* utilizing it as anti-wrinkle agent due to its stimulatory action on production of extracellular matrix compounds [66]. Researchers evaluated the regenerating potential of *Morinda citrifolia* juice in diabetic rats induced with streptozotocin using an excision wound model [67]. *Morinda citrifolia* juice was given with drinking water to few rats for 10 days, the lesion region reduced up to 73% in *Morinda citrifolia* treated group in comparisons to diabetic controls which was 63%. Histological detection unveiled that in *Morinda citrifolia* treated group deposition of collagen was quicker than that of control groups. All results were indicating the fact that significant decrease in blood sugar levels and accelerated lesion healing in diabetic rats was reported by treating with *Morinda citrifolia* fruit juice.

Hypotensive Activity

Hot water and ethanolic extracts of *Morinda citrifolia* roots helps to reduce the blood pressure in anesthetized dogs [68]. Diuretic activity has been shown by *Morinda citrifolia* fruit juice that may have antihypertensive effect. It has been reported that *Morinda citrifolia* has substantial inhibitory activity on Angiotensin I Converting Enzyme (ACE) and hence produces antihypertensive effect. It also has been observed that the ACE activity of ripened fruit was more compared to the immature *Morinda citrifolia* fruit. Furthermore, single organization of the *Morinda citrifolia* juice orally decline the systolic blood pressure in hypertensive rats [69]. The 70% of aqueous ethanolic extract of *Morinda citrifolia* roots has vasodilator, cardiovascular relaxant and antispasmodic effects and the gut and cardiovascular disorder can be treated by this ethanolic extract [70]. The relaxation spontaneous and high k^+ induced contraction in a concentration-dependent manner produced by the extract in isolated rabbit jejunum preparations. Like verapamil, the concentration response of c^{++} shifted right ward due to its cause. It has been reported that the root extract of *Morinda citrifolia* help in the treatment of diarrhea and hypertension [71].

Analgesic activity

Morinda citrifolia plants' extract maintain important transquiling and central analgesic activity in a dose related manner. However, it has no side effect and it is non-addictive and the analgesic effect of *Morinda citrifolia* extract is 75% more than morphine [72]. The hot plate assay and "twisted method" animal model tested the analgesic property of TNJ. The administration of antimony potassium tartrate intraperitoneally bears twisting by reason of pain. After injection the number of twists is estimated to determine the

level or measure of pain within 15 minutes. It is analytically important when compared with the control group and the analgesic of TNJ is dose dependent [31]. For the treatment of painful inflammatory conditions, like arthritis, *Morinda citrifolia* is used. The freeze concentration of *Morinda citrifolia* fruit puree at concentration of 10% solution in drinking water to mice suppress the pain signals when correlate to standard tramadol that was the central analgesic drug. This analgesic activity was moderately reversed by the drug naloxone, which is a known morphine antagonist. An alcohol extract of freeze concentrated *Morinda citrifolia* fruit puree helps in the reduction of clemency of MMP-9 from the monocytes of human origin after incitement with LPS. This effect was proportionate to accepted drug hydrocortisone. These results showed that *Morinda citrifolia* fruits are efficient in suppressing pain and arthritis [73].

Probiotic potential of *Morinda citrifolia* juice

Lactic acid bacteria such as *Lactobacillus plantum*, *Lactobacillus casei*, and *Bifidobacterium longum* are used in manufacturing probiotic *Morinda citrifolia* juice, always assessing a probability of *Morinda citrifolia* as raw substrate for manufacturing [74]. Strains of bacteria grew sumptuous on *Morinda citrifolia* juice after 48 hours of fermentation process. As compared to *L. plantum*, *B. longum* production of lactic acid in *L. casei* is less under cold storage and low pH conditions, high exalted antioxidant activity was shown by *B. longum* fermented *Morinda citrifolia* juice. These observations pointed that *B. longum* and *L. plantum* were best Probiotic for fermentation of *Morinda citrifolia* juice. By appraising the histomorphological changes in the duodenal villi the *Morinda citrifolia* fruit juice probiotic potential was elevated by Lactic acid bacteria (LAB) [75]. The duodenal function was enhanced by administering the *Morinda citrifolia* juice leading to nutrient absorption and development of immune response. Morical an additive of herbal feed prepared from *Morinda citrifolia* fruit elevates the production and ameliorate the quality of egg Japanese quail [76].

Future Perspectives and Conclusion

Lactic acid bacteria such as *Lactobacillus plantum*, *Lactobacillus casei*, and *Bifidobacterium longum* are used in manufacturing probiotic *Morinda citrifolia* juice, always assessing a probability of *Morinda citrifolia* as raw substrate for manufacturing [74]. Strains of bacteria grew sumptuous on *Morinda citrifolia* juice after 48 hours of fermentation process. As compared to *L. plantum*, *B. longum* production of lactic acid in *L. casei* is less under cold storage and low pH conditions, high exalted antioxidant activity was shown by *B. longum* fermented *Morinda citrifolia* juice. These observations pointed that *B. longum* and *L. plantum* were best Probiotic for fermentation of *Morinda citrifolia* juice. By appraising the histomorphological changes in the duodenal villi the *Morinda citrifolia* fruit juice probiotic potential was elevated by Lactic acid bacteria (LAB) [75]. The duodenal function was enhanced by administering the *Morinda citrifolia* juice leading to nutrient absorption and development of immune response. Morical an additive of herbal feed prepared from *Morinda citrifolia* fruit elevates the production and ameliorate the quality of egg Japanese quail [76].

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