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Systematic Review on Anticancer Potential and other Health Beneficial Pharmacological Activities of Novel Medicinal Plant *Morinda citrifolia* (Noni)

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Abstract: The miracle medicinal plant *Morinda citrifolia* L., also called as Noni, Great Morinda or Indian mulberry, belongs to the family Rubiaceae. Its fruit has been used traditionally for more than 2000 years by native Polynesians. However, all parts of the plant have medicinal properties. More than 160 phytochemicals have been isolated from the plant Noni which makes it an amazing herbal remedy for the treatment of numerous disorders including cancer. Recently, the Noni juice has been in high demand in market as Complementary and Alternative Medicine (CAM) for its multi-dimensional health benefits. It is a potent antibacterial, antiviral, antifungal, antihelminthic, anticancer, analgesic, anti-inflammatory, anti-oxidant, hypotensive, cardiovascular protective, wound healer, anxiolytic, sedative, antigout, antiobesity and immune enhancing agent. Anticancerous activity of *Morinda citrifolia* is attributable to its anti-inflammatory, antioxidant and apoptosis-inducing effects. Based on toxicological and mutagenicity assessment, Noni juice has been considered as safe. Few reports of hepatotoxicity exist, although there are many evidences suggesting hepatoprotective effects of Noni. Even though large number of *in vitro* studies has been carried out but only few clinical trials exist in the literature to suggest real beneficial effects of Noni in humans. Recently, Noni fruit juice has been accepted as a novel food element in the European Union. A number of scientific studies have been conducted to elucidate the mechanism of action of phytoconstituents of Noni. In this review, active phytochemical constituents, pharmacological properties, mechanism of action and various immunomodulatory and therapeutic potentials of Noni usage as a useful herbal medicine are discussed in detail which could be very helpful in safeguarding health of humans and their companion animals. A special focus has been made on the potent utility of this wonderful herbal plant in preventing and treating the deadly malady of cancer.

Key words: *Morinda citrifolia*, Noni, herb, phtochemicals, pharmacological activities, pharmacokinetics, immunomodulation, antimicrobial, anticancer, health, disease

INTRODUCTION

Herbal therapy denotes the use of plants for the promotion of immunity, maintenance of health and prevention and cure of diseases. In developing countries, more than 80% of human population still relies on Complementary and Alternative Medicine (CAM) for their health related issues (Ernst, 2000; Wanchai *et al*., 2010; Archana *et al*., 2011; Umashanker and Shruti, 2011; Mahima *et al*., 2012; Tiwari *et al*., 2012; Yarney *et al*., 2013). In the present era of emerging drug resistance, various kinds of stresses, immune pressures, global warming, liberalized trade, biodiversity variations, increasing population, changing life styles and food habbits and other predisposing factors, several kinds of general health problems and diseases are flaring up with increasing trend worldwide. These include diabetes, obesity, blood pressure, heart problems, arthritis, organ failures, cancers, immunosuppression along with increasing emergence of infectious and non-infectious

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diseases/disorders (Dhama *et al*., 2013a, b; Tiwari *et al*., 2013a). To counter these various diseases and general health problems, nowadays several novel and alternative/complementary therapeutic modalities are getting attention and popularization. These comprises of phages, cytokines, si-RNA, apoptins, nanomedicines, avian egg antibodies, stem cells, probiotics, immunomodulators, antioxidants, panchgavya elements, herbs, phytonutrients, fruits and vegetables (Dhama *et al*., 2008, 2013c, d, e, 2014; Amarpal *et al*., 2013; Mahima *et al*., 2012, 2013a, b; Karthik *et al*., 2014; Rahal *et al*., 2014a, b; Tiwari *et al*., 2012; 2014a, b). Of all these, the wonder world of ancient herbal heritage and the treasure of natural medicine is gaining much popularity due to their low toxicity and costs, changing ethical values, availability worldwide and usefulness as alternative/complementary medicines. Their need and demand is increasing day by day owing to their multi-dimensional health benefits and having several advantages over other medicinal options, possessing useful prophylactic as well as therapeutic potentials with wide practical applications at global level (Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Dhama *et al*., 2013f; Kumar *et al*., 2013a; Yarney *et al*., 2013; Tiwari *et al*., 2012, 2013b, 2014c, d).

Cancer remains as one of the most dreaded ailments for both human and animals. It claims about 7.6 millions of human lives every year (Ferlay *et al*., 2010; Dhanamani *et al*., 2011; Dhama *et al*., 2013b) in spite of innumerable interdisciplinary approaches efforts invested in cancer diagnosis and treatment. The basis of cancer therapy is surgery when the tumour gets localized, with feasible chemotherapy, radiotherapy, hormonal therapy, targeted therapies and immune therapy. However, these treatment options do not guarantee that cancer will not relapse (Yarney *et al*., 2013). Moreover, many adverse side effects of chemotherapy and radiotherapy make the life of patients miserable with more sufferings than the cancer alone (Ernst, 2000). Sophisticated therapeutic strategies in modern medicine, though effective but affect humanity and are not reachable to all human populations worldwide. This is because of the problems of affordability and as a consequence, large number of human populations still depends upon traditional herbal medicines as alternatives, to counter many infectious and non-infectious diseases as well as other general health disorders (Ernst, 2000; Mahima *et al*., 2012; Tiwari *et al*., 2012; Dhama *et al*., 2013b). In this context, the dietary plant elements and products and other nutraceuticals restricting the multiplication of cancer cells without showing any adverse effect on normal cells, are being considered as promising regiments for developing novel anti-cancer therapuetics as well as preventive approaches (Wargovich *et al*., 2001; Diwanay *et al*., 2004; Balachandran and Govindarajan, 2005; Agarwal *et al*., 2011; Kitagishi *et al*., 2012; Yarney *et al*., 2013).

India has a rich heritage of medicinal plants and herbs and a large number of plant extracts have been reported to be having high utility against several diseases and disorders including of cancers and tumours in medicinal systems of Ayurveda, Siddha and Unani (Archana *et al*., 2011; Umashanker and Shruti, 2011; Mahima *et al*., 2012). Among these traditional medicine systems, the Ayurveda is being used since ancient times, mostly utilizing the wealth of herbs to prevent or cure various diseases (Ernst, 2000). In recent times, thousands of herbs and their preparations are being studied worldwide to identify their pharmacologically active components and scientific validation purposes which are playing crucial role in propagating and popularizing the use of these wonderful drugs/medicines (Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Tiwari *et al*., 2012). The list of useful plants goes endless but most commonly used herbal medicinal plants include *Azadirachta indica* (neem), *Tinospora cardifolia* (giloy), *Astragalus membranaceus, Withania somnifera* (ashwagandha), *Emblica officinalis* (amla), *Ocimum sanctum* (tulsi), *Piper longum* (pipali), Aloe vera, *Allium sativum* (garlic), *Zingiber officinale*, (ginger), *Curcuma longa,* (turmeric) etc., (Archana *et al*., 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Dhama *et al*., 2013b; Kumar *et al*., 2013a, b, c; Yakout *et al*., 2013; Midrarullah *et al*., 2014; Tiwari *et al*., 2012, 2014c, d). Of these, *Morinda citrifolia* L., popularly known as Noni, an Indian herb, has been found to offer many health benefits and fight various disease conditions. This plant has also been utilized as potent food supplement since ancient times throughout the globe. The Noni juice had been commercialized in the USA as "functional food" products in 1990s and is increasingly distributed all over the world (Brown, 2012; Singh, 2012). The pharmacologically active compounds derived from *M. citrifolia* fruits, leaves and roots are nowadays available as readymade capsules, teas and juices, the fruit juice being the most popular. Noni fruit contains alkaloids, scopoletin, damnacanthal and lots of other molecules, as a result the consumption of Noni juice is currently high, not only in US but also in Japan, Europe and India. It is claimed that the marketing of Noni has reached US $ 1.3 billion in annual sales (Chan-Blanco *et al*., 2006; Singh, 2012). Some companies producing flavoured Noni juices by addition of other fruit juices to render the product more palatable and more acceptable in market (Mathivanan *et al*., 2005). In

response to this demand, some countries including India have increased the commercial cultivation of Noni and this plant has come up as a source of livelihood for farmers especially in Andaman and Nicobar Islands (Singh and Rai, 2007). Noni juice has been recently accepted in European Union as a novel food (EFSA, 2006). Noni plant, by virtue of its immunomodulating and nutritive properties, helps minimize the adverse effects of cancer maladies and side effects of various cancer therapies. Many bio anticarcinogenic agents present in Noni have also been reported to improve the potency of the cancer therapies. This herb also has been found to be beneficial for primary prevention and as a synergistic immune potentiating element in conjunction with common treatment modalities for various ailments (Chan-Blanco *et al*., 2006; Brown, 2012; Singh, 2012; Gupta and Patel, 2013).

The present manuscript is an updated review compilation on this wonderful herbal plant and its different health beneficial aspects, active phytochemical constituents, pharmacological properties, mechanism of action and various immunomodulatory and therapeutic potentials. A special focus has been made on the potent utility of Noni as a herbal remedy in preventing and treating the deadly malady of cancer. No such review compilation is available on this useful herbal plant having multidimensional health benefits. The manuscript would be highly helpful for pharmaceutists, Ayurveda medicinal system, researchers, medicos, veterinarians, livestock and poultry producers/industry and common man. Altogether, it would help propagate and promote this plant to be used in complementary and alternative medicinal treatment options as a herbal remedy for safeguarduing health of humans and their companion animals.

General description of *Morinda citrifolia L.* (Noni): An edible and tropical plant *Morinda citrifolia* L., has been widely used by Polynesians in folk medicine for more than 2,000 years. It is commonly known as great morinda, Indian mulberry, nunaakai and Noni in India, Ba Jitiamin in China, dog dumpling in Barbados, mengkudu in Indonesia and Malaysia, Nono in Tahiti, painkiller bush in the Caribbean, cheese fruit in Australia and beach mulberry or Noni in Hawaii (Morton, 1992; Wang *et al*., 2002a; Cardon, 2003; Serafini *et al*., 2011). *Morinda citrifolia* from the coffee family, Rubiaceae is made up of around 80 species. *M. citrifolia* is a short tropical evergreen plant and is found in open coastal and forest areas upto 1300 feet above sea level. It is native to the Pacific islands, Hawaii, Caribbean, Asia and Australia (Chan-Blanco *et al*., 2006; Brown, 2012). In Southern India *M. citrifolia* is found in the coastal regions of the Tamil Nadu and Kerala and also in the Mangalore area of Karnataka. Noni is well suited for extremely broad range of adverse environmental conditions. Noni can grow well in acidic, alkaline and infertile soils and it is also suitable for cultivation in extremely wet to dry areas (Cardon, 2003; Singh, 2012). The leaves are oval shaped, 8-10 inches long, dark green, shiny and with deep veins. The grenade-like yellow fruits can grow to a size of upto 12 cm and it arises due to coalescence of many inferior ovaries of closely packed flowers. The fruit has a lumpy surface with many polygonal shaped areas. The unripened fruit of *M. citrifolia* is green in colour. As it ripens the fruit becomes white in colour and it simply falls to the ground unless harvested at this stage. When the fruit becomes ripened, it has a very pungent smell, like the odour of blue vein cheese and it has a sour taste. The seeds are triangular in shape and reddish brown in colour, have air sac at one end which makes them buoyant (Wang *et al*., 2002a; Chan-Blanco *et al*., 2006). Other species of Morinda used therapeutically include *Morinda lucida*, *Morinda morindoides*, *Morinda officinalis* and *Morinda tinctoria*. *Morinda officinalis* (also known as Ba Ji Tian) specifically has been used for antidepressant effects (Schripsema *et al*., 2006; Mathivanan *et al*., 2006; Bao *et al*., 2011). It has also been used to treat kidney disorders in Chinese medicine. *Morinda lucida* is used in Nigeria for febrile illnesses and sickle cell anemia (Mpiana *et al*., 2007). *Morinda morindoides* has been used for anti-cancer treatments. *Morinda tintoria* has been demonstrated to possess anti-bacterial effects pre-clinically (Alitheen *et al*., 2010).

Pharmacological activities of *Morinda citrifolia*: Different parts of the Noni plant have been traditionally used for treatment of various complaints for their therapeutic activities, including hypotensive action (Youngken, 1958, Youngken *et al*., 1960; Moorthy and Reddy, 1970; Yamaguchi *et al*., 2002; Gilani *et al*., 2010), analgesia (Younos *et al*., 1990; Wang *et al*., 2002a; Punjanon and Nandhasri, 2005; Basar *et al*., 2010), antibacterial effects (Atkinson, 1956; Bushnell *et al*., 1950; Leach *et al*., 1988; Sundarrao *et al*., 1993; Dittmar, 1993; Locher *et al*., 1995; Duncan *et al*., 1998; Wei *et al*., 2008; Jayaraman *et al*., 2008; Selvam *et al*., 2009; Kumar *et al*., 2010; Usha *et al*., 2010; Natheer *et al*., 2012; Murray *et al*., 2008; West *et al*., 2012), antituberculosis properties (Anonymous, 2001; Saludes *et al*., 2002), anti-inflamatory action (Takahashi *et al*., 2002; Colville-Nash and Gilroy, 2001; Su *et al*., 2001; Wang and Su, 2001; McKoy *et al*., 2002; Li *et al*., 2003; Akihisa *et al*., 2007; Deng *et al*., 2007a; Dussossoy *et al*., 2011; Palu *et al*., 2012) and

antioxidant effects (Wang and Su, 2001; Wang *et al*., 2002b; Chow, 1993; Wang *et al*., 2009a, b; Anitha and Mohandass, 2006; Zin *et al*., 2002; Liu *et al*., 2007; Ikeda *et al*., 2009; West *et al*., 2009; Thani *et al*., 2010; Dussossoy *et al*., 2011; Serafini *et al*., 2011; West *et al*., 2011). It is also used for curing osteoporosis and auditory improvement (Langford *et al*., 2004; Li *et al*., 2008; Bao *et al*., 2011), wound healing (Kim *et al*., 2005; Nayak *et al*., 2007, 2009; Palu *et al*., 2010), antiviral activity (Umezawa, 1992; Kamata *et al*., 2006), anticataract (Gacche and Dhole, 2011; Saminathan *et al*., 2014), antigout (Palu *et al*., 2009), antifungal (Banerjee *et al*., 2006; Usha *et al*., 2010; Jayaraman *et al*., 2008; Jainkittivong *et al*., 2009), neuronal protective (Harada *et al*., 2010), antidiabetes (Jensen *et al*., 2005; Nayak *et al*., 2007, 2011; Horsfall *et al*., 2007; Kamiya *et al*., 2008; Owen *et al*., 2008; Nerurkar *et al*., 2011), anti-postoperative nausea and vomiting (Prapaitrakool and Itharat, 2010), anti-hypercholesterolemia (Kamiya *et al*., 2004; Mandukhail *et al*., 2010), anti-gastric ulcer and reflux esophagitis (Mahattanadul *et al*., 2011) and anticancer (Hiramatsu *et al*., 1993; Hirazumi and Furusawa, 1999; Liu *et al*., 2001; Jayaraman *et al*., 2008; Arpornsuwan and Punjanon, 2006; Taskin *et al*., 2009; Hutheyfa, 2010; Thani *et al*., 2010; Nualsanit *et al*., 2012; Lv *et al*., 2011; Clafshenkel *et al*., 2012; Gupta *et al*., 2013; Saminathan *et al*., 2013a, b) effects. Noni is also found useful in cancer chemoprevention (Tepsuwan and Kusamran, 1977; Hirazumi *et al*., 1992, 1994, 1996; Wang and Su, 2001, Wang *et al*., 2002c, 2009a, b, 2013; Li *et al*., 2008; Hazilawati *et al*., 2010a, b; Stoner *et al*., 2010; Saminathan *et al*., 2013c), inhibition of angiogenesis (Hornick *et al*., 2003) and immune stimulation (Hokama, 1993; Asahina *et al*., 1994; Hirazumi and Furusawa, 1999; Pansuebchue *et al*., 2002; Wang *et al*., 2002a; Brooks *et al*., 2009; Zhang *et al*., 2009; Nayak and Mengi, 2010). *M. citrifolia* prevents the formation and proliferation of tumors, including malignant tumors. It regulates of cell function and regeneration of damaged cells (Singh and Rai, 2007). The major bioactive constituents identified in various parts of *M. citrifolia* are presented in Table 1.

Table 1: Major bioactive constituents in various parts of *Morinda citrifolia*

Chemical constituents	Structure	References
Flower		
2-Methyl-4-hydroxy-5,7-dimethoxyanthraquinone 4-O-β-D-glucopyranosyl-(1-4)-α-L-rhamnopyranoside	Anthraquinone glycosides	Sang *et al*. (2002)
5,8-Dimethyl-apigenin 4'-O-β-D-galactopyranoside	Flavonoid glycosides	Elkins (1998) and Sang *et al*. (2002)
Acacetin 7-O-β-D-glucopyranoside		
6,8-Dimethoxy-3-methylanthraquinone-a-L-O-β-rhamnosyl glucopyranoside	Anthraquinone glycosides	Tiwari and Singh (1977)
Acacetin 7-O-β-D-glucopyranoside	Flavonoids	Tiwari and Singh (1977)
5,7-Dimethyl apigenin 4'-O-β-D-galactopyranoside		
Fruit		
Asperulosidic acid	Iridoids	Elkins (1998), McClatchey (2002), Kamiya *et al*. (2005) and Samoylenko *et al*. (2006)
Asperuloside tetraacetate	Iridoids	Liu *et al*. (2001), Cardon (2003) and Su *et al*. (2005)
Asperulosidic acid methyl ester	Iridoids	Sang *et al*. (2002)
Borreriagenin (previously morindacin)	Iridoids	Kamiya *et al*. (2005); Su *et al*. (2005)
4-epi-Borreriagenin	Iridoids	Samoylenko *et al*. (2006)
Deacetylasperuloside	Iridoids	Su *et al*. (2005) and Takashima *et al*. (2007)
Deacetylasperulosidic acid	Iridoids	Kamiya *et al*. (2005) and Samoylenko *et al*. (2006)
Deacetylasperulosidic acid methyl ester	Iridoids	Sang *et al*. (2002)
Dehydromethoxygaertneroside	Iridoids	Su *et al*. (2005)
6β,7 β-Epoxy-8-epi-splendoside		
6α-Hydroxyadoxoside		
1,3a,4,7a-Tetrahydro-6-(hydroxymethyl)-3H-furo[3,4-clpyran-4-carboxylic acid	Iridoids	Sang *et al*. (2002)
Acubin	Iridoid glycoside	Pawlus *et al*. (2005)
Ethyl caprylate	Saturated fatty acid	Solomon (1999), Dittmar (1993), Cardon (2003), Elkins (1998) and Levand and Larson (1979)
Ethyl caproate	Saturated fatty acid	Dittmar (1993)
Quercetin** 3-O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranoside	Flavonoid	Sang *et al*. (2002), Cardon (2003) and Deng *et al*. (2007b)
Kaempferol	Flavonoid	Deng *et al*. (2007b)
Narcissoside	Flavonoid	Su *et al*. (2005)

Table 1: Continue

Chemical constituents	Structure	References
Nicotifloroside	Flavonoid	Sang *et al.* (2001) and Su *et al.* (2005)
Rutin	Flavonoid	Wang *et al.* (1999) and Sang *et al.* (2001)
2-Heptanone	Ketone	Farine *et al.* (1996)
3-Hydroxy-2-butanone		
(E)-6-Dodeceno-γ-lactone	Lactone	Farine *et al.* (1996)
(Z)-6-Dodeceno-γ-lactone		
Americanin A	Lignans	Kamiya *et al.* (2004)
Americanoic acid		
Americanol A		
Balanophonin	Lignans	Pawlus *et al.* (2005)
3,3'-Bisdemethylpinoresinol	Lignans	Kamiya *et al.* (2004); Deng *et al.* (2007b)
3,3'-Bisdemethyltanegool	Lignans	Deng *et al.* (2007b)
Isoprincepin	Lignans	Kamiya *et al.* (2004)
Morindolin		
(-)-Pinoresinol	Lignans	Deng *et al.* (2007b)
(+)-3,4,3',4'-Tetrahydroxy-9,7'*a*-epoxylignano-7 *a*,9'-lactone		
Cytidine	Nucleosides	Sang *et al.* (2002) and Su *et al.* (2005)
Nonioside A	Saccharides	Wang *et al.* (2000) and Dalsgaard *et al.* (2006)
Nonioside B		
Nonioside C		
Nonioside D	Saccharides	Wang *et al.* (2000)
Nonioside E	Saccharides	Dalsgaard *et al.* (2006)
Nonioside F		
Nonioside G		
Nonioside H		
α and β-Glucose	Saccharides	Levand and Larson (1979) and Samoylenko *et al.* (2006)
Methyl α-D-fructofuranoside	Saccharides	Su *et al.* (2005)
Methyl β-D-fructofuranoside		
1-O-(3'-Methylbut-3'-enyl)-β-D-glucopyranose	Saccharides	Samoylenko *et al.* (2006)
β-D-glucopyranose penta acetate	Saccharides	Elkins (1998) and Sang *et al.* (2002)
2,6-di-O-(β-D-glucopyranosyl-1-O-octanoyl-β-D-glucopyranose	Saccharides	Dittmar (1993)
6-O-(β-D-glucopyranosyl-1-O-octanoyl-β-D-glucopyranose	Saccharides	Wang *et al.* (1999)
2-O-(beta-D-glucopyranosyl)-1-O-hexanoyl-beta-D-gluropyranose	Saccharide fatty acid esters	Akihisa *et al.* (2007)
2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-gluropyranose		
3,19-Dihydroxyursolic acid	Triterpenoids and sterols	Sang *et al.* (2002)
19 α-Methylursolic acid		
(Ethylthiomethyl) benzene	Miscellaneous compounds	Farine *et al.* (1996)
Hexanamide	Amide	
Limonene	Cyclic terpene	
Vomifoliol	Ionones/ester	
Scopoletin	Coumarin	Pawlus *et al.* (2005) and Samoylenko *et al.* (2006)
Vanillin	Phenolic aldehyde	Pawlus *et al.* (2005) and Deng *et al.* (2007b)
Isoscopoletin	Coumarin	Deng *et al.* (2007b)
β-Hydroxypropiovanillone	Miscellaneous compounds	Pawlus *et al.* (2005)
4-Hydroxy-3-methoxyciunamaldehyde		
1-Palmitin		
Acetic acid	Acids	Farine *et al.* (1996)
Benzoic acid		
Butanoic acid		
Decanoic acid		
(Z, Z, Z)-8, 11, 14-Eicosatrienoic acid		
Elaidic acid		
Heptanoic acid		
Hexanedioic acid		
Lauric acid		
Linoleic acid		
2-Methylbutanoic acid		
2-Methylpropanoic acid		
3-Methylthiopropanoic acid		
Myristic acid		
Nonanoic acid		
Oleic acid		
Palmitic acid		

Table 1: Continue

Chemical constituents	Structure	References
Undecanoic acid		
Hexanoic acid	Acids	Dittmar (1993); Sang *et al.* (2002)
Octanoic acid		
Ascorbic acid	Acids	Liu *et al.* (2001)
Caproic acid	Acids	Dittmar (1993)
Caprylic acid	Acids	Elkins (1998); Sang *et al.* (2002)
Benzyl alcohol	Alcohols and phenols	Farine *et al.* (1996)
1-Butanol		
Eugenol		
1-Hexanol		
3-Methyl-2-buten-1-ol		
3-Methyl-3-buten-1-ol		
(Z, Z)-2, 5-Undecadien-1-ol		
Anthragallol 1,3-di-O-methyl ether	Anthraquinones	Kamiya *et al.* (2005) and Pawlus *et al.* (2005)
Anthragallol 2-O-methyl ether		
Austrocortinin		Kim *et al.* (2005)
5,15-Dimethylmorindol	Anthraquinones	Kamiya *et al.* (2005) and Takashima *et al.* (2007)
6-Hydroxyanthragallol-1,3-di-O-methyl ether		Kamiya *et al.* (2005)
2-Methoxy-1, 3, 6-trihydroxyanthraquinone		Pawlus *et al.* (2005)
Morindone-5-O-methyl ether		Kamiya *et al.* (2005)
1,5,15-tri-O-methylmorindol	Anthraquinone	Akihisa *et al.* (2007)
Alizarin		
1-n-Butyl-4-(5'-formyl-2'-furanyl) methyl succinate	Esters	Samoylenko *et al.* (2006)
1-n-Butyl-4-methyl-2-hydroxysuccinate		
1-n-Butyl-4-methyl-3-hydroxysuccinate		
Ethyl decanoate	Esters	Farine *et al.* (1996)
Ethyl hexanoate		
Ethyl octanoate		
Ethyl palmitate		
Methyl decanoate		
Methyl elaidate		
Methyl hexanoate		
Methyl 3-methylthio-propanoate		
Methyl octanoate		
Methyl oleate		
Methyl palmitate		
Heartwood		
Physcion-8-O-α-L-arabinopyranosyl-(1-3)-β-D-galactopyranosyl-(1-6)-β-D-galactopyranoside	Anthraquinone glycosides	Wang and Su (2001)
Alizarin	Anthraquinone	Thomson (1971)
Anthragallol 2,3-di-O-methyl ether		
Damnacanthal		
Morindone		
Rubiadin-1-O-methyl ether		
Physcion	Anthraquinone	Srivastava and Singh (1993)
Leaves		
Quercetin** 3-O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranoside	Flavonoids	Sang *et al.* (2002)
Quercetin 3-O-β-D-glucopyranosyl-(1-2)-α-L-rhamnopyranosyl-(1-6)-β-D-galactopyranoside	Flavonoids	Sang *et al.* (2002)
Quercetin 3-O-β-D-glucopyranoside	Flavonoids	Sang *et al.* (2002)
Rutin	Flavonoids	Sang *et al.* (2001)
Kaempferol** 3-O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranoside	Flavonoids	Sang *et al.* (2002)
Kaempferol 3-O-β-D-glucopyranosyl-(1-2)-α-L-rhamnopyranosyl-(1-6)-β-D-galactopyranoside	Flavonoids	Sang *et al.* (2002)
Nicotifloroside	Flavonoids	Sang *et al.* (2001) and Su *et al.* (2005)
Asperuloside	Iridoids	Sang *et al.* (2001) and Su *et al.* (2005)
Asperulosidic acid	Iridoids	Sang *et al.* (2001), Kamiya *et al.* (2005), Su *et al.* (2005) and Samoylenko *et al.* (2006)
Citrifolinin A-1	Iridoids	Sang *et al.* (2003)
Citrifolinin Ba		
Citrifolinin Bb		
Citrifolinoside A		
Citrifolinoside B	Iridoids	Sang *et al.* (2002)
Citrifoside	Iridoids	Takashima *et al.* (2007)

Table 1: Continue

Chemical constituents	Structure	References
Deacetylaspernloside	Iridoids	Su *et al.* (2005) and Takashima *et al.* (2007)
Dehydroepoxymethoxygaertneroside	Iridoids	Sang *et al.* (2001) and Schripsema *et al.* (2006)
Alanine	Amino acids	Sang *et al.* (2002) and Cardon (2003)
Serine		Dittmar (1993); Elkins (1998)
Threonine		
Tryptophan		
Tyrosine		
Valine		
Arginine		
Aspartic acid		
Cysteine	Sulphur containing	Dittmar (1993) and Elkins (1998)
Cystine	amino acids	
Glutamic acid	Amino acids	Dittmar (1993) and Elkins (1998)
Glycine		
Histidine		
Isoleucine		
Leucine		
Methionine		
Phenylalanine		
Proline		
3-O-Acetylpomolic acid	Triterpenoids and sterols	Saludes *et al.* (2002) and
Barbinervic acid		Takashima *et al.* (2007)
Campesta-5,7,22-trien-3 β-ol		
Clethric acid		
Cycloartenol		
Hederagenin		
Oleanolic acid		
Rotungenic acid		
β-sitosterol	Triterpenoids and sterols	Elkins (1998), Sang *et al.* (2002) and Cardon (2003)
Ursolic acid		
Stigmasta-4-en-3-one	Triterpenoids and sterols	Saludes *et al.* (2002)
Stigmasta-4-22-dien-3-one		
Stigmasterol	Triterpenoids and sterols	Saludes *et al.* (2002)
13-Hydroxy-9,11,15-octadecatrienoic acid	Acids	Takashima *et al.* (2007)
5,15-Dimethylmorindol	Anthraquinones	Kamiya *et al.* (2005) and
1,5,15-Trimethylmorindol		Takashima *et al.* (2007)
β-Carotene	Carotenoids	Elkins (1998)
132(R)-Hydroxypheophorbide a methyl ester	Chlorophyll derivatives	Takashima *et al.* (2007)
132(S)-Hydroxypheophorbide a methyl ester		
151(R)-Hydropurpurin-7 lactone dimethyl ester		
151(S)-Hydropurpurin-7 lactone dimethyl ester		
Methyl pheophorbide a		
Methyl pheophorbide b		
Pheophorbide a		
13-epi-Phaeophorbide a methyl ester		
Peucedanocoumarin III	Miscellaneous compounds	Takashima *et al.* (2007)
Phytol		
Pteryxin		
Roseoside II		
Stems		
2-Hydroxyanthraquinone	Anthraquinones	Siddiqui *et al.* (2006)
2-Methoxyanthraquinone		
Morindicininone		
Root		
8-Hhydroxy-8-methoxy-2-methyl-anthraquinone	Anthraquinones	Solomon (1999) and Cardon (2003)
Rubichloric acid	Acid	Morton (1992) and Elkins (1998)
1,3-Dihydroxy-6-methyl Anthraquinone	Anthraquinones	Morton (1992)
Morenone 1	Anthraquinones	Solomon (1999)
Morenone 2		
Ruberythric acid*	Acid	Cardon (2003)
Rubiadin	Anthraquinones	Cardon (2003), Elkins (1998) and Ross (2001)
Rubiadin-1-O-methyl ether	Anthraquinones	Thomson (1971)
Soranjidiol	Anthraquinones	Thomson (1971)
Tectoquinone	Anthraquinones	Thomson (1971)
Alizarin 1-O-methyl ether	Anthraquinones	Pawlus *et al.* (2005)

Table 1: Continue

Chemical constituents	Structure	References
Anthragallol 1,2-di-O-methyl ether	Anthraquinones	Thomson (1971)
Damnacanthal	Anthraquinones	Thomson (1971) and Hiramatsu *et al.* (1993)
Damnacanthol		
2-Formylanthraquinone	Anthraquinones	Thomson (1971) and Cardon (2003)
1-Hydroxy-2-methylanthraquinone		
2-Hydroxy-1-methoxy-7-methylanthraquinone	Anthraquinones	
Ibericin	Anthraquinones	
1-Methoxy-3-hydroxyanthraquinone		
Morindone	Anthraquinones	Thomson (1971)
Nordamnacanthal	Anthraquinones	Thomson (1971)
Root bark		
Chlororubin	Chlorophyll derivatives	Dittmar (1993) and Elkins (1998)
Hexose	Saccharides	
Morindadiol	Anthraquinones	
Morindanidrine	Anthraquinones	
Morindine	Anthraquinones	Morton (1992), Dittmar (1993), Elkins (1998) and Cardon (2003)
Pentose	Saccharides	Dittmar (1993)
Physcion	Anthraquinone	Solomon (1999)
Rubiadin monomethyl ether	Phenol	Dittmar (1993)
Soranjidiol	Anthraquinone	Dittmar (1993), Elkins (1998) and Ross (2001)
Trioxymethyl anthraquinone monoethyl ether	Anthraquinone	Dittmar (1993)
Plant		
2-Methyl-3, 5, 6-trihydroxyanthraquinone	Anthraquinone	Inoue *et al.* (1981) and Cardon (2003)
2-Methyl-3, 5, 6-trihydroxyanthraquinone*		
6-O-β-D-xylopyranosyl-(1-6)-β-D-glucopyranoside	Anthraquinone glycoside	
3-Hydroxymorindone	Anthaquinone	
3-Hydroxymorindone* 6-O-β-D-xylopyranosyl-(1-6)-β-D-glucopyranoside	Anthraquinone glycoside	
5,6-Dihydorxylucidin* 3-O-β-D-xylopyranosyl-(1-6)-β-D-glucopyranoside	Anthraquinone glycoside	
5,6-Dihydroxylucidin	Anthraquinone	
Aucubin	Iridoid glycoside	Elkins (1998)
Linoleic acid	Unsaturated fatty acid	Inoue *et al.* (1981) and Cardon (2003)
Lucidin	Anthraquinone	Cardon (2003), Inoue *et al.* (1981) and Ross (2001)
Lucidin* 3-O-β-Dxylopyranosyl-(1-6)-β-D-glucopyranoside	Anthraquinone	Cardon (2003), Inoue *et al.* (1981)
Scopoletin	Coumarin	Farine *et al.* (1996)
Root, heartwood, root bark		
Morindone	Anthraquinones	Inoue *et al.* (1981), Dittmar (1993), Ross (2001), Sang *et al.* (2002) and Cardon (2003)
Root, heartwood, seeds		
Damnacanthal	Anthraquinones	Sang *et al.* (2002) and Cardon (2003)
Root, root bark, fruit		
Alizarin	Anthraquinones	Dittmar (1993), Elkins (1998), Ross (2001) and Cardon (2003)
Seeds		
Ricinoleic acid	Acids	Solomon (1999)

*Glycosides are primeverosides [=O-β-D-xylopyranosyl-(1-6)-β-D-glucopyranosides], **Glycosides are rutinosides [=O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranosides]

Pharmacokinetics of Noni: Wang *et al.* (2002a) studied the pharmacokinetics of Noni by administration of Noni puree at a dose of 1 mL/100 g body weight, orally in female SD rats. The major component in Noni is scopoletin, a naturally occurring coumarin which was used as a marker and it was estimated from different organs and plasma. The plasma concentration of scopoletin reached maximum at 2 h after administration of Noni and it is decreased to 50% in 4 h. After 12 and 24 h only 12 and 2% of the scopoletin, respectively, was present in the plasma. Absorption was rapid during first 30 min and achieved 50% of maximal concentration. Noni intake at every 2-4 h is must to maintain an elevated blood level of scopoletin. For overall maintenance of health, one-ounce of Tahitian Noni Juice (TNJ) every 12 h is necessary. Overall results indicated that the frequency of drinking of TNJ is more essential than the amount. Estimation of the concentration of scopoletin in various organs indicated that Noni is absorbed into different tissues within 1 h after its administration. The scopoletin level was amusingly higher in breast tissue when compared to other extra GI tract tissues.

Mechanism of action of various compounds present in Noni: Noni has more than 160 phytochemical compounds. The major micronutrients are alkaloids, phenolic compounds, proteins, organic acids, minerals and vitamins. Among phenolic compounds, most important are anthraquinones damnacanthal, nordamnacanthal, morindone, rubiadin-1-methyl ether, alizarin, rubiadin, aucubin, asperuloside and scopoletin (Wang and Su, 2001). The organic acids mainly are caproic and caprylic acids (Dittmar, 1993) while the principal alkaloid is xeronine (Heinicke, 1985). The *M. citrifolia* fruit contains 90% of water and the chief components of the dry matter are dietary fibers, soluble solids and proteins. The protein content of the fruit is surprisingly high and the main amino acids are glutamic acid, aspartic acid and isoleucine. Noni has six major substances namely anthraquinones, polysaccharides, epigallocatechin gallate (EGCg), coumarins, monoterpenes and terpenoid compounds.which have been shown to fight cancer in different ways (Mathivanan *et al*., 2005).

Anthraquinones: Morindone, morindin and damnacanthal are important anthraquinone compounds that have a variety of biological activities including anti-inflammatory, anti-oxidant, antibacterial, anthelmintic and immunomodulating effect. Damnacanthal is vital compound found in Noni and prevents the formation of cancers by inhibiting ras gene activation. It has potent inhibitory activity on tyrosine kinases including EGF, Lck, Lyn and Src receptor (Hiramatsu *et al*., 1993; Hisawa *et al*., 1999). Alizarin is another anthraquinone compound that shows antiangiogenic function. It prevents blood circulation to malignant cancers results in arrest of the growth of tumour cells. Alizarin also inhibits the activity of cancer producing agent cytochrome C without production of free radicals (Tarasiuk *et al*., 1996).

Polysaccharides: Ethanol precipitate of Noni contains a unique polysaccharide which is composed of four sugars namely rhamnose, glucoronic acid, arabinose and galactose. It has immunomodulatory effects (Hirazumi and Furusawa, 1999) and blocks the adhesion of mutated cells to other cells and thereby stopping metastasis (Mathivanan *et al*., 2005).

Epigallocatechin gallate (EGCg): EGCg is a polyphenolic flavonoid that has antioxidant activity and is present in excellent amount in *M. citrifolia*. EGCg prevents the enzyme quinol oxidase (NOX) in tumours which leads to antiangiogenesis, inhibition of proliferation of cancer cells and death of these cells (Mathivanan *et al*., 2005).

Coumarins: Scopoletin is a naturally occurring coumarin that was isolated from Noni. It has analgesic activity and also controls the serotonin levels in the body significantly (Duncan *et al*., 1998; Liu *et al*., 2007). It also has anti-microbial (Duncan *et al*., 1998) and anti-hypertensive effects (Solomon, 1999).

Monoterpenes: Monoterpenes prevent the carcinogenic process at both the beginning and progression stages of cancers with no toxic effects on the body. One of the most common monoterpenes found in Noni juice is limonene. It also prevents liver, mammary, lung and other tissue cancers. Stimulation of thymus gland is done by limonene to produce more T cells that demolish the tumour cells. *In vitro* studies indicate that it is also effective in the treatment of leukaemia (Mathivanan *et al*., 2005).

Terpenoid compounds: Most common terpenoid compounds found in Noni are beta carotene, eugenol and urosolic acid. Beta carotene reduces various types of cancers and by quenching the free radicals and prevents oxidative damage. Urosolic acid is a penta cyclic terpenoid that has anti carcinogenic effect by preventing the growth of tumour cells and induces apoptosis by enhancing the immune system (Wang *et al*., 2002a).

Xeronine system: Even though Noni fruits contain slight amount of xeronine in free form, they contain precursor of xeronine called proxeronine in significant quantity. The molecular weight of proxeronine is comparatively large and about 16,000 Da. Proxeronine is converted into xeronine in the body by proxeroninase. Xeronine is a small alkaloid and is physiologically active in the picogram range. Xeronine is present in all healthy cells of animals, plants and microorganisms. The Noni juice should be taken on an empty stomach, the essential proenzyme, proxeroninase does not undergo digestion in the stomach and enters quickly into the intestine, where it may be converted into the active enzyme. If the juice is taken on a full stomach, it will have very little advantageous action. In the stomach, the enzyme, proxeroninase is destroyed by pepsin and acid. The most important function of xeronine is to regulate the rigidity and shape of specific proteins and is also a critical metabolic coregulator. Xeronine will act on abnormal protein and make it fold into its correct conformation that results in properly functioning protein (Heinicke, 1985).

***In vitro* anticancer effects of Noni:** An anthraquinone compound, damnacanthal was separated from the chloroform extract of the root of *Morinda citrifolia*. It

inhibits the ras oncogene function which is associated with signal transduction in leukemia, lung, colon and pancreatic cancers. Damnacanthal induced normal morphology and cytoskeletal structure in K-rasts-NRK cells without changing the localization and amount of ras. This effect was reversible and it had no effect on the morphology of RSVts-NRK cells expressing the src oncogene (Hiramatsu *et al*., 1993). Sundarrao *et al*. (1993) reported that Noni has antitumor activity against sarcoma 180 cells in mice.

Noni fruit juice contains a polysaccharide-rich substance which has antitumor activity that increases the production of cytokine IFN-gamma from thymocytes. This polysaccharide-rich substance is a water-soluble, ethanol precipitate containing a gum arabic heteropolysaccharide, composed of the sugars rhamnose, glucuronic acid, arabinose and galactose, however, ethanol-soluble fraction of Noni fruit juice has no antitumor activity. But it has antitumour activity against Lewis lung peritoneal carcinomatosis (LLC) by potentiating the immune system through release of tumor necrosis factor-alpha (TNF-α), interleukin-1β(IL-1β),interleukin-10(IL-10),interleukin-12 (IL-12) p70, interferon-gamma (IFN-γ) and nitric oxide (NO) but had no effect on IL-2 and decreased the IL-4 release (Hirazumi and Furusawa, 1999).

Hisawa *et al*. (1999) studied the action of damnacanthal on ultraviolet ray-induced apoptosis in ultraviolet-resistant human UVr-1 cells. Damnacanthal has potent inhibitory activity on tyrosine kinases including EGF, Lck, Lyn and Src receptor. Ultraviolet light induces a stress-activated protein kinases and phosphorylated extracellular signal regulated kinases. Stimulatory effect on ultraviolet-induced apoptosis was noticed when the cells were treated with damnacanthal prior to ultraviolet irradiation. This is beneficial effect of damnacanthal because apoptosis eliminates UV radiation induced potential mutagenic or transformed cells. Failure of apoptosis inducing effect of the body results in development of skin cancer. Two novel glycosides NB10 (6-O-(β-D-glucopyranosyl)-1-O-octanoyl-β-D-glucopyranose) and NB11 (asperulosidic acid) had anticancerous activity. They are isolated from the n-butyl alcohol soluble fraction of Noni fruit juice. They suppress the TPA-(12-O-tedtradecanoylphorbol-13-acetate) and EGF-(epidermal growth factor) induced cell transformation and associated AP-1 transactivation in the mouse epidermal JB6 cell line. Growth factors, TPA and UV radiation induce AP-1 transactivation that results in tumorigenesis. These compounds also prevent the phosphorylation of c-Jun (a substrate of JNKs) which suggests that JNKs are a crucial target in mediating the AP-1 activity and cell transformation (Liu *et al*., 2001).

Morinda citrifolia fruit juice with concentrations of 5% (v/v) or more prevents the initiation of new blood vessel sprouts from placental vein explants and decreases the proliferation and growth rate of newly developing capillary sprouts. Concentration of 2.5% Noni juice in the media was ineffective in blocking initiation of angiogenesis. In human breast tumor explants, 10% Noni juice in growth medium inhibits capillary initiation, vessel degeneration and apoptosis in wells within 2-3 days (Hornick *et al*., 2003). An anthraquinone with extremely potent quinone reductase-inducing activity, 2-methoxy-1, 3, 6-trihydroxyanthraquinone was isolated from MeOH extract of Noni fruits. It was nearly 40 times more potent than a positive control, l-sulforaphane. It has no discernible cytotoxicity at the highest dose levels (Pawlus *et al*., 2005). A new saccharide fatty acid ester, 2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-gluropyranose, four saccharide fatty acid esters and a flavanol glycoside have been separated from a methanol extract of the fruits of *Morinda citrifolia*. These compounds exhibit inhibitory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA) potentiated inflammation (1 μg ear^{-1}) in mice ear and saccharide fatty acid esters exhibited potent anti-inflammatory activity with ID_{50} values of 0.46-0.79 mg ear^{-1}. These compounds also exhibited moderate inhibitory effects against the Epstein-Barr Virus Early Antigen (EBV-EA) activation induced by TPA, with IC_{50} values of 386-578 mol ratio/32 pmol TPA (Akihisa *et al*., 2007). The methanolic extract of *M. citrifolia* fruits have tumour cell suppression potential on human laryngeal epithiloma (Hep2) cells and showed maximum cytotoxicity on Hep 2 cells (50%) followed by ethyl acetate extract. The hexane extract showed no cytotoxic activity on Hep 2 cells (Jayaraman *et al*., 2008).

Methanol extract of *Morinda citrifolia* fruits has cytotoxic activity in a concentration dependent manner against various cancer cell lines but it has no cytotoxic activity against normal cell lines. The median lethal concentration (LC_{50}) of the extract in Baby Hamster Kidney (BHK) cells is 2.5 mg mL^{-1}, African green monkey kidney (Vero) cell is 3 mg mL^{-1} and human laryngeal carcinoma (Hep2) cells is 5 mg mL^{-1}. A concentration of 0.1 mg mL^{-1} of crude extract has cytotoxic activity against neuroblastoma (LAN5) cell lines (36%), breast cancer (MCF7) cell lines (29%) and very little cytotoxicity to Hep 2 cells (13%), BHK cells (6%) and has no cytotoxic activity against Vero cells (Arpornsuwan and Punjanon, 2006). Tumour Necrosis Factor (TNF) Related Apoptosis-Inducing Ligand (TRAIL) selectively increases the apoptosis of a wide variety of tumour and transformed cells without damaging normal cells. A new

anthraquinone, 1, 5, 15-trimethylmorindol was isolated from the leaves of *Morinda citrifolia* which has synergistic activity with TRAIL with no side effects. But it did not show significant cytotoxic activity alone (Takashima *et al*., 2007).

Morinda citrifolia fresh leaf extract also has anticancer activity against human cervical carcinoma (HeLa), human epidermoid carcinoma (KB), human breast carcinoma (MCF-7), vero (African green monkey kidney) and human hepatocellular carcinoma (HepG2) cell lines. The non-aqueous extracts from the leaves of Noni exhibited antioxidant activity with IC_{50} values of 0.20 to 0.35 mg mL^{-1}. The median lethal concentration (LC_{50}) of the dichloromethane extract of the fresh leaves of Noni in KB cell line is 21.67 μg mL^{-1} and HeLa cell line is 68.50 μg mL^{-1}. The methanolic extract from the dried leaves of *M. citrifolia* showed cytotoxic activity against the KB cell line with an IC_{50} value of 39 μg mL^{-1}. These two extracts have a higher safety ratio than damnacanthal which provides baseline information for their use as anticancer agents because the extracts prevent the proliferation of tumour cells but not normal cells (Thani *et al*., 2010).

An anthraquinone compound, damnacanthal, isolated from the roots of *Morinda citrifolia,* exhibited inhibitory activity on cell growth and enhanced caspase activity in colorectal cancer cells (HCT-116, SW480 and LoVo cells). Damnacanthal showed transcriptional up-regulation of the NAG-1 which is a nonsteroidal anti-inflammatory activated gene-1 and proapoptotic protein which controls cell growth and apoptosis. Damnacanthal promotes the retinoic acid receptor (ERK) pathway and enhances expression of transcription factor CCAAT/enhancer binding protein β (C/EBPβ) that helps in controlling NAG-1 transcriptional activity. This results in enhanced apoptosis in human colorectal cancer cells. It is a potent inhibitor of $p56^{lck}$ tyrosine kinase activity (Faltynek *et al*., 1995; Nualsanit *et al*., 2012). Anthraquinones from the roots of *M. citrifolia* showed significant proliferation and growth inhibitory activity on human colon and lung cancer cells (Lv *et al*., 2011).

Gupta *et al*. (2013) demonstrated that Noni, cisplatin and combination of Noni with cisplatin were able to induce apoptosis through the mitochondrial pathway, in both HeLa and SiHa cells. They demonstrated the anticancerous activity through the p53 and Bax proteins (pro-apoptotic) up regulating pathways and Bcl-2 (anti-apoptotic gene), survivin and Bcl-XL proteins down regulating mechanisms. In addition there was increase in activity of caspases-9 and -3, thus primarily activating intrinsic pathway of apoptosis. Hence, Noni offers can be used as chemo adjuvants for treating cervical cancer specially.

***In vivo* anticancer effect of Noni:** Alcohol-precipitate of *Morinda citrifolia* fruit juice showed antitumour activity against intraperitoneally injected Lewis Lung Carcinoma (LLC) in C57BL/6 mice. The Noni juice has therapeutic effects from 3-20 mg $mouse^{-1}$ and significant anticancerous activity was noticed at the doses of between 6-15 mg $mouse^{-1}$. Noni juice also prolonged the life span of the mice for more than 75% (Hirazumi *et al*., 1992). Ethanol-precipitated fractions of Noni fruit juice (0.8 mg in 0.1 mL of juice) have clear antitumor activity against intraperitoneally implanted LLC in syngeneic C57BL/6 mice. Intraperitoneally injection of Noni ppt (0.1 mL $mouse^{-1}$) cured 4 out of 13 mice and increased life span to 119%. Ethanol-soluble fractions of Noni fruit juice (5.2 mg solid in 0.1 mL of juice) have no antitumor activity (Hirazumi *et al*., 1994). Noni-precipitate prevents ascites in mice (0 out of 5 mice) but untreated mice develops ascites (5 out of 5 mice) (Hirazumi *et al*., 1996).

Tahitian Noni® Juice (TNJ) 10% made from *Morinda citrifolia* fruit prevents the DMBA induced mammary gland carcinogenesis in female Sprague-Dawley (SD) rats at the initiation stage of multiple step carcinogenesis. It inhibits DMBA-DNA adduct formation in mammary tissue. DMBA-DNA adduct formation was detected by ^{32}P-postlabeling assay and it is an important marker for "DNA damage" to examine the preventive effect of Noni juice in a DMBA induced mammary gland carcinogenesis model. The DMBA-DNA adduct levels were reduced to 41% in the lung, 30% in the heart, 80% in the kidney and 42% in the liver of female SD rats. Male C57 BL-6 mice showed more dramatic reduction of DMBA-DNA adduct formation by 50% in the lung, 60% in the heart, 90% in the kidney and 70% in the liver. This preventive effect of TNJ was due to the antioxidant activity by dose-dependent inhibition of both lipid hydroperoxide (LPO) and Superoxide Anion Radicals (SAR) (Wang and Su, 2001). The tumour latency period was delayed to 60-90 days in TNJ group when compared to positive control group. Tumour multiplicity, number of palpable tumours per group and malignancy of lesions were significantly reduced and survival rate of animals was significantly increased in the TNJ group when compared to positive control groups. The DMBA treated control group showed epithelial hyperplasia (12.5%), benign tumours (25%) and *in situ* carcinomas (25%). In the TNJ group no benign tumours or carcinomas were found and tissues showed normal histology or only mild hyperplasia. These results indicate that TNJ may prevent mammary gland carcinogenesis at the initiation stage of chemical carcinogenesis (Wang *et al*., 2002c, 2013). *Morinda citrifolia* fruit juice contains an immunomodulatory polysaccharide-rich substance which possesses both prophylactic and therapeutic activity

against the Sarcoma 180 tumour in mice, an immunomodulator sensitive tumour. Intraperitoneal injection of sarcoma tumor cells (S180) in mice followed by treatment with Noni-precipitate (0.5 mg mouse^{-1}, i.p.) resulted in a cure rate of 25-45%. This therapeutic rate was eliminated by macrophage inhibitors (2-chloroadenosine), T cells (cyclosporine) and Natural Killer (NK) cells (anti-asialo GM1 antibody), whereas interferon increased the survival rate by 71-100%. Noni precipitate shows synergistic beneficial effects with broad spectrum of chemotherapeutic drugs especially, adriamycin, bleomycin, camptothecin, cisplatin, etoposide, 5-fluorouracil, interferon, mitomycin-C and vincristine. Noni precipitate showed antagonistic activity when it is combined with cytosine arabinoside, paclitaxel and immunosuppressive anticancer drugs such as methotrexate, cyclophosphamideand 6-thioguamine. Noni-ppt shows beneficial effects with imexon, a synthetic immunomodulator but not with MVE-2 (Maleic anhydride divinylether) which is a high molecular weight immunomodulator. Noni-ppt also has beneficial effects when combined with Th1 cytokinesinterferon gamma but there is gradual deterioration of activity when combined with Th2 cytokines, interleukin-4 and interleukin-10. So, Noni-ppt potentiates a Th1 predominant immune status *in vivo* (Furusawa *et al*., 2003).

Tahitian Noni juice (1% or 1 mg mL^{-1}) and Noni Fruit Juice Concentrates (NFJC) (5% or 5 mg mL^{-1}) potentially activate cannabinoid 2 (CB2) receptors but inhibit cannabinoid 1 (CB1) receptors in a concentration-dependant manner. The CB2 receptors are involved in immunomodulation, anti-inflammatory activity by counteracting the proinflammatory signals and inhibiting the neuropathic pain without psychoactive effects (Massa *et al*., 2004). The CB2 receptors also suppresses the microbial activation and protect hippocampal neurons from excitotoxicity (Ehrhart *et al*., 2005). *Morinda citrifolia* potentiates the immune system by activating of the CB2 receptors and increasing the production of IFN-γ cytokines but suppresses IL-4 production (Palu *et al*., 2008). Fermented Noni Exudate (fNE) has the ability to stimulate both arms of the immune system such as innate and the adaptive immune system to eliminate cancer cells. Intraperitoneally injected fNE significantly increases the amount of NK cells and granulocytes in the peripheral blood, spleen and peritoneum. Surprisingly, the fNE significantly decreases the percentage of B lymphocyte and the percentage of T cells in the spleen and significantly increases the percentages of $CD8^+$ T cells and $CD25^+$ cells in the peritoneum. The fNE treatment increased the total peritoneal leukocyte counts more than 10 folds. More than 85% of the normal C57BL/6J mice completely rejected S180 tumor cells and 62% of mice rejected Lewis lung carcinoma (LL/2) cells after treatment with three doses of fNE (500 μL/mouse/day, i.p.). In case of C57 nude mice which lack functional lymphocytes, partial tumor rejection was noticed whereas no cancer rejection was noticed in beige mice which are lacking NK cells. So, NK cells are the major quick responders of fNE treatment and innate immune system is the major player for fNE treatment while the adaptive immune system reacts slowly with sustained memory (Li *et al*., 2008). Noni juice has antigrowth, cytotoxic and apoptosis inducing effects on breast cancer (Ehrlich ascites tumor) in female Balb-c mice. When Noni was administered with the potent anticancer drug doxorubicin, the action was greater than either doxorubicin or Noni alone. It significantly decreased the proliferation rate and size of the tumor about 40-50%. This anti-proliferative effect of Noni was due to stimulation of apoptosis and activation of caspase-3 cells in tissues (Taskin *et al*., 2009).

Noni prevents chemical induced esophagus tumorigenesis in the rat. In a study tumor incidence was 60% in the Noni group as compared to 95% in the carcinogen group (Stoner *et al*., 2010). *M. citrifolia* fruit can reduce the N-Methyl N-Nitrosourea (NMU) induced peripheral T-cell non-Hodgkin's lymphoma when used as a dietary supplement to Sprague Dawley (SD) rats at a daily dose of 750 mg kg^{-1} body weight (Hutheyfa, 2010). *M. citrifolia* has apoptotic effects against peripheral T-cell Non-Hodgkin's lymphoma induced by Dibenzo [a,l] pyrene (DBP) in BALB/c mice. DBP is the most powerful genotoxic carcinogenic polycyclic aromatic hydrocarbons (PAHs) and it is found all over the environment in the water, air and soil. *M. citrifolia* has anti-tumour activity against experimentally induced leukaemia in male SD rats using the NMU. Daily supplementations of *M. citrifolia* dried fruit at a dose of 5000 mg kg^{-1} b.wt. reduced the proliferation of circulating leukaemic cells and 3000 mg kg^{-1} reduced the incidence of early stage of leukaemia to 60% (Hazilawati *et al*., 2010a, 2010b).

Noni juice enhances differentiation of the mammary gland and decreases the mammary cancer proliferation in MMTV-neu transgenic mice. In this model, Mouse Mammary Tumor Virus (MMTV) promoter transcriptionally controls the expression of unactivated rat neu (c-erbB2) gene. This mouse model exhibits various features of similarities to HER2/neu$^+$ breast cancer that include onset of stochastic tumor, focal tumors that occurs near the hyperplastic tissue, estrogen-dependent tumor development, long latency period and metastatic progression to the lungs. Prolonged administration of 10% TNJ decreased mammary tumor size, volume and

weight, slows the tumor growth kinetics and increased doubling time of tumor. TNJ increases central necrosis in mammary tumors by its antiangiogenic and cytotoxic actions. The anti-inflammatory actions of Noni by directly inhibiting COX-2 activity and its corresponding PGE2 levels are important for the tumor inhibition. TNJ-treatment causes augmented differentiation of mammary gland which has been inversely associated with malignant potential of mammary epithelial cells (Clafshenkel *et al*., 2012). Saminathan *et al*. (2013a, b) evaluated the anticancer efficacy of *Morinda citrifolia* Leaf Extract (MCLE) and fruit juice against N-Methyl-N-Nitrosourea (NMU) induced mammary tumours in female Sprague-Dawley rats. During 28th weeks of experimental period, tumour frequency and average tumour volume was significantly reduced in *M. citrifolia* treated groups when compared to control. The immunohistochemical expression of cell proliferation marker PCNA, angiogenic markers VEGF and PECAM-1 and anti-inflammatory marker COX-2 expression was significantly ($p<0.05$) reduced in *M. citrifolia* treated groups when compared to the control. The TUNEL positive apoptotic cells were significantly higher in Noni treated groups as compared to the control. These results provide promising baseline information for the potential uses of *Morinda citrifolia* leaf extract in the treatment of cancer. Saminathan *et al*. (2013c) also studied the chemopreventive activity of Noni fruit juice against N-Methyl-N-Nitrosourea (NMU) induced mammary tumours in female Sprague-Dawley rats. The average latency period was significantly increased (182±0.0 days) in Noni fruit juice treated group whereas in control group decreased to 107±4.1 days. The tumour frequency and tumour incidence were significantly decreased in Noni fruit juice treated groups. Interestingly, in treated groups only benign tumour was observed whereas in control group more malignant tumours were developed.

***In vivo* anticancer studies in human:** Noni juice is used for treatment of gastric cancers. A 69 year old male patient suffering from gastric cancer was expected to die within a few months without surgery. The patient denied surgery and became bedridden and his weight had reduced from 165-79 pounds. Then he started to take household Noni juice regularly. After taking Noni juice his condition improved within a month and after 6 months he was completely cured and did not developed any gastric symptoms during a follow up period of 7 years (Wong, 2004). Another 64 year old male patient underwent surgery, gastrectomy for gastric cancer. The cancer had metastasized to 17 of 28 examined lymph nodes and doctors informed that he would live only for 5 years. The patient consumed home-based Noni juice and lived for 16 more years until he died at age 80 due to starvation that results from gastric cancer (Wong, 2004).

National Institute of Health (NIH) performed phase 1 clinical trials in humans to find the dose and to examine the effect of ripened *M. citrifolia* fruit extract as dietary supplement in the form of freeze-dried pills in end stage cancer patients. A 29 year old advanced cancer patient was provided with a daily dose of four capsules each containing 500 mg of Noni fruit extract. In consequent days the dosage levels were increased by 2 g daily upto a highest dose level of 10 g daily. After treatment the level of tumour regressions was assessed by using Response Evaluation Criteria in Solid Tumours (RECIST) criteria. The dose response relationship was assessed by measuring the fatigue by using Brief Fatigue Inventory (BFI) and depressed mood by Centre for Epidemiologic Studies Depression scale (CES-D). Finally the results showed that Noni fruit extract has no significant effect on tumour regression and no dose response relationship was noticed. However, there was a significant reduction in sensitivity to pain and no adverse effects to Noni were noticed (Issell *et al*., 2005).

Tahitian Noni Juice (TNJ) decreases cancer hazard in cigarette smokers by reducing aromatic DNA adducts in peripheral blood lymphocytes. Measurement of aromatic DNA adduct levels are good biomarker for cancer, genotoxicity and DNA damage for all degenerative diseases associated with smoking. After drinking of 1-4 oz of TNJ for 1 a month period of time aromatic DNA adduct levels were significantly reduced to 44.9% in all cigarette smoking participants. Dose-dependent analyses of aromatic DNA adduct levels showed, 49.7 and 37.6% reductions in 1 oz TNJ and the 4 oz TNJ group, respectively. In the gender specific analyses the 4 oz TNJ group showed no significant differences. But interestingly, in the 1-oz TNJ group female smokers showed a reduction of 43.1% when compared to 56.1% in males. The TNJ significantly reduced the levels of Superoxide Anion Radicals (SAR) and lipid hydroperoxide (LOOH) in plasma of the smokers (Wang *et al*., 2009a, b).

Protective effect of Noni on liver injury induced by a liver carcinogen: Noni Juice (NJ) has preventive effect on carbon tetrachloride (CCl_4) produced liver injury in female SD rats. The placebo and NJ groups showed normal lobular architecture of liver. The placebo+CCl_4 group showed acute liver damage like vacuolated cytoplasm, fatty change, centrilobular necrosis and focal inflammatory cells scattered throughout the lobule. But NJ+CCl_4 group showed significant reduction in swollen, lipid containing and apoptotic hepatocytes. Glycogen

depletion, lipid droplets in the plasma membrane, disorganization of Rough Endoplasmic Reticulum (RER) with loss of ribosome and swollen mitochondria were observed in both CCl_4 treated groups at the Electron Microscopic (EM) level. The NJ+CCl_4 group showed golgi complexes with larger vesicles, increased electron density and well developed golgi cisternal stacks. Whereas the placebo+CCl4 group showed golgi complexes with small low-density vesicles (Wang *et al*., 2002b, 2008; Nayak *et al*., 2011).

Other pharmacological activities of Noni

Antibacterial activity: Acubin, L-asperuloside and alizarin in the Noni fruit and scopoletin and anthraquinone compounds in Noni roots have antibacterial properties (Atkinson, 1956). *M. cirifolia* fight against many infectious bacteria like *Baciillis subtilis, Staphylococcus aureus*, *Escherichia coli*, *Proteus morgaii*, *Salmonella typhosa*, *Salmonella montevideo*, *Pseudomonas aeruginosa*, *Salmonella schottmuelleri* and *Shigella paradys*. So, Noni is frequently used for treatment of broken bones, bruises, sores and wounds, colds, fevers, skin infections and other bacteria induced ailments (Bushnell *et al*., 1950; Leach *et al*., 1988; Sundarrao *et al*., 1993; Dittmar, 1993; Locher *et al*., 1995). A coumarin compound scopoletin isolated from Noni plant inhibits the activity of *E. coli* and also helps in healing of stomach ulcers by inhibiting the bacteria *Helicobacter pylori* (Duncan *et al*., 1998). The methanol and aqueous extracts of the Noni fruit have also been reported to possess antibacterial activity against *E. coli*, *Streptococcus* sp., *Vibrio alginolyticus*, *Vibrio harveyi*, *Klebsiella*, *B. subtilis*, *Lactobacillus lactis*, *P. aeruginosa*, *Salmonella typhi*, *S. aureus*, *Streptococcus thermophilus*, *Shigella flexneri* and *Chromobacterium violaceum* (Wei *et al*., 2008; Jayaraman *et al*., 2008; Selvam *et al*., 2009; Kumar *et al*., 2010; Usha *et al*., 2010; Natheer *et al*., 2012).

Murray *et al*. (2008) compared the *in vitro* effectiveness of Noni juice with chlorhexidine gluconate and sodium hypochlorite (NaOCl) to remove the smear layer of *Enterococcus faecalis* from the canal walls of endodontically instrumented teeth. The result indicated that Noni fruit juice and NaOCl treatment have similar effects. West *et al*. (2012) reported the antibacterial activity of iridoids (deacetyl asperulosidic acid and asperulosidic acid) in *Morinda citrifolia* fruits against *Candida albicans*, *E. coli* and *Staphylococcus aureus*.

Anti-tubercular activity: *M. citrifolia* leaf extract effectively kills 89% of *Mycobacterium tuberculosis* bacteria, whereas the standard antituberculosis drug Rifampcin has 97% growth inhibition rate at the same concentration (American Chemical Society, 2000; Anonymous, 2001). Various components like E-phytol, stigmasterol, campesta-5,7,22-trien-3beta-ol, beta-sitosterol, ketosteroids stigmasta-4-en-3-one,cycloartenol and stigmasta-4-22-dien-3-one isolated from hexane fraction from *M. citrifolia* showed pronounced antitubercular activity (Saludes *et al*., 2002).

Antiviral activity: An anthraquinone compound 1-methoxy-2-formyl-3-hydroxyanthraquinone extracted from *M. citrifolia* roots reduced the cytopathic effect in MT-4 cells infected with HIV, without inhibiting growth of the cells (Umezawa, 1992). The mechanisms of Vpr have been intensely studied because it is believed that they underlie HIV-1 pathogenesis. Another anthraquinone compound, damnacanthal from Noni inhibits Vpr induced cell death which has major role in HIV-1 pathogenesis. These results formed a novel base for drug screening and development in anti-HIV therapy (Kamata *et al*., 2006).

Antifungal activity: An aqueous extract of *Morinda citrifolia* has the ability to hinder the *in vitro* serum-induced morphological conversion of *Candida albicans* from the cellular yeast to a filamentous form. The aqueous extract also has inhibiting potential on the germination of *Apergillus nidulans* spores. The antifungal activity of *M. citrifolia* aqueous extract may be due to its water-soluble components which have potential therapeutic value against candidiasis and aspergillosis (Banerjee *et al*., 2006; Usha *et al*., 2010). Noni has maximum percentage of inhibition against *Trichophyton mentagrophytes* in the extracts of methanol (79.3%) and ethyl acetate (62.06%). The methanol extract showed 50% inhibition rate against *Penicillium* sp., *Fusarium* sp. and *Rhizopus* sp. Both the extracts were not, however, effective against *Candida albicans* and Aspergillus species (Jayaraman *et al*., 2008). Jainkittivong *et al*. (2009), on the other hand, reported the *in vitro* antifungal activity of *M. citrifolia* fruit extract on *Candida albicans*. In cultures, there was no growth of *C. albicans* at a concentration of 50 mg mL^{-1} of extract for 30 min contact time and at a concentration of 60 mg mL^{-1} of extract for 15 min contact time. In broth dilution method, the extract has minimum fungicidal concentration of 40 mg mL^{-1} for 90 min contact time and 50 mg mL^{-1} for 15 min contact time against *C. albicans*.

Anthelmintic activity: An ethanolic extract of the immature Noni leaves showed anthelmintic activity by enhancing paralysis and killing of the nematode worm *Ascaris lumbricoides*, within 24 h (Raj, 1975). At several

places such as Philippines and Hawaii Noni has been used as an effective insecticide for control of various arthropod populations (Morton, 1992). The alcoholic extract of *M. citrifolia* leaves produced more significant anthelmintic activity against adult Indian earthworms (*Pheretima posithuma*) when compared to petroleum ether extract and the activities were almost equal to activity of the standard anthelminthic drug piperazine citrate (Kumar *et al*., 2010).

Immunomodulating activity: Alcoholic extract of the Noni fruit at various concentrations has inhibiting effect on tumour necrosis factor-alpha (TNF-α) production. The TNF-α is an endogenous tumor promoter which is responsible for tumour progression (Hokama, 1993; Asahina *et al*., 1994). Noni fruit juice contains a polysaccharide-rich substance which has anti cancerous activity that increases the release of cytokine IFN-gamma from thymocytes. It has antitumor activity against Lewis Lung Peritoneal Carcinomatosis (LLC) by potentiating the immune system through macrophages to secrete TNF-α, IFN-γ, IL-1β, IL-10, IL-12 and nitric oxide but it had no effect on IL-2 secretion whereas it reduced the secretion of IL-4. These results suggested that the Noni-ppt reduces the tumour growth by potentiating the host immune system (Hirazumi and Furusawa, 1999). Hokama (1993) separated 50% aqueous alcohol and precipitated fractions from the ripe Noni fruit juice that inhibits the Lewis lung tumours in BALB/c mice through activation of the T-cell immune response from thymocytes. In one study, the wet weight of the thymus was increased to 1.7 times than normal, seven days after drinking of 10% TNJ in drinking water. This clearly indicates that TNJ may enhance immune function through stimulation of thymus growth which results in anti-aging and protection from degenerative disease (Pansuebchue *et al*., 2002; Wang *et al*., 2002a). Noni fruit juice has potential immune-modulating effects on feeding to neonatal Holstein calves, through increased expression of CD25 on $CD4^+$, $CD8^+$ and γδ T cells. Noni up regulates IL-1β, TNF-α and IFN-γ in bovine colostrums and results in direct increase in natural cell-mediated immunity through the enhanced activation of $CD4^+$ and $CD8^+$ T cells (Brooks *et al*., 2009).

Dendritic Cells (DCs) treated with fermented Noni Exudate (fNE) stimulate proliferation of splenocytes and B cells, promote its differentiation and immunoglobulin class switching to produce IgG and IgM but fNE alone could not directly stimulate B cell proliferation. The fNE contains 0.25 μg mL^{-1} of endotoxin. The proliferative response of B cells to fNE-treated DCs was cell contact dependent but CD40L-independent (Zhang *et al*., 2009). The extracts of *M. citrifolia* fruits have stimulatory effects on T and B lymphocytes which are the important components of the adaptive immune system. The hydroalcoholic (0.5 and 1.0 mg mL^{-1}) and aqueous extracts (0.5 and 1.0 mg mL^{-1}) significantly enhanced the splenocyte proliferation and the cell-mediated immune response. All these results provide baseline information that *M. citrifolia* fruits have both the humoral and cell mediated immunostimulatory effects (Nayak and Mengi, 2010).

Antioxidant activity: Noni juice has excellent antioxidant activity which may guard individuals from oxygen free radicals and lipid peroxidation induced damage. The Superoxide Anion Radicals (SAR) and quenched lipid peroxides (LPO) scavenging activity of TNJ was estimated *in vitro* by tetrazolium nitroblue (TNB) assay and LMB assay, respectively. TNJ showed a concentration dependent inhibition of both LPO and SAR. The SAR scavenging activity of TNJ was 2.8 times that of vitamin C, 1.1 times that of grape seed powder and 1.4 times that of Pycnogenol. These results confirmed the antioxidant potential of TNJ by quenching the reactive oxygen free radicals (Wang and Su, 2001; Wang *et al*., 2002b). The Noni juice also has *in vivo* antioxidant activity against carbon tetrachloride (CCl_4) induced liver injury model in female SD rats. CCl_4 is a hepatic carcinogen and potent inducer of lipid hydroperoxidation. Administration of 10% of TNJ in drinking water for a period of 12 days suppressed the levels of LPO and SAR in liver to 20 and 50%, respectively 3 hrs after administration of CCl_4 (Wang and Su, 2001; Wang *et al*., 2002b). In cigarette smoke was reported to contain 227 possible carcinogens and each puff of cigarette smoke contains 1×10^{17} oxidant molecules (Chow, 1993). Wang *et al*. (2009a, b) assessed the antioxidant activity of TNJ on plasma by estimating the SAR and LPO levels in current cigarette smokers. The smokers were provided daily with a dose of two ounces of TNJ twice a day for a period of 30 days. The LPO and SAR levels in the TNJ group showed 23% reduction and 27% reduction, respectively when compared to placebo group. These results indicate that TNJ may guard individuals from tobacco smoke free radical induced damage.

Anitha and Mohandass (2006) reported that oral administration of 50 mg kg^{-1} day^{-1} of crude methanol extract of *M. citrifolia* leaves for a period of 14 days significantly enhanced the anti-oxidant enzymes, such as glutathione peroxidase (GSHPx), catalase (CAT) and superoxide dismutase (SOD). Duo to anti-oxidant activity there was reduction in lymphoma in mice. Zin *et al*. (2002) and Su *et al*. (2005) reported that various parts of

M. citrifolia (leaf, fruit and root) have antioxidative activities. When compared to either leaf or fruit the polar and non-polar extracts of the root exhibited stronger antioxidative potential. Ikeda *et al.* (2009) observed that both Noni and coumarin derivatives have scavenging activity on ROS such as superoxide (O^{-}_{2}), singlet oxygen ($^{1}O_{2}$), hydroxyl radical (OH) and peroxymitrite ($ONOO^{-}$) in a dose-dependent manner. Liu *et al.* (2007) have reported that the antioxidative mechanism of Noni fruit juice was partially attributable to the group of phenolic compounds, such as isoscopoletin, quercetin and aesculetin in the EtOAc (ethanolic) extract. Thani *et al.* (2010) recorded that the non-aqueous extracts from the leaves of Thai Noni/Yor showed antioxidant properties, giving IC_{50} values of 0.20-0.35 mg mL^{-1}. These results suggest that the leaves of *M. citrifolia* could be preferred as a food supplement for its antioxidative activities in epidermoid and cervical cancers over damnacanthal, rutin and scopoletin. Dussossoy *et al.* (2011) showed that Noni's anti-oxidant activities are possibly due to phenolic compounds, iridoids and ascorbic acid. Serafini *et al.* (2011) investigated the antioxidant activity of aqueous extract from *M. citrifolia* leaves against lipid peroxidation, hydroxyl and nitric oxide induced radicals. West *et al.* (2011) evaluated the antioxidant activity of *Morinda citrifolia* seed extract. The seed extract exhibited significant antioxidant potential against various types of free radical induced damage. West *et al.* (2009) also evaluated the antioxidant properties of roasted Noni leaf infusion. The infusion has 2, 2-diphenylpicrylhydrazyl (DPPH) radical scavenging activity which was higher when compared to green tea infusion.

Anti-inflammatory activity: Increased expression of COX-2 receptors is associated with development of breast, colon and lung cancer (Takahashi *et al.*, 2002). In chemical carcinogenesis COX-2 is induced at a rapid rate and its over expression may lead to increased signals for angiogenesis and inflammatory reaction (Colville-Nash and Gilroy, 2001). Noni juice selectively inhibits expression of COX-2 receptors resulting in cancer chemoprevention especially colon and breast cancers in a similar way as aspirin, indomethacin and selective COX-2 inhibitor celebrex. Inhibition of COX-2 results in anti-inflammatory activity and decrease angiogenesis. The COX-1 and COX-2 activities were estimated by the Amershani ELA assay which is based on the level of PGE2 produced during the incubation of tested compounds and vehicle with human platelets. The results in this assay provide a strong evidence of its anti-inflammatory activity which may be responsible for cancer prevention (Su *et al.*, 2001). Noni juice has anti-inflammatory activity against CCl_4 induced acute liver damage in female SD rats. The pretreatment with 10% TNJ for a period of 12 days in drinking water reduced inflammatory reaction and lymphocytes around the central vein in the liver were noticed at 6 h post CCl_4 administration (Wang and Su, 2001). McKoy *et al.* (2002) tested the anti-inflammatory property of an aqueous extract from *M. citrifolia* fruit juice against local acute inflammatory response induced by potent pro-inflammatory agent bradykinin. He demonstrated that oral drenching of Noni juice extract at a dose of 200 mg quite rapidly prevented the formation of rat paw edema. This anti-inflammatory effect may be due to the inhibition of B2 receptor mediated mechanism of bradykinin. Okusada *et al.* (2011) reported that damnacanthal isolated from Noni root mediates its anti-inflammatory activity through the histamine H1 receptor. One study showed that ethanol extract of fruit powder has a selective inhibitory effect on cyclooxygenase-1 (COX-1) with IC_{50} value of 163 μg mL^{-1} and it was lower than that produced by aspirin (241 μg mL^{-1}), whereas much higher than indomethacin (1.2 μg mL^{-1}) used as the reference COX-1 inhibitors. But it did not exhibit (*in vitro* and *in vivo*) Nitric Oxide (NO) scavenging activity, a key mediator in the phenomenon of inflammation (Li *et al.*, 2003).

Several polyphenols belonging to the coumarin, flavonoids, phenolic compounds, iridoids and ascorbic acid present in Noni juice have free radical scavenging activity. These compounds also decrease the carrageenan induced paw edema by directly inhibiting the cyclooxygenase COX-1 and COX-2 activities. The anti-inflammatory activity of Noni may attributed due to inhibition, in a dose dependent manner, of the production of prostaglandins E_2 (PGE_2) and Nitric Oxide (NO) in activated J774 cells. These results showed that Noni's anti-inflammatory properties are probably due to NO and PGE_2 pathways (Dussossoy *et al.*, 2011). New saccharide fatty acid ester 2-O-(beta-D-glucopyranosyl)-1-O-octanoylbeta-D-gluropyranose isolated from Noni juice exhibited potent anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA) induced inflammation (1 μg ear^{-1}) in mice (Akihisa *et al.*, 2007). Song *et al.* (2010) reported that the methanol extracts of *Morinda citrifolia* suppressed melittin-induced arachidonic acid release and inhibited phospholipase A2 induced hydrolysis in a concentration and time dependent manner. Therefore, *Morinda citrifolia* may possess anti-inflammatory activity secondary to Ca^{2+} dependent phospholipase A2 inhibition.

Noni Seed Oil (NSO) has potential beneficial effects in human skin problems like acne. NSO reduced the number of open and closed comedones in the

comedogenicity test. NSO has potential anti-inflammatory activity by inhibiting COX-2 and 5-LOX enzymes in a concentration dependent manner. However COX-2 inhibition is more pronounced than 5-LOX. So, Noni seed oil is safe for topical use for skin care applications and is non-comedogenic (Palu *et al*., 2012). Two new lignans, (+)-3,3'-bisdemethyltanegool and (+)-3,4,3',4'-tetrahydroxy-9,7'alpha-epoxylignano-7 alpha, 9'-lactone as well as seven known compounds isolated from Noni fruits exhibited 5- and 15-lipoxygenase inhibiting activity (IC_{50} 0.43-16.5 μM). Quercetin exhibited weak inhibitory activity toward COX-2 (Deng *et al*., 2007a).

Analgesic activity: Extracts from the *M. citrifolia* plant possess significant tranquilizing and central analgesic activities in a dose related manner. The analgesic effect of the Noni extract is 75% more strong than morphine, however it is non-addictive and absence of side effect (Younos *et al*., 1990). The analgesic property of TNJ was tested by the hot plate assay and "twisted method" animal model. Administration of antimony potassium tartrate intraperitoneally produces twisting due to pain. The number of twists is counted to assess the level or extent of pain within the first 15 min after injection. The analgesic effect of TNJ is dose dependent and is statistically significant when compared with the control group (Wang *et al*., 2002a). Punjanon and Nandhasri (2005) evaluated the pain-relieving potential of fruits of Noni and its alcoholic extract by means of acetic acid-induced writhing test in mice. Fifteen min before intraperitoneal administration of acetic acid (0.75%), Noni extract was administered intraperitoneally at the doses of 1, 2, 3 and 4 g kg^{-1} b.wt. The alcoholic extracts of Noni produced a significant reduction of acetic acid induced abdominal constriction in a dose dependent manner. At a dose of 4 g kg^{-1} of extract produces significant analgesic effect which was almost equal to analgesic effect produced by standard analgesic drug morphine at a dose rate of 1.5 mg kg^{-1} body weight. The analgesic efficacy of Noni by acetic acid induced writhing test for 15 min was statistically significant until 5 h of administration. These results suggest that the alcoholic extract of fruits have analgesic effect (Okusada *et al*., 2011). *M. citrifolia* is used for the treatment of painful inflammatory conditions, such as arthritis. The freeze concentrated Noni fruit puree at a concentration of 10% solution in the drinking water to mice inhibited the pain signals when compared to standard tramadol which was the central analgesic drug. This analgesic action was partially reversed by the drug naloxone, a known morphine antagonist. An alcohol extract of freeze concentrated Noni fruit puree produces reduction of release of MMP-9 from the monocytes of human origin after stimulation with LPS. This effect was comparable to standard drug hydrocortisone. These results proved that extracts of Noni fruits are efficient in inhibiting pain and arthritis (Basar *et al*., 2010).

Wound healing activity: An anthraquinone, 1, 4-dihydroxy-2-methoxy-7-methylanthraquinone, isolated from the extracts of Noni fruit stimulates production of glycosaminoglycans and type 1 collagen from the normal human fibroblast primary cultures. This compound demonstrated significantly improved biosynthesis of glycosaminoglycans and procollagen type 1 C-terminal peptide. The compound also decreases the production of the collagenase matrix metalloproteinase-1 from the human dermal fibroblasts in a dose-dependent manner. These results indicate that anthraquinone isolated from *M. citrifolia* fruit extract is a potential candidate for usage as anti-wrinkle agent because of its potent stimulatory action on production of extracellular matrix components (Kim *et al*., 2005).

Nayak *et al*. (2007) evaluated the wound regenerating potential of Noni fruit juice in streptozotocin inuced diabetic rats using an excision wound model. The rats were given Noni juice at 100 mL kg^{-1} b.wt. in drinking water for 10 days. The wound area reduced to 73% in the Noni treated group as compared to 63% in diabetic controls. The weight of granulation tissue, protein and hydroxyproline content was significant increased in the Noni treated group. Histological findings revealed that deposition of collagen was quicker in the Noni treated group than that in the control group. In the Noni juice treated group, fasting blood glucose values were reduced to 29% when compared to diabetic control animals. They also reported a strong association between the blood glucose level and wound contraction rate. These results demonstrated that Noni fruit juice significantly decreases the blood sugar levels and accelerates wound healing in diabetic rats.

Nayak *et al*. (2009) evaluated the wound-healing activity of ethanol extract of Noni leaves (150 mg kg/day), using dead space and excision wound models on rats. The rats were administered orally with the ethanol extract by mixing in drinking water. The extract administered group showed 71% reduction in the wound area on day 11, as compared to control group which showed 57% reduction in the wound area. The weight of granulation tissue, protein and hydroxyproline content was significant increased in the dead space wounds in Noni treated animals. Accelerated wound contraction, reduced epithelialization time and improved hydroxyproline contents indicated that Noni leaf extract may have curative potential in wound healing. Palu *et al*. (2010)

reported that *M. citrifolia* leaves significantly hastened the rate of wound healing in mice due to its possible mechanisms of action of ligand binding to the PDGF and A(2A) receptors .

Hypotensive activity: Ethanolic and hot water extracts of the Noni roots reduced the blood pressure in anesthetized dogs (Dang, 1954; Youngken, 1958; Youngken *et al*., 1960; Moorthy and Reddy, 1970). Noni fruit juice also has diuretic activity that may have antihypertensive effect. *M. citrifolia* juice has strong inhibitory activity on Angiotensin I Converting Enzyme (ACE) and thus produces antihypertensive effect. The ACE inhibitory activity of ripened Noni fruit was more potent than that of green immature fruit. Moreover, single administration of the Noni juice orally decreased the systolic blood pressure in hypertensive rats (Yamaguchi *et al*., 2002). The 70% aqueous-ethanolic extract of *M. citrifolia* roots (Mc.Cr) has antispasmodic, vasodilator and cardiovascular relaxant effects and can be used in the treatment of gut and cardiovascular disorders (Youngken *et al*., 1960; Moorthy and Reddy, 1970). The extract also produced a relaxation of spontaneous and high K^+ induced contractions in a concentration-dependent manner in isolated rabbit jejunum preparations. Like verapamil, it caused the right ward shift in the concentration response curves of Ca^{++}. Mc.Cr also produced reduction in both atrial force and the rate of contractions in guinea pig right atria. Similar to verapamil, Mc.Cr also decreased the contractions produced by phenylephrine in rabbit and rat thoracic aortic preparations in which the level of Ca^{++} is normal and the level of K^+ is high. These results indicate that the vasodilator and spasmolytic activities of *M. citrifolia* root extract are governed by the inhibition of voltage dependent calcium channels and secretion of intracellular calcium. Taking advantages of these activities, *M. citrifolia* root extract was used for the trearment of diarrhea and hypertension (Gilani *et al*., 2010).

Cardiovascular activity: The lignans 3, 3'-bisdemethylpinoresinol, americanol A, morindolin and isoprincepin were isolated from the EtOAc-soluble phase of the fruits of *Morinda citrifolia*. These compounds prevent arteriosclerosis by inhibiting copper-induced Low-Density Lipoprotein (LDL) oxidation. The MeOH extract showed 88% inhibition and EtOAc-soluble phase showed 96% inhibition. These compounds reduced the low-density lipoprotein levels in a dose-dependent manner. These compounds also showed more potent anti-oxidant activities when compared to standard antioxidant compound 2, 6-di-tert-butyl-p-cresol. The antioxidant activity of these compounds may be attributable mainly to the presence of phenolic hydroxyl groups (Kamiya *et al*., 2004).

Mandukhail *et al*. (2010) studied the antidyslipidemic effects of aqueous-ethanolic extracts of Noni fruits (Mc.Cr.F), leaves (Mc.Cr.L) and roots (Mc.Cr.R) in both high fat diet and triton (WR-1339) induced dyslipidemic models in rats. All three extracts caused reduction in triglyceride, total cholesterol, LDL-cholesterol, atherogenic index and TC/HDL ratio. The Mc.Cr.L and Mc.Cr.R caused reduction in body weight gain with a reduction in daily diet consumption whereas Mc.Cr.F had no effect. They concluded that antidyslipidemic effect was governed through the reduction in production absorption and secretion of lipids. This antidyslipidemic effect may be due to the existence of antioxidant compounds in Noni plant.

Hypoglycemic effect: Jensen *et al*. (2005) treated type 2 diabetes using *M. citrifolia* leaf extract. Anthraquinones damnacanthol-3-O-beta-D-primeveroside and lucidin 3-O-beta-D-primeveroside were isolated from n-BuOH soluble phase of the MeOH extract of *M. citrifolia* roots. These compounds exhibited the hypoglycemic effects when administrated orally to streptozotocin (STZ)-induced diabetic mice (Kamiya *et al*., 2008). Horsfall *et al*. (2007) examined the antidiabetic potential of *M. citrifolia* fruit juice alone or in combination with insulin in diabetic rats. Fruit juice of *M. citrifolia* showed synergistic action with insulin and reduced blood glucose level. Owen *et al*. (2008) reported that consumption of Noni fruit and extract from leaves showed insulinmimetic activity but had no effect on insulin action. The usual intake of Noni and guava provides better protection against type 2 diabetes (DM2) and betel quid diabetogenicity than cooked mangrove bean. Nerurkar *et al*. (2011) investigated anti-diabetic potential of fermented Noni fruit juice (fNJ) in High-Fat Diet (HFD) induced model in mice. The fNJ improves glucose metabolism via modulating transcription factor forkhead box O (FoxO1) regulation. One more study suggested that the fermented fruit juice of the *M. citrifolia* has hypoglycaemic effect in Streptozotocin (50 mg kg^{-1} b.wt.) induced diabetic rats. Diabetic rats were administered with *M. citrifolia* juice at a dose of 2 mL kg^{-1} b.wt. and glibenclamide, a known reference hypoglycemic drug, orally for a period of 20 days. There was significant decrease in blood glucose level in both groups when compared to control group. Diabetic rats showed a reduction in body mass on the 10th day of experiment, albeit it was increased significantly in treatment group by the 20th day of the experiment (Nayak *et al*., 2011).

Anti-obesity effects: Palu *et al.* (2011) conducted one study to assess the effect of Noni based formulations as dietary supplementation and exercise interventions on body composition in overweight men and women. Body weight, body mass index and percent body fat were measured before and after the trial. The weight reduction and average reduction in fat mass was very significant and resulted in reduction in body mass index and percent body fat. Noni juice caused loss of body weight by 40% in a control diet fed mice whereas it caused 25% loss of body weight in High-Fat-Diet (HFD)-fed mice. Noni juice also increased glucose tolerance and decreased the plasma triglyceride levels. These results suggested that Noni juice has anti-obesity and hypoglycemic effects (Nishioka and Nerurkar, 2007).

Anti-cataract activity: *M. citrifolia* (IC_{50} 0.132 mg mL^{-1}) strongly inhibits Aldose Reductase (AR) which plays an important role in cataractogenesis. Anti-cataract activity was established by means of sugar promoted lens opacity model (Gacche and Dhole, 2011). Saminathan *et al.* (2014) evaluated the anti-cataract activity of *Morinda citrifolia* Fruit Juice (MCFJ) and ethanolic leaf extract (MCELE) in N-methyl-N-nitrosourea (NMU) induced cataract in Sprague-Dawley rats. The MCFJ was administered at 10% solution of 5 mL/rat/day and MCELE at 1500 mg kg^{-1} b.wt/rat/day, in two divided doses, orally by gavage. The *M. citrifolia* treated rats showed significant ($p<0.05$) increase in anti-oxidant enzymes such as Glutathione Reductase (GR), CAT, SOD and significant decrease in LPO enzymes in lens homogenate as compared to NMU control group. These results suggested that *M. citrifolia* have significant anti-cataract potential.

Mental health and improved high frequency hearing: Langford *et al.* (2004) conducted a clinical trial in humans to assess the efficiency of TNJ against auditory function and decreased bone mineral density in the patients. They reported that TNJ affords encouraging results on improved high frequency hearing and mental health but this study also showed that excess amounts or prolonged duration of TNJ uptake may be required to overcome these conditions.

Effect on stress-induced impairment of cognitive function: Supplementation of Noni fruit juice safeguards the brain from stress-induced derangement of cognitive function. This defensive beneficial effect may be due to enhancement in stress-induced reduction in blood vessel mass in the area of hippocampal dentate gyrus which was analysed immunohistochemically with BrdU or CD31 antibody (Muto *et al.*, 2010).

Effect on ischemic neuronal damage: Ingestion of 10% Noni juice orally by mixing in drinking water for a period of 7 days in male ddY mice followed by exposure to 2 h of Middle Cerebral Artery Occlusion (MCAO) reduced the progress of neuronal injury. After Noni juice administration MCAO completely disappeared and glucose intolerance abolished on the 1st day. Noni juice administration significantly enhanced the serum insulin levels when compared to the control group on the 1st day but the levels of adiponectin in serum were not changed. These results suggested that Noni juice might enhance insulin secretion after ischemic tension and this may lead to reduction in the progress of post-ischemic glucose intolerance (Harada *et al.*, 2010).

Anxiolytic and sedative effect: Deng *et al.* (2007b) investigated *in vitro* anxiolytic and sedative effects of Noni fruit by competitive gamma-aminobutyric acid A (GABAa) receptor-binding assay. They reported that methanol extract of Noni fruit exhibited high specificity to the inhibitory neurotransmitter GABAa receptor and agonist muscimol exhibited 75% inhibition at a concentration of 100 μg mL^{-1}. These results indicate that Noni fruit is agonistic to the GABAa receptor and thus induces anxiolytic and sedative effects (Kalandakanond *et al.*, 2004).

Prevention of postoperative nausea and vomiting: Prapaitrakool and Itharat (2010) evaluated the preventive potential of Noni against the postoperative nausea and vomiting (PONV) in patients who were at great risk of developing PONV after different kinds of surgery. Administration of Noni extract at a dose of 600 mg which is equivalent to 8.712 μg of scopoletin, significantly reduced the PONV in 48% of the patients during the first 6 h, whereas PONV was recorded in 80% patients in the control group. In all groups no side effects were reported. These results suggested that Noni has an antiemetic property and can be used as prophylactic agent for early postoperative nausea (0-6 h).

Reflux esophagitis and gastric ulcer: Mahattanadul *et al.* (2011) evaluated the efficiency of aqueous extract of dried mature unripe Noni fruit and its biomarker scopoletin on gastro-esophageal inflammatory model in rats. The aqueous extract at a dose of 0.63-2.50 g kg^{-1} b.wt. significantly inhibited the development of acid induced reflux esophagitis, acute gastric lesions induced by ethanol and decreased the serotonin induced gastric lesions. It also hastened the healing of acetic acid-induced chronic gastric ulcer when compared to the standard antisecretory drugs such as lansoprazole and ranitidine. In pylorus ligated rats, aqueous extract of Noni

also significantly prevented gastric acid secretion and pepsin activity. Moreover, aqueous extract significantly enhanced the gastrointestinal transit which was better than cisapride. Like of Noni, pure scopoletin also have parallel antisecretory and antiulcer properties but it has a less prokinetic activity. These results suggested that scopoletin can be used as a biomarker ingredient for the quality estimation of Noni fruit based products which are used for the treatment of gastro-esophageal inflammatory disorders.

Antigout activity: In one *in vitro* study, Noni juice prevented the Xanthine Oxidase (XO) in a concentration dependent manner. A dose of 1, 5 and 10 mg mL^{-1} of TNJ (IC_{50} 3.8 mg) prevented XO by 11, 113 and 148%, respectively, as compared to allopurinol (IC_{50} 2.4 microm). These results indicated that the Noni fruit juice inhibits XO enzyme which may be the possible mechanism of action of Noni for curative effect against gout (Palu *et al*., 2009).

Estrogenic activity: *M. citrifolia* has been reported to have very weak estrogenic activity *in vivo*. The relative estrogenic potency of alcoholic extract (1:1000) and water extract (1:10,000), indicated that the estrogenic activity is only seen at low doses. It has very low potency as compared to estradiol, suggesting that the beneficial effects of Noni are not closely linked to estrogen mediated action (Chearskul *et al*., 2004). Basar *et al*. (2006) conducted two *in vitro* assays to assess the estrogenic properties of the fruit by the estrogen receptor binding assay using both ER-α and ER-β estrogen receptors. Second, estrogen-receptor dependent induction of alkaline phosphatase has been reported in Ishikawa cells. Hexane extracts prepared from the fruit exhibited high activity in both systems. A preferential binding for ER-β was observed.

Probiotic potential of noni juice: Wang *et al*. (2009c) assessed the possibility of Noni as a raw substrate for the manufacture of probiotic Noni juice by using lactic acid bacteria such as *Lactobacillus plantarum*, *L. casei* and *Bifidobacterium longum*. After 48 h of fermentation all the strains of bacteria grew luxuriously on Noni juice and attained nearly 10 CFU mL^{-1}. The production of lactic acid was less in *L. casei* when compared to *L. Plantarum* and *B. Longum*, *B. longum* and *L. plantarum* survived under low-pH and cold storage (4°C) conditions for 4 weeks in fermented Noni juice. But after 3 weeks *L. casei* showed no cell viability. In addition, *B. longum* fermented Noni juice has highly elevated antioxidant activity. These results suggested that *L. plantarum* and *B. longum* are best probiotics for fermentation of Noni juice. A herbal feed additive namely Morical prepared from *M.citrifolia* fruits has been found to increase the production and improve quality of eggs Japanese quail (Sunder *et al*., 2013). The probiotic potential of *M. citrifolia* fruit juice with *Lactobacillus acidophilus* (LAB) has been evaluated recently by assessing the hisotmorphological changes in the duodenal villi of commercial broiler chick (Ven-cob) (Sunder *et al*., 2014). In *M. citrifolia* treated group the villi height and crypt depth showed significant changes in the duodenum when compared to control group. Whereas LAB fed chickens showed significant increase in the villi height and crypt depth as compared to Noni treated group. These results indicate that the administration of Noni fruit juice enhanced the duodenal function which is the major site for the nutrient absorption and development of the immune response.

Safety of Noni juice: A dose of 750 mL of Tahitian Noni juice per day for 28 days was used in a human clinical study. Several parameters were investigated and all parameters were within the range of normal values. Noni juice exhibited no dose-related adverse effects (West *et al*., 2006). The oral toxicity test for the aqueous extract of Noni fruit was carried out at a dose of 1000 mg kg^{-1} body weight for 28 days. There were no changes in weight gain, clinical signs, food consumption, haematological and biochemical values and macroscopic or histopathological findings. In Wistar rats *M. citrifolia* fruit juice showed significant anxiolytic effects. On the other hand, there was no change in food consumption, weight gain and clinical biochemistry parameters (Kalandakanond *et al*., 2004). *In vitro* primary gene mutation potential of Noni juice was assessed in the Chinese hamster V79 cell line. The ethyl acetate extract of the Noni juice showed no gene mutations at the hypoxanthine phosphoribosyl transferase (HPRT) gene locus at a dosage of 0.003-3 μL mL^{-1} with 100 fold concentration. These results indicate that the Noni juice does not have any mutagenic potential (Westendorf, 2002a).

An *in vivo* and *in vitro* unscheduled DNA synthesis (UDS) assay of Noni juice was performed to examine the DNA damage by estimating the DNA adducts formation. The counting of silver grains in cell nuclei signifies the repair of DNA damage. The Tahitian Noni juice showed normal silver grain count in cell nuclei which was similar to that of the saline control and it was significantly lower when compared to positive controls (N, N-dimethyl nitrosamine and 2-acetyl aminoflourene). Therefore, all these indicate that Noni juice does not have any genotoxic action (Westendorf, 2002b; Westendorf *et al*., 2007).

The mouse micronucleus test of Noni juice was performed to evaluate the clastogenic activity. The dehydrated Noni juice was administered at a dose of 10 g kg b.wt. The bone marrow of the animals shows no micronucleated polychromatic erythrocytes, clastogenic activity and no evidence of systemic toxicity (Edwards, 2002). Noni juice contains an average potassium content of 56.3±2.5 meq L^{-1}. This potassium content is almost equal to orange, grapefruit and tomato juices values. The other fruit juices which have same potassium content must be limited in the foods of patients with chronic renal failure. It may causes hyperkalemia in a patient with chronic renal insufficiency kept on a low-potassium diet (Mueller *et al*., 2000). The Noni fruits have negligible vitamin K content (Palu *et al*., 2005).

Hepatotoxicity associated with drinking Noni juice has been reported in Austria and southern Germany (Millonig *et al*., 2005; Stadlbauer *et al*., 2005; Yuce *et al*., 2006). A 45 year old man has been reported to suffer from hepatotoxicity, who had been drinking 1 glass day^{-1} of Noni juice. After several weeks the patient had highly increased levels of hepatic enzymes such as aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alamine aminotransferase (ALT) and Gamma Glutamyl Transferase (GGT). Following termination of Noni juice, his hepatic enzyme levels returned to normal within one month. The possible cause of the liver dysfunction could be associated with high level of anthraquinones in Noni fruit juice (Millonig *et al*., 2005). In another study a 29 year an old man who consumed Noni juice at a rate of 71 mL day^{-1} and a 62 year old woman who consumed Noni juice at a rate of 16 mL day^{-1} also showed increased bilirubin, alkaline phosphatase (ALP), ALT, AST and GGT. The liver biopsies from both patients confirmed acute hepatitis which may be attributed to idiosyncratic reactions. These enzyme levels were normalized in 11 month after cessation of the juice. The cause of liver dysfunction could be due to herbal toxicity of Noni juice (Stadlbauer *et al*., 2005; Yuce *et al*., 2006).

However, West *et al*. (2006) contradicted the hepatotoxic effect of Noni, as the quantity of anthraquinones in Noni fruits is too small (<1 ppm). Such a small quantity does not have any toxicological significance and does not cause hepatotoxicity. The chemical structures of anthraquinones do not become reduced to reactive anthrone radicals which have a capacity to cause tissue damage. All these results indicate that Noni juice has no toxicological significance on the liver. The hepatotoxic substances pyrrolizidine alkaloids and patulin are absent in Noni juice. Based on all these toxicological assessment, finally they concluded that Noni juice is safe. The European food safety authority reported that there is no association between the undesirable effects recorded on liver and consumption of Noni fruit juice (Potterat and Hamburger, 2007). The hepatic dysfunction recorded in a few studies in aged patients thus may not be attributable to the consumption of Noni fruit juice.

Toxicity, mutagenicity and allergenicity studies of Noni: Acute toxicity of puree of Noni fruit juice was assessed by administering TNJ to Sprague-Dawley rats by oral gavage at a dose of 15,000 mg kg^{-1}. Following administration, the animals were observed for 14 days. All animals lived the observation period and exhibited no evidences of toxicity. Rather the animals appeared healthy and gained body weight. No signs of gross toxicity were seen in the organs at necropsy. So, it could be inferred that the LD_{50} of Noni fruit would be greater than 15,000 mg kg^{-1}. If the acute oral LD_{50} is greater than 15,000 mg kg^{-1} and acute intraperitoneal LD_{50} is greater than 2,000 mg kg^{-1}, then the compound may be considered as nontoxic (Product Safety Labs, 2000).

The allergenic risk of Tahitian Noni juice was studied using guinea pigs. Subcutaneous injections of TNJ with Freund's adjuvant in guinea pigs resulted in no allergic reactions (Kaaber, 2000). A 13 weeks oral toxicity study in Sprague Dawley rats was conducted to assess the systemic safety of TNJ. The rats were administered with daily gavage doses of 0.4, 4, 8, 50 and 80 mL kg^{-1} b.wt. There was no significant difference in body and organ weights, clinical signs, food consumption, hematological and biochemical parameters and histological examination of tissues among the groups. Based on the results No Observable Adverse Effect Level (NOAEL) was at least 80 mL TNJ/kg/day. This quantity of Noni juice is equal to 8% of the animal's body weight (Glerup, 2001). It is confirmed through extensive microbiological, chemical and toxicological analysis that TNJ is safe for human consumption. West *et al*. (2011) evaluated the potential toxicity of *M. citrifolia* seed extract by using brine shrimp toxicity test. The result of this test showed that the extract is non-cytoxic (LC_{50} >1 mg mL^{-1}). The results of the subacute (28 days) oral toxicity test in SD rats also showed that the extract has no signs of toxicity. Noni seed extract also did not contain genotoxic or mutagenic potential. West *et al*. (2009) evaluated the toxicity and mutagenicity potential of roasted Noni leaf infusion by using reverse mutation test in *Salmonella typhimurium* and primary DNA damage test in *E. coli* PQ37. The infusion showed no mutagenic potential and did not induce any primary DNA damage. In addition, the infusion does not have any cytotoxic potential (LC_{50} >1 mg mL^{-1}) and also the freeze-dried infusion does not have any evidence of acute oral toxicity in SD rats (LD_{50} >2000 mg kg^{-1} b.wt.).

CONCLUSION AND FUTURE PERSPECTIVES

Novel compounds with high levels of pharmacological activity are urgently required to develop effective therapeutic armoury against the health problems arising from population growth and increased incidences of the human and animal diseases. Changing climate, increased atmospheric pollution, stressful environment, emergence of new pathogens, changing life style and increased life expectancy have led to the development of numerous conditions that require extended medication using drugs with minimal side effects. In the want of safer medicines the alternative therapeutic approaches utilising herbal treasure are being explored and exploited extensively worldwide. *Morinda citrifolia* L. (Noni) is a miracle herb of tropical regions and has been used for over 2000 years by Polynesians. All parts of this plant are useful for the management of many disease conditions. Now-a-days Noni is grown around the world, popularly as a nutritional or dietary supplement with multiple health advantages. Although, most of the studies carried out so far have been limited to *in vitro* experiments, several *in vivo* (animal) studies demonstrated the potentially beneficial effects of Noni but the clinical data are largely insufficient to draw logical conclusions. So, randomized clinical trials are necessary to know the exact effect of Noni in human diseases. Research and development (R and D) programs should be undertaken to develop modern drugs with defined compounds but before that, a comprehensive phytochemical analysis, extensive study of its pharmacokinetics, mechanism of action, pharmacotherapeutics, toxicity and clinical trials are essential to provide sufficient data. Furthermore, research should be initiated for identification of elite active compounds through TLC, HPTLC, HPLC, Nuclear Magnetic Resonance (NMR) spectroscopy and other standard methods. Standardization of cell culture techniques for production of bioactive compounds and identification of pathway related to the production of potent bioactive compounds are also necessary. Several nutraceutical and pharmaceutical companies are already engaged marketing of various product of Noni. The companies engaged in production and marketing of Noni juice should provide all relevant information regarding bioactive components present in juice. Once the medicinal values of Noni are scientifically explored, especially of its all pharmacological activities, this plant would have bright market future.

REFERENCES

Agarwal, N., A. Chandra and L.K. Tyagi, 2011. Herbal medicine: Alternative treatment for cancer therapy. Int. J. Pharm. Sci. Res., 2: 2249-2258.

Akihisa, T., K. Matsumoto, H. Tokuda, K. Yasukawa and K.I. Seino *et al*., 2007. Anti-inflammatory and potential cancer chemopreventive constituents of the fruits of *Morinda citrifolia* (Noni). J. Nat. Prod., 70: 754-757.

Alitheen, N.B., A.A. Manaf, S.K. Yeap, M. Shuhaimi, L. Nordin and A.R. Mashitoh, 2010. Immunomodulatory effects of damnacanthal isolated from roots of *Morinda elliptica*. Pharm. Biol., 48: 446-452.

Amarpal, K. Dhama, S. Chakraborty, R. Tiwari and S. Natesan, 2013. Stem cells and their clinical/therapeutic applications in biomedical and veterinary science-the perspectives. Res. Opin. Anim. Vet. Sci., 3: 261-279.

American Chemical Society, 2000. Noni plant may yield new drugs to fight tuberculosis. Proceedings of the International Chemical Congress of Pacific Basin Societies, December 14-19, 2000, Honolulu, HI., USA.

Anitha, T. and S. Mohandass, 2006. Anti-oxidant activity of *Morinda citrifolia* on lymphoma-bearing mice. Ancient Sci. Life, 26: 85-88.

Anonymous, 2001. Noni plant may help TB. AIDS Patient Care STDS, 15: 175-175.

Archana, S.J., R. Paul and A. Tiwari, 2011. Indian medicinal plants: A rich source of natural immuno-modulator. Int. J. Pharmacol., 7: 198-205.

Arpornsuwan, T. and T. Punjanon, 2006. Tumor cell-selective antiproliferative effect of the extract from *Morinda citrifolia* fruits. Phytother. Res., 20: 515-517.

Asahina, A.Y., J.S.M. Ebesu, D. Ichinotsubo, J. Tongson and Y. Hokama, 1994. Effect of Okadaic Acid (OA) and Noni fruit extraction in the synthesis of Tumor Necrosis Factor-á (TNF-á) by Peripheral Blood Mononuclear (PBN) cells *in vitro*. Proceedings of the International Symposium of Ciguatera and Marine Natural Products, August 8-10, 1994, Honolulu, HI., USA., pp: 197-205.

Atkinson, N., 1956. Antibacterial substances from flowering plants. 3. Antibacterial activity of dried Australian plants by a rapid direct plate test. Aust. J. Exp. Biol. Med. Sci., 34: 17-26.

Balachandran, P. and R. Govindarajan, 2005. Cancer: An ayurvedic perspective. Pharma. Res., 51: 19-30.

Banerjee, S., A.D. Johnson, K. Csiszar, D.L. Wansley and P. McGeady, 2006. An extract of *Morinda citrifolia* interferes with the serum-induced formation of filamentous structures in *Candida albicans* and inhibits germination of *Aspergillus nidulans*. Am. J. Chin. Med., 34: 503-509.

Bao, L., L. Qin, L. Liu, Y. Wu, T. Han, L. Xue and Q. Zhang, 2011. Anthraquinone compounds from *Morinda officinalis* inhibit osteoclastic bone resorption *in vitro*. Chem. Biol. Interact., 194: 97-105.

Basar, S., H. Iznaguen, A. Zeglin and J. Westendorf, 2006. Phytoestrogenic activity of *Morinda citrifolia* L. fruits. Planta Medica, 72: 234-234.

Basar, S., K. Uhlenhut, P. Hogger, F. Schone and J. Westendorf, 2010. Analgesic and antiinflammatory activity of *Morinda citrifolia* L.(Noni) fruit. Phytother. Res., 24: 38-42.

Brooks, V.J., M. Schafer, P. Sharp, J. Xu and J. Cai *et al*., 2009. Effects of *Morinda citrifolia* (noni) on $CD4^+$ and $CD8^+$ T-cell activation in neonatal calves. Profess. Anim. Sci., 25: 262-265.

Brown, A.C., 2012. Anticancer activity of *Morinda citrifolia* (Noni) fruit: A review. Phytother. Res., 26: 1427-1440.

Bushnell, O.A., M., Fukuda and T., Makinodian, 1950. The antibacterial properties of some plants found in Hawaii. Pac. Sci., 46: 167-183.

Cardon, D., 2003. [The World of Natural Dyes]. Belin Publishers, Paris, Farance, ISBN-13: 978-2701161433 (In French).

Chan-Blanco, Y., F. Vaillant, A. Mercedes Perez, M. Reynes, J.M. Brillouet and P. Brat, 2006. The noni fruit (*Morinda citrifolia* L.): A review of agricultural research, nutritional and therapeutic properties. J. Food Compos. Anal., 19: 645-654.

Chearskul, S., S. Kooptiwut, S. Chatchawalvanit, S. Onreabroi, M. Churintrapun, P. Saralamp and N. Soonthornchareonnon, 2004. *Morinda citrifolia* has very weak estrogenic activity *in vivo*. Thai. J. Physiol. Sci., 17: 22-29.

Chow, C.K., 1993. Cigarette smoking and oxidative damage in the Lunga. Ann. N. Y. Acad. Sci., 686: 289-298.

Clafshenkel, P., T.L. King, M.B. Kotlarczyk, J.M. Cline, W.G. Foster, V.L. Davis and P. Witt-Enderby, 2012. *Morinda citrifolia* (Noni) juice augments mammary gland differentiation and reduces mammary tumor growth in mice expressing the unactivated c-*erb*B2 transgene. Evidence-Based Complementary Altern. Med. 10.1155/2012/487423

Colville-Nash, P.R. and D.W. Gilroy, 2001. Potential adverse effects of cyclooxygenase-2 inhibition: Evidence from animal models of inflammation. Biodrugs, 15: 1-9.

Dalsgaard, P.W., O. Potterat, F. Dieterle, T. Paululat, T. Kuhn and M. Hamburger, 2006. Noniosides E-H, New trisaccharide fatty acid esters from the fruit of *Morinda citrifolia* (Noni). Planta Med., 72: 1322-1327.

Dang, V.H., 1954. [A basic treatment for arterial hypertension with extracts of the roots of *Morinda citrifolia* (Cay-Nhau)]. Presse Med., 62: 1020-1021, (In French).

Deng, S., A.K. Palu, B.J. West, C.X. Su, B.N. Zhou and J.C. Jensen, 2007a. Lipoxygenase inhibitory constituents of the fruits of Noni (*Morinda citrifolia*) collected in Tahiti. J. Nat. Prod., 70: 859-862.

Deng, S., B.J. West, A.K. Palu, B.N. Zhou and C.J. Jensen, 2007b. Noni as an anxiolytic and sedative: A mechanism involving its ã-aminobutyric acidergic effects. Phytomedicine, 14: 517-522.

Dhama, K., M. Mahendran, S. Tomar and R.S. Chauhan, 2008. Beneficial effects of probiotics and prebiotics in livestock and poultry: The current perspectives. Intas Polivet, 9: 1-12.

Dhama, K., R. Tiwari, S. Chakraborty, A. Kumar, M. Karikalan, R. Singh and R.B. Rai, 2013a. Global warming and emerging infectious diseases of animals and humans: Current scenario, challenges, solutions and future perspectives: A review. Int. J. Curr. Res., 5: 1942-1958.

Dhama, K., S. Chakraborty, S. Kapoor, R. Tiwari and A. Kumar *et al*., 2013b. One world, one health-veterinary perspectives. Adv. Anim. Vet. Sci., 1: 5-13.

Dhama, K., S. Chakraborty, Mahima, M.Y. Wani and A.K. Verma *et al*., 2013c. Novel and emerging therapies safeguarding health of humans and their companion animals: A review. Pak. J. Biol. Sci., 16: 101-111.

Dhama, K., S. Chakraborty and R. Tiwari, 2013d. Panchgavya therapy (Cowpathy) in safeguarding health of animals and humans: A review. Res. Opin. Anim. Vet. Sci., 3: 170-178.

Dhama, K., S. Chakraborty, M.Y. Wani, R. Tiwari and R. Barathidasan, 2013e. Cytokine therapy for combating animal and human diseases: A review. Res. Opin. Anim. Vet. Sci., 3: 195-208.

Dhama, K., S. Mani, S. Chakraborty, R. Tiwari, A. Kumar, P. Selvaraj and R.B. Rai, 2013f. Herbal remedies to combat cancers in humans and animals: A review. Int. J. Curr. Res., 5: 1908-1919.

Dhama, K., S. Chakraborty, R. Tiwari, A.K. Verma and M. Saminathan *et al*., 2014. A concept paper on novel technologies boosting production and safeguarding health of humans and animals. Res. Opin. Anim. Vet. Sci., (In Press).

Dhanamani, M., S.L. Devi and S. Kannan, 2011. Ethnomedicinal plants for cancer therapy: A review. Hygeia: J. D. Med., 3: 1-10.

Dittmar, A., 1993. *Morinda citrifolia* L.: Use in indigenous Samoan medicine. J. Herbs Spices Med. Plants, 1: 77-92.

Diwanay, S., D. Chitre and B. Patwardhan, 2004. Immunoprotection by botanical drugs in cancer chemotherapy. J. Ethnopharmacol., 90: 49-55.

Duncan, S.H., H.J. Flint and C.S. Stewart, 1998. Inhibitory activity of gut bacteria against *Escherichia coli* O157 mediated by dietary plant metabolites. FEMS Microbiol. Lett., 164: 283-288.

Dussossoy, E., P. Brat, E. Bony, F. Boudard and P. Poucheret *et al*., 2011. Characterization, anti-oxidative and anti-inflammatory effects of Costa Rican noni juice (*Morinda citrifolia* L.). J. Ethnopharmacol., 133: 108-115.

EFSA, 2006. Opinion on a request from the commission related to the safety of Noni juice (juice of the fruits of *Morinda citrifolia*). EFSA J., 376: 1-12.

Edwards, C.N., 2002. Tahitian Noni Juice-mouse micronucleus test. Test Report, Scantox Biological Laboratory, Lab No. 47053, Lille Skensved, Denmark.

Ehrhart, J., D. Obregon, T. Mori, H. Hou and N. Sun *et al*., 2005. Stimulation of cannabinoid receptor 2 (CB_2) suppresses microglial activation. J. Neuroinflamm., Vol. 2. 10.1186/1742-2094-2-29

Elkins, R., 1998. Hawaiian Noni (*Morinda citrifolia*) Prize Herb of Hawaii and the South Pacific. Woodland Publishing, Utah, USA.

Ernst, E., 2000. Prevalence of use of complementary/ alternative medicine: A systematic review. Bull. World Health Org., 78: 258-266.

Faltynek, C.R., J. Schroeder, P. Mauvais, D. Miller and S. Wang *et al*., 1995. Damnacanthal is a highly potent, selective inhibitor of p56lck tyrosine kinase activity. Biochemistry, 34: 12404-12410.

Farine, J.P., L. Legal, B. Moreteau and J.L.L. Quere, 1996. Volatile compounds of ripe fruits of *Morinda citrifolia* and their effects on *Drosophila*. Phytochemistry, 41: 433-438.

Ferlay, J., H.R. Shin, F. Bray, D. Forman, C. Mathers and D.M. Parkin, 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer, 127: 2893-2917.

Furusawa, E., A. Hirazumi, S. Story and J. Jensen, 2003. Antitumour potential of a polysaccharide-rich substance from the fruit juice of *Morinda citrifolia* (Noni) on sarcoma 180 ascites tumour in mice. Phytother. Res., 17: 1158-1164.

Gacche, R.N. and N.A. Dhole, 2011. Profile of aldose reductase inhibition, anti-cataract and free radical scavenging activity of selected medicinal plants: An attempt to standardize the botamicals for amelioration of diabetes complications. Food Chem. Toxicol., 49: 1806-1813.

Gilani, A.H., S.U.R. Mandukhail, J. Iqbal, M. Yasinzai, N. Aziz, A. Khan and N.U. Rehman, 2010. Antispasmodic and vasodilator activities of *Morinda citrifolia* root extract are mediated through blockade of voltage dependent calcium channels. BMC Complement Altern Med., Vol. 10. 10.1186/1472-6882-10-2

Glerup, P., 2001. Tahitian TNJ: A 13-week oral (gavage) toxicity study in rats. Test Report, Scantox Biological Laboratory, Lab No. A/S, DK-426, Lille Skensved, Denmark.

Gupta, R.K. and A.K. Patel, 2013. Do the health claims made for *Morinda citrifolia* (Noni) harmonize with current scientific knowledge and evaluation of its biological effects. Asian Pac. J. Cancer Prev., 14: 4495-4499.

Gupta, R.K., A. Banerjee, S. Pathak, C. Sharma and N. Singh, 2013. Induction of mitochondrial-mediated apoptosis by *Morinda citrifolia* (Noni) in human cervical cancer cells. Asian Pac. J. Cancer Prev., 14: 237-242.

Harada, S., W. Fujita-Hamabe, K. Kamiya, Y. Mizushina, T. Satake and S. Tokuyama, 2010. *Morinda citrifolia* fruit juice prevents ischemic neuronal damage through suppression of the development of post-ischemic glucose intolerance. J. Nat. Med., 64: 468-473.

Hazilawati, H., A.H. Hutheyfa, S.M. Rosly, S. Jasni, M.M. Noordin and S. Shanmugavelu, 2010a. Haematological parameters of leukaemic rats supplemented with *Morinda citrifolia*. Med. J. Malaysia, 65: 125-126.

Hazilawati, H., H. Nursyuhada, A.H. Hutheyfa, S.M. Rosly, S. Shanmugavelu, S.M. Rosly and S. Jasni, 2010b. Effects of *Morinda citrifolia* on early stage of leukaemic in rats. Malaysian Med. J., 65: 135-136.

Heinicke, R.M., 1985. The pharmacologically active ingredient of Noni. Bull. Natl. Trop. Bot. Garden, 15: 10-14.

Hiramatsu, T., M. Imoto, T. Koyano and K. Umezawa, 1993. Induction of normal phenotypes in *ras*-transformed cells by damnacanthal from *Morinda citrifolia*. Cancer Lett., 73: 161-166.

Hirazumi, A., E. Furusawa, S.C. Chou, C. Okano and C. Ching, 1992. Antitumor activity of *Morinda citrifolia* on intraperitoneally implanted Lewis lung carcinoma in mice. Proc. Am. Soc. Cancer Res., 33: 515-515.

Hirazumi, A., E. Furusawa, S.C. Chou and Y. Hokama, 1994. Anticancer activity of *Morinda citrifolia* (Noni) on intraperitoneally implanted Lewis lung carcinoma in syngeneic mice. Proc. Western Pharmacol. Soc., 37: 145-146.

Hirazumi, A., E. Furusawa, S.C. Chou and Y. Hokama, 1996. Immunomodulation contributes to the anticancer activity of *Morinda citrifolia* (Noni) fruit juice. Proc. Western Pharmacol. Soc., 39: 7-9.

Hirazumi, A. and E. Furusawa, 1999. An immunomodulatory polysaccharide-rich substance from the fruit juice of *Morinda citrifolia* (Noni) with antitumour activity. Phytother. Res., 13: 380-387.

Hisawa, T., Y. Arase, Z. Chen, K. Kita, K. Umezawa, H. Ito and N. Suzuki, 1999. Stimulation of ultraviolet-induced apoptosis of human fibroblast UVr-1 cells by tyrosine kinase inhibitors. FEBS Lett., 444: 173-176.

Hokama, Y., 1993. The effect of Noni fruit extract (*Morinda citrifolia*, Indian mulberry) on thymocytes of BALB/c mouse. FASEB J., 7: A866-A866.

Hornick, C.A., A. Myers, H. Sadowska-Krowicka, C.T. Anthony and E.A. Woltering, 2003. Inhibition of angiogenic initiation and disruption of newly established human vascular networks by juice from *Morinda citrifolia* (Noni). Angiogenesis, 6: 143-149.

Horsfall, A.U., O. Olabiyi, A. Aiyegbusi, C.C. Noronha and A.O. Okanlawon, 2007. *Morinda citrifolia* fruit juice augments insulin action in Sprague-Dawley rats with experimentally induced diabetes. Niger. Q. J. Hosp. Med., 18: 162-165.

Hutheyfa, A.H., 2010. Effects of *Morinda citrifolia* on N-methyl N-nitrosourea induced peripheral T cell non-Hodgkin's lymphoma in Sprague Dawley rats. Master's Thesis, Universiti Putra Malaysia, Malaysia.

Ikeda, R., M. Wada, T. Nishigaki and K. Nakashima, 2009. Quantification of coumarin derivatives in Noni (*Morinda citrifolia*) and their contribution of quenching effect on reactive oxygen species. Food Chem., 113: 1169-1172.

Inoue, K., H. Nayeshiro, H. Inouye and M. Zenk, 1981. Anthraquinones in cell suspension cultures of *Morinda citrifolia*. Phytochemistry, 20: 1691-1700.

Issell, B.F., C. Gotay, I. Pagano and A. Franke, 2005. Quality of life measures in a phase I trial of noni. J. Clin. Oncol., Vol. 23.

Jainkittivong, A., T. Butsarakamruha and R.P. Langlais, 2009. Antifungal activity of *Morinda citrifolia* fruit extract against *Candida albicans*. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol., 108: 394-398.

Jayaraman, S.K., M.S. Manoharan and S. Illanchezian, 2008. Antibacterial, Antifungal and Tumor cell suppression potential of *Morinda citrifolia* fruit extracts. Int. J. Integr. Biol., 3: 44-49.

Jensen, C.J., A.K. Palu, H. Ohishi and H. Tani, 2005. Preventative and treatment effects of *Morinda citrifolia* on diabetes and its related conditions. US Patent No US6855345 B2. http://www.google.com/patents/US6855345.

Kaaber, K., 2000. Tahitian Noni® juice: Active systemic anaphylaxis test in the guinea pig. Test Report, Scantox Biological Laboratory, Lab No. A/S, DK-426, Lille Skensved, Denmark.

Kalandakanond, S., J. Pandaranandaga, S. Komolvanich and S. Poonyachoti, 2004. A study on the anxiolytic effect of juice from the fruit of noni (*Morinda citrifolia* L. Ruciaceae) on wistar rats. Thai J. Pharm., 34: 99-105.

Kamata, M., R.P. Wu, D.S. An, J.P. Saxe and R. Damoiseaux *et al*., 2006. Cell-based chemical genetic screen identifies damnacanthal as an inhibitor of HIV-1 Vpr induced cell death. Biochem. Biophys. Res. Commun., 348: 1101-1106.

Kamiya, K., Y. Tanaka, H. Endang, M. Umar and T. Satake, 2004. Chemical constituents of *Morinda citrifolia* fruits inhibit copper-induced low-density lipoprotein oxidation. J. Agric. Food Chem., 52: 5843-5848.

Kamiya, K., Y. Tanaka, H. Endang, M. Umar and T. Satake, 2005. New anthraquinone and iridoid from the fruits of *Morinda citrifolia*. Chem. Pharm. Bull., 53: 1597-1599.

Kamiya, K., W. Hamabe, S. Harada, R. Murakami, S. Tokuyama and T. Satake, 2008. Chemical constituents of *Morinda citrifolia* roots exhibit hypoglycemic effects in streptozotocin-induced diabetic mice. Biol. Pharm. Bull., 31: 935-938.

Karthik, K., N.S. Muneeswaran, H.V. Manjunathachar, M. Gopi, A. Elamurugan and S. Kalaiyarasu, 2014. Bacteriophages: Effective alternative to antibiotics. Adv. Anim. Vet. Sci., 2: 1-7.

Kim, S.W., B.K. Jo, J.H. Jeong, S.U. Choi and Y.I. Hwang, 2005. Induction of extracellular matrix synthesis in normal human fibroblasts by anthraquinone isolated from *Morinda citrifolia* (Noni) fruit. J. Med. Food, 8: 552-555.

Kitagishi, Y., M. Kobayashi and S. Matsuda, 2012. Protection against cancer with medicinal herbs via., activation of tumor suppressor. J. Oncol. 10.1155/2012/236530

Kumar, K.T., D.S. Panda, U.N. Nanda and S. Khuntia, 2010. Evaluation of antibacterial, antifungal and anthelmintic activity of *Morinda citrifolia* L. (Noni). Int. J. PharmaTech Res., 2: 1030-1032.

Kumar, S., A.K. Singh, S.K. Verma, R. Misra and C. Seniya, 2013a. Antibacterial and phyto-chemical analysis of some medicinal plants and their efficacy on multidrug resistant bacteria. J. Pure Applied Microbiol., 7: 2191-2204.

Kumar, A., A. Rahal, S. Chakraborty, R. Tiwari, S.K. Latheef and K. Dhama, 2013b. *Ocimum sanctum* (Tulsi): A miracle herb and boon to medical science-A review. Int. J. Agron. Plant Prod., 4: 1580-1589.

Kumar, H., B. Singh, T.K. Goswami and M. Rawat, 2013c. Use of neem preparations for the treatment of endometritis in cows. Adv. Anim. Vet. Sci., 1: 194-196.

Langford, J., A. Doughty, M. Wang, L. Clayton and M. Babich, 2004. Effects of *Morinda citrifolia* on quality of life and auditory function in postmenopausal women. J. Altern. Complement. Med., 10: 737-742.

Leach, A.J., D.N. Leach and G.J. Leach, 1988. Antibacterial activity of some medicinal plants of Papua New Guinea. Sci. New Guinea, 14: 1-7.

Levand, O. and H.O. Larson, 1979. Some chemical constituents of *Morinda citrifolia*. Planta Med., 36: 186-187.

Li, N., H.M. Wang, S.H. Guo, X. Lin, L.P. Zheng and L. Wang, 2008. [Protection of apoptosis of osteoblast cultured *in vitro* by *Morinda* root polysaccharide]. Zhongguo Gu Shang, 21: 39-41, (In Chinese).

Li, R.W., S.P. Myers, D.N. Leach, G.D. Lin and G. Leach, 2003. A cross-cultural study: Anti-inflammatory activity of Australian and Chinese plants. J. Ethnopharmacol., 85: 25-32.

Liu, C.H., Y.R. Xue, Y.H. Ye, F.F. Yuan, J.Y. Liu and J.L. Shuang, 2007. Extraction and characterization of antioxidant compositions from fermented fruit juice of *Morinda citrifolia* (Noni). Agric. Sci. Chin., 6: 1494-1501.

Liu, G., A. Bode, W.Y. Ma, S. Sang, C.T. Ho and Z. Dong, 2001. Two novel glycosides from the fruits of *Morinda citrifolia* (noni) inhibit AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line. Cancer Res., 61: 5749-5756.

Locher, C.P., M.T. Burch, H.F. Mower, J. Berestecky and H. Davis *et al*., 1995. Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. J. Ethnopharmacol., 49: 23-32.

Lv, L., H. Chen, C.T. Ho and S. Sang, 2011. Chemical components of the roots of Noni (*Morinda citrifolia*) and their cytotoxic effects. Fitoterapia, 82: 704-708.

Mahattanadul, S., W. Ridtitid, S. Nima, N. Phdoongsombut, P. Ratanasuwon and S. Kasiwong, 2011. Effects of *Morinda citrifolia* aqueous fruit extract and its biomarker scopoletin on reflux esophagitis and gastric ulcer in rats. J. Ethnopharmacol., 134: 243-250.

Mahima, A. Rahal, R. Deb, S.K. Latheef and H.A. Samad *et al*., 2012. Immunomodulatory and therapeutic potentials of herbal, traditional/ indigenous and ethnoveterinary medicines. Pak. J. Biol. Sci., 15: 754-774.

Mahima, A.K. Verma, R. Tiwari, K. Karthik, S. Chakraborty, R. Deb and K. Dhama, 2013a. Nutraceuticals from fruits and vegetables at a glance: A review. J. Biol. Sci., 13: 38-47.

Mahima, A.M. Ingle, A.K. Verma, R. Tiwari and K. Karthik *et al*., 2013b. Immunomodulators in day to day life: A review. Pak. J. Biol. Sci., 16: 826-843.

Mandukhail, S.U., N. Aziz and A.H. Gilani, 2010. Studies on antidyslipidemic effects of *Morinda citrifolia* (Noni) fruit, leaves and root extracts. Lipids Health Dis., Vol. 9. 10.1186/1476-511X-9-88

Massa, F., G. Marsicano, H. Hermann, A. Cannich and K. Monory *et al*., 2004. The endogenous cannabinoid system protects against colonic inflammation. J. Clin. Invest., 113: 1202-1209.

Mathivanan, N., G. Surendiran, K. Srinivasan, E. Sagadevan and K. Malarvizhi, 2005. Review on the current scenario of Noni research: Taxonomy, distribution, chemistry, medicinal and therapeutic values of *Morinda citrifolia*. Int. J. Noni Res., 1: 1-16.

Mathivanan, N., G. Surendiran, K. Srinivasan and K. Malarvizhi, 2006. Morinda pubescens JE Smith (*Morinda tinctoria* Roxb.) fruit extract accelerates wound healing in rats. J. Med. Food, 9: 591-593.

McClatchey, W., 2002. From polynesian healers to health food stores: Changing perspectives of *Morinda citrifolia* (Rubiaceae). Integr. Cancer Ther., 1: 110-120.

Mckoy, M.L., E.A. Thomas and O.R. Simon, 2002. Preliminary investigation of the anti-inflammatory properties of an aqueous extract from *Morinda citrifolia* (Noni). Proc. Western Pharmacol. Soc., 45: 76-78.

Midrarullah, H. Sher, Attaullah, Samiullah, Sikandar and M.S. Ali, 2014. Traditional uses of medicinal plants for the treatment of livestock ailments in Udigram Swat, Khyber Pakhtunkhwa, Pakistan. Res. Opin. Anim. Vet. Sci., 4: 138-141.

Millonig, G., S. Stadlmann and W. Vogel, 2005. Herbal hepatotoxicity: Acute hepatitis caused by a Noni preparation (*Morinda citrifolia*). Eur. J. Gastroenterol. Hepatol., 17: 445-447.

Mizaei-Aghsaghali, A., 2012. Importance of medical herbs in animal feeding: A review. Ann. Biol. Res., 3: 918-923.

Moorthy, N.K. and G.S. Reddy, 1970. Preliminary phytochemical and pharmacological study of *Morinda citrifolia* Linn. Antiseptic, 67: 167-171.

Morton, J.F., 1992. The ocean-going noni, or Indian mulberry (*Morinda citrifolia*, Rubiaceae) and some of its colorful relatives. Ecol. Bot., 46: 241-256.

Mpiana, P.T., D.S.T. Tshibangu, O.M. Shetonde and K.N. Ngbolua, 2007. *In vitro* antidrepanocytary actvity (anti-sickle cell anemia) of some congolese plants. Phytomedicine, 14: 192-195.

Mueller, B.A., M.K. Scott, K.M. Sowinski and K.A. Prag, 2000. Noni juice (*Morinda citrifolia*): Hidden potential for hyperkalemia? Am. J. Kidney Dis., 35: 310-312.

Murray, P.E., R.M. Farber, K.N. Namerow, S. Kuttler and F. Garcia-Godoy, 2008. Evaluation of *Morinda citrifolia* as an endodontic irrigant. J. Endodontics, 34: 66-70.

Muto, J., L. Hosung, A. Uwaya, F. Isami, M. Ohno and T. Mikami, 2010. *Morinda citrifolia* fruit reduces stress-induced impairment of cognitive function accompanied by vasculature improvement in mice. Physiol. Behav., 101: 211-217.

Natheer, S.E., C. Sekar, P. Amutharaj, M.S.A. Rahman and K.F. Khan, 2012. Evaluation of antibacterial activity of *Morinda citrifolia*, *Vitex trifolia* and *Chromolaena odorata*. Afr. J. Pharm. Pharmacol., 6: 783-788.

Nayak, B.S., G.N. Isitor, A. Maxwell, V. Bhogadi and D.D. Ramdath, 2007. Wound-healing activity of *Morinda citrifolia* fruit juice on diabetes-induced rats. J. Wound Care, 16: 83-86.

Nayak, B.S., S. Sandiford and A. Maxwell, 2009. Evaluation of the wound-healing activity of ethanolic extract of *Morinda citrifolia* L. leaf. Evidence-Based Complement. Altern. Med., 6: 351-356.

Nayak, S. and S. Mengi, 2010. Immunostimulant activity of noni (*Morinda citrifolia*) on T and B lymphocytes. Pharm. Biol., 48: 724-731.

Nayak, B.S., J.R. Marshall, G. Isitor and A. Adogwa, 2011. Hypoglycemic and hepatoprotective activity of fermented fruit juice of *Morinda citrifolia* (Noni) in diabetic rats. Evidence-Based Complementary Altern. Med. 10.1155/2011/875293

Nerurkar, P.V., A. Nishioka, P.O. Eck, L.M. Johns, E. Volper and V.R. Nerurkar, 2011. Regulation of glucose metabolism via hepatic forkhead transcription factor 1 (FoxO1) by *Morinda citrifolia* (noni) in high-fat diet-induced obese mice. Br. J. Nutr., 108: 218-228.

Nishioka, A. and P. Nerurkar, 2007. Effects of *Morinda citrifolia* (noni) on obesity and glucose tolerance in C57BL/6 mice. FASEB J., 21: A982-A982.

Nualsanit, T., P. Rojanapanthu, W. Gritsanapan, S.H. Lee, D. Lawson and S.J. Baek, 2012. Damnacanthal, a noni component, exhibits antitumorigenic activity in human colorectal cancer cells. J. Nutr. Biochem., 23: 915-923.

Okusada, K., K. Nakamoto, M. Nishida, W. Fujita-Hamabe, K. Kamiya, Y. Mizushina and T.S. Shogo, 2011. The antinociceptive and anti-inflammatory action of the CHCl3-soluble phase and its main active component, damnacanthal, isolated from the root of *Morinda citrifolia*. Biol. Pharm. Bull., 34: 103-107.

Owen, P.L., L.C. Martineau, D. Caves, P.S. Haddad, T. Matainaho and T. Johns, 2008. Consumption of guava (*Psidium guajava* L.) and noni (*Morinda citrifolia* L.) may protect betel quid-chewing Papua New Guineans against diabetes. Asia Pac. J. Clin. Nutr., 17: 635-643.

Palu, A.K., B. West and J. Jensen, 2005. Not all noni liquid dietary supplements are created equal. Am. J. Hematol., 79: 1-81.

Palu, A.K., A.H. Kim, B.J. West, S. Deng, J. Jensen and L. White, 2008. The effects of *Morinda citrifolia* L. (noni) on the immune system: Its molecular mechanisms of action. J. Ethnopharmacol., 115: 502-506.

Palu, A., S. Deng, B. West and J. Jensen, 2009. Xanthine oxidase inhibiting effects of Noni (*Morinda citrifolia*) fruit juice. Phytother. Res., 23: 1790-1791.

Palu, A., C. Su, B.N. Zhou, B. West and J. Jensen, 2010. Wound healing effects of noni (*Morinda citrifolia* L.) leaves: A mechanism involving its PDGF/A2A receptor ligand binding and promotion of wound closure. Phyto. Res., 24: 1437-1441.

Palu, A.K., B.J. West and J. Jensen, 2011. Noni-based nutritional supplementation and exercise interventions influence body composition. N. Am. J. Med. Sci., 30: 552-55.

Palu, A.K., B.J. West and C.J. Jensen, 2012. Noni seed oil topical safety, efficacy and potential mechanisms of action. J. Cosmet. Dermatol. Sci. Appl., 2: 74-78.

Pansuebchue, N., N. Soonthornchareonnon and K. Pattanapanyasat, 2002. Chemical study and immunostimulating activity of *Morinda citrifolia*. Thai J. Pharm. Sci., Vol. 26.

Pawlus, A.D., B.N. Su, W.J. Keller and A.D. Kinghorn, 2005. An anthraquinone with potent quinone reductase-inducing activity and other constituents of the fruits of *Morinda citrifolia* (Noni). J. Nat. Prod., 68: 1720-1722.

Potterat, O. and M. Hamburger, 2007. *Morinda citrifolia* (Noni) fruit-phytochemistry, pharmacology, safety. Planta Med., 73: 191-199.

Prapaitrakool, S. and A. Itharat, 2010. *Morinda citrifolia* Linn. for prevention of postoperative nausea and vomiting. J. Med. Assoc. Thai., 93: S204-S209.

Product Safety Labs, 2000. Guinea pig antigenicity study: Tahitian Noni puree, Tahitian Noni juice and Tahitian Noni Concentrate. Eurofins Scientific Inc., East Brunswick, NJ., USA.

Punjanon, T. and P. Nandhasri, 2005. Analgesic effect of the alcoholic extract from the fruits of *Morinda citrifolia*. Acta Hort., 678: 103-106.

Rahal, A., Mahima, A.K. Verma, A. Kumar and R. Tiwari *et al*., 2014a. Phytonutrients and nutraceuticals in vegetables and their multi-dimensional medicinal and health benefits for humans and their companion animals: A review. J. Biol. Sci., 14: 1-19.

Rahal, A., A. Kumar, V. Singh, B. Yadav, R. Tiwari, S. Chakraborty and K. Dhama, 2014b. Oxidative stress, prooxidants and antioxidants: The interplay. BioMed. Res. Int. 10.1155/2014/761264

Raj, R.K., 1975. Screening of indigenous plants for anthelmintic action against human *Ascaris Lumbricoides*: Part-II. Indian J. Physiol. Pharmacol., 19: 47-49.

Ross, I.A., 2001. Medical Plants of the World: Chemical Constituents, Traditional and Modern Medical Uses. Humana Press, New Jersey, ISBN-13: 9780896038776, Pages: 487.

Saludes, J.P., M.J. Garson, S.G. Franzblau and A.M. Aguinaldo, 2002. Antitubercular constituents from the hexane fraction of *Morinda citrifolia* Linn. (Rubiaceae). Phytother. Res., 16: 683-685.

Saminathan, M., R.B. Rai, G.J. Ranganath, K. Dhama and B.L. Jangir *et al*., 2013a. Evaluation of anticancerous activity of fuit juice of *Morinda citrifolia* in N-Methyl-N-Nitrosourea (NMU) induced mammary tumours in rats. Proceedings of the 30th Annual Conference of Indian Association of Veterinary Pathologists and National Symposium, November 21-23, 2013, Odisha, India, pp: 283.

Saminathan, M., R.B. Rai, G.J. Ranganath, K. Dhama and B.L. Jangir *et al*., 2013b. Evaluation of anticancerous activity of leaf extract of *Morinda citrifolia* in N-Methyl-N-Nitrosourea (NMU) induced mammary tumours in rats. Proceedings of the 30th Annual Conference of Indian Association of Veterinary Pathologists and National Symposium, November 21-23, 2013, Odisha, India, pp: 49.

Saminathan, M., R.B. Rai, K. Dhama, G.J. Ranganath, M. Palanivelu, G. Rajesh and S.S. Kumar, 2013c. Evaluation of chemopreventive effect of *Morinda citrifolia* fruit juice in N-Methyl-N-Nitrosourea (NMU) induced mammary tumours in rats. Proceedings of the 27th Annual Conference on National Symposium and Indian Association of Veterinary Microbiologists, Immunologists, December 13-15, 2013, Uttar Pradesh, India, pp: 20-21.

Saminathan, M., R.B. Rai, V. Murugesan, S.S. Kumar, M. Baqir and P.L. Lalruatfela, 2014. Induction of cataract by N-methyl-N-nitrosourea (NMU) and anti-cataract activity of *Morinda citrifolia* fruit juice and ethanolic leaf extract in rats. Indian Vet. J., (In Press).

Samoylenko, V., J. Zhao, D.C. Dunbar, I.A. Khan, J.W. Rushing and I. Muhammad, 2006. New constituents from Noni (*Morinda citrifolia*) Fruit Juice. J. Agric. Food Chem., 54: 6398-6402.

Sang, S., X. Cheng, N. Z hu, R.E. Stark and V. Badmaev *et al*., 2001. Flavonol glycosides and novel iridoid glycoside from the leaves of *Morinda Citrifolia*. J. Agric. Food Chem., 49: 4478-4481.

Sang, S., M. Wang, K. He, G. Liu and Z. Dong *et al*., 2002. Chemical components in Noni fruits and leaves (*Morinda citrifolia* L.). In: Quality Management of Nutraceuticals, Ho, C.T. and Q.Y. Zheng (Eds.). American Chemistry Society, Washington, DC., pp: 134-150.

Sang, S., G. Liu, K. He, N. Zhu and Z. Dong *et al*., 2003. New unusual iridoids from the leaves of noni (*Morinda citrifolia* L.) show inhibitory effect on ultraviolet B-induced transcriptional activator protein-1 (AP-1) activity. Bioorg. Med. Chem., 11: 2499-2502.

Schripsema, J., G.P. Caprini and D. Dagnino, 2006. Revision of the structures of citrifolinin a, citrifolinoside, yopaaoside a, yopaaoside b, and morindacin, iridoids from *Morinda citrifolia* L. and *Morinda coreia*. Ham. Org. Lett., 9: 5337-5340.

Selvam, P., K. Raj, V. Vimisha, R. Harikrishnan, K.S. Sarija and R. Umalekshmi, 2009. Antimicrobial activity of fruit extracts of *Morinda citrifolia*. J. Applied Chem. Res., 10: 61-63.

Serafini, M.R., R.C. Santos, A.G. Guimaraes, J.P. Dos Santos and A.D. da Conceicao Santos *et al*., 2011. *Morinda citrifolia* Linn leaf extract possesses antioxidant activities and reduces nociceptive behavior and leukocyte migration. J. Med. Food, 14: 1159-1166.

Siddiqui, B.S., F.A. Sattar, S. Begum, T. Gulzara and F. Ahmad, 2006. New anthraquinones from the stem of *Morinda citrifolia* Linn. Nat. Prod. Res., 20: 1136-1144.

Singh, D.R. and R.B. Rai, 2007. *Morinda citrifolia* Linn.: An important fruit tree of Andaman and Nicobar Islands. Nat. Prod., Radiance, 6: 62-65.

Singh, D.R., 2012. *Morinda citrifolia* L. (Noni): A review of the scientific validation for its nutritional and therapeutic properties. J. Diabetes Endocrinol., 3: 77-91.

Solomon, N., 1999. The Noni Phenomenon. Direct Source Publishing, Utah, USA.

Song, H.S., S.H. Park, M.S. Ko, J.M. Jeong, U.D. Sohn and S.S. Sim, 2010. *Morinda citrifolia* inhibits both cytosolic Ca^{2+}-dependent phospholipase A_2- and secretory Ca-dependent phospholipase A_2. Korean J. Physiol. Pharmacol., 14: 163-167.

Srivastava, M. and J. Singh, 1993. A new anthraquinone glycoside form *Morinda citrifolia*. J. Pharmacol., 31: 182-184.

Stadlbauer, V., P. Fickert, C. Lackner, J. Schmerlaib, P. Krisper, M. Trauner and R.E. Stauber, 2005. Hepatotoxicity of noni juice: Report of two cases. World J. Gastroenterol., 11: 4758-4760.

Stoner, G.D., LS. Wang, C. Seguin, C. Rocha, K. Stoner, S. Chiu and A.D. Kinghorn, 2010. Multiple berry types prevent *N*-nitrosomethylbenzylamine-induced esophageal cancer in rats. Pharm. Res., 27: 1138-1145.

Su, C., M.Y. Wang, D. Nowicki, J. Jensen and G. Anderson, 2001. Selective COX-2 inhibition of *Morinda citrifolia* (Noni) *in vitro*. Proceedings of the The 7th Annual Conference on Eicosanoids and other Bioactive Lipids in Cancer, Inflammation and Related Disease, October 14-17, 2001, Loews Vanderbilt Plaza, Nashville, Tennessee, USA.

Su, B.N., A.D. Pawlus, H.A. Jung, W.J. Keller, J.L. McLaughlin and A.D. Kinghorn, 2005. Chemical constituents of the fruits of *Morinda citrifolia* (noni) and their antioxidant activity. J. Nat. Prod., 68: 592-595.

Sundarrao, K., I. Burrows, M. Kuduk, Y.D. Yi, M.H. Chung, N.J. Suh and I.M. Chang, 1993. Preliminary screening of antibacterial and antitumor activities of Papua New Guinean native medicinal plants. Pharm. Biol., 31: 3-6.

Sunder, J., S. Jeyakumar, T. Sujatha and A. Kundu, 2013. Effect of feeding of morical: A herbal based supplement on production and egg quality in Japanese quail. Adv. Anim. Vet. Sci., 1: 157-160.

Sunder, J., T. Sujatha, N. Pazhamivel, A. Kundu and M.S. Kundu, 2014. Effect of *Morinda citrifolia* fruit juice and lactobacillus acidophilus on broiler duodenal morphology. Adv. Anim. Vet. Sci., 2: 28-30.

Takahashi, T., K. Kozaki, Y. Yatabe, H. Achiwa and T. Hida, 2002. Increased expression of COX-2 in the development of human lung cancer. J. Environ. Pathol. Toxicol. Oncol., 21: 177-181.

Takashima, J., Y. Ikeda, K. Komiyama, M. Hayashi, A. Kishida and A. Ohsaki, 2007. New constituents from the leaves of *Morinda citrifolia*. Chem. Pharm. Bull., 55: 343-345.

Tarasiuk, J., B. Stefanska and E. Borowski, 1996. The direct reduction of cytochrome c by some anthraquinone antitumor compounds. Anticancer Drug Des., 11: 183-192.

Taskin, E.I., K. Akgun-Dar, A. Kapucu, E. Osanc, H. Dogruman, H. Eraltan and E. Ulukaya, 2009. Apoptosis-inducing effects of *Morinda citrifolia* L. and doxorubicin on the Ehrlich ascites tumor in Balb-c mice. Cell Biochem. Funct., 27: 542-546.

Tepsuwan, A. and W.R. Kusamran, 1977. Effect of the leaves of Siamese cassia, Indian mulberry and Asiatic pennywort on the metamobilizing enzymes of chemical carcinogens in rat liver. Bull. Dept. Med. Serv., 22: 425-437.

Thani, W., O. Vallisuta, P. Siripong and N. Ruangwises, 2010. Anti-proliferative and antioxidative activities of Thai noni/Yor (*Morinda citrifolia* Linn.) leaf extract. Southeast Asian J. Trop. Med. Public Health, 41: 482-489.

Thomson, R.H., 1971. Naturally Occurring Quinones. Academic Press, New York.

Tiwari, R.D. and J. Singh, 1977. Structural study of the anthraquinone glycosides from the flowers of *Morinda citrifolia*. J. Indian Chem. Soc., 54: 429-430.

Tiwari, R., A. Latchumikanthan, R.K. Yadav and K. Dhama, 2012. Herbal and traditional botanical medicines for safeguarding animal and human health. Livestock Line, 6: 29-33.

Tiwari, R., S. Chakraborty, K. Dhama, S. Rajagunalan and S.V. Singh, 2013a. Antibiotic resistance-an emerging health problem: Causes, worries, challenges and solutions: A review. Int. J. Curr. Res., 5: 1880-1892.

Tiwari, R., S. Chakraborty and K. Dhama, 2013b. Miracle of herbs in antibiotic resistant wounds and skin infections: Treasure of nature-a review/ perspective. Pharm. Sci. Monitor, 4: 214-248.

Tiwari, R., K. Dhama, S. Chakraborty, A. Kumar, A. Rahal and S. Kapoor, 2014a. Bacteriophage therapy for safeguarding animal and human health: A review. Pak. J. Biol. Sci., 17: 301-315.

Tiwari, R., A.K. Verma, S. Chakraborty, K. Dhama and S.V. Singh, 2014b. Neem (*Azadirachta indica*) and its potential for safeguarding health of animals and humans: a review. J. Biol. Sci., 14: 110-123.

Tiwari, R., S. Chakraborty, K. Dhama, M.Y. Wani, A. Kumar and S. Kapoor, 2014c. Wonder world of phages: Potential biocontrol agents safeguarding biosphere and health of animals and humans-current scenario and perspectives. Pak. J. Biol. Sci., 17: 316-328.

Tiwari, R., S. Chakraborty, M. Saminathan, K. Dhama and S.V. Singh, 2014d. Ashwagandha (*Withania somnifera*): Role in safeguarding health, immunomodulatory effects, combating infections and therapeutic applications: A review. J. Biol. Sci., 14: 77-94.

Umashanker, M. and S. Shruti, 2011. Traditional Indian herbal medicine used as antipyretic, antiulcer, anti-diabetic and anticancer: A review. Int. J. Res. Pharmacy Chem., 1: 1152-1159.

Umezawa, K., 1992. Isolation of 1-methoxy-2-foremyl-3-hydroxyanthraquinone from M citrifolia and neoplasm inhibitors containing the same. Japan Kokai Tokyo. Applied, 92: 311-317.

Usha, R., S. Sashidharan and M. Palamiswamy, 2010. Antimicrobial activity of a rarely known species, *Morinda citrifolia* L. Ethanobotanical Leafl., 14: 306-311.

Wanchai, A., J.M. Armer and B.R. Stewart, 2010. Complementary and alternative medicine use among women with breast cancer: A systematic review. Clin. J. Oncol. Nursing, 14: E45-E55.

Wang, M., H. Kikuzaki, K. Csiszar, C.D. Boyd and A. Maunakea *et al*., 1999. Novel trisaccharide fatty acid ester identified from the fruits of *Morinda citrifolia* (Noni). J. Agric. Food Chem., 47: 4880-4882.

Wang, M., H. Kikuzaki, Y. Jin, N. Nakatani and N. Zhu *et al*., 2000. Novel glycosides from Noni (*Morinda citrifolia*). J. Nat. Prod., 63: 1182-1183.

Wang, M.Y. and C. Su, 2001. Cancer preventive effect of *Morinda citrifolia* (Noni). Ann. N. Y. Acad. Sci., 952: 161-168.

Wang, M.Y., B.J. West, C.J. Jensen, D. Nowicki, C. Su, A.K. Palu and G. Anderson, 2002a. *Morinda citrifolia* (Noni): A literature review and recent advances in noni research. Acta Pharmacol. Sin., 12: 1127-1141.

Wang, M.Y., D. Nowicki and G. Anderson, 2002b. Protective effect of *Morinda citrifolia* on hepatic injury induced by a liver carcinogen. Proceedings of the 93rd Annual Meeting of American Association for Cancer Research, Volume 43, April 6-10, 2002, San Francisco, CA., USA., pp: 477.

Wang, M.Y., G.L. Anderson and D. Nowicki, 2002c. Preventative effect of *Morinda citrifolia* (Noni) at the initiation stage of mammary breast carcinogenesis induced by 7,12-dimethylbenzo(a) anthracene (DMBA) in female Sprague-Dawley (SD) rats. Cancer Epidemiol. Biomarkers Prev., 11: 1218S-1218S.

Wang, M.Y., D. Nowicki, G. Anderson, J. Jensen and B. West, 2008. Liver protective effects of *Morinda citrifolia* (Noni). Plant Foods Human Nutr., 63: 59-63.

Wang, M.Y., M.N. Lutfiyya, V. Weidenbacher-Hoper, G. Anderson, C.X. Su and B.J. West, 2009a. Antioxidant activity of noni juice in heavy smokers. Chem. Cent. J., Vol. 3. 10.1186/1752-153X-3-13

Wang, M.Y., L. Peng, M.N. Lutfiyya, E. Henley, V. Weidenbacher-Hoper and G. Anderson, 2009b. *Morinda citrifolia* (noni) reduces cancer risk in current smokers by decreasing aromatic DNA adducts. Nutr. Cancer, 61: 634-639.

Wang, C.Y., C.C. Ng, H. Su, W.S. Tzeng and Y.T. Shyu, 2009c. Probiotic potential of noni juice fermented with lactic acid bacteria and bifidobacteria. Int. J. Food Sci. Nutr., 60: 98-106.

Wang, M.Y., L. Peng, G. Anderson and D. Nowicki, 2013. Breast cancer prevention with *Morinda citrifolia* (noni) at the initiation stage. Funct. Foods Health Dis., 3: 203-222.

Wargovich, M.J., C. Woods, D.M. Hollis and M.E. Zander, 2001. Herbals, cancer prevention and health. J. Nutr., 131: 3034S-3036S.

Wei, L.S., N.M. Sengm, C.T. Sengm, W. Wee and M. Shazili, 2008. Antimicrobial properties of tropical plants against 12 pathogenic bacteria isolated from aquatic organisms. Afr. J. Biotechnol., 7: 2275-2278.

West, B.J., C.J. Jensen and J. Westendorf, 2006. Noni juice is not hepatotoxic. World J. Gastroenterol., 12: 3616-3619.

West, B.J., S. Deng and A.K. Palu, 2009. Antioxidant and toxicity tests of roasted noni (*Morinda citrifolia*) leaf infusion. Int. J. Food Sci. Technol., 44: 2142-2146.

West, B.J., C.J. Jensen, A.K. Palu and S. Deng, 2011. Toxicity and antioxidant tests of *Morinda citrifolia* (noni) seed extract. Adv. J. Food Sci. Technol., 3: 303-307.

West, B.J., S.K. Palmer, S. Deng and A.K. Palu, 2012. Antimicrobial activity of an Iridoid rich extract from *Morinda citrifolia* fruit. Curr. Res. J. Biol. Sci., 4: 52-54.

Westendorf, J., 2002a. Investigation of Tahitian Noni Juice in the *in vivo-in vitro* UDS assay in rat hepatocytes. Institute of Experimental and Clinical Toxicology, University of Medical, School of Hamburg-Eppendorf, GDR.

Westendorf, J., 2002b. Investigation of Tahitian Noni_ juice in the V79-HPRT-test. Institute of Experimental and Clinical Toxicology, University of Medical, School of Hamburg-Eppendorf, GDR.

Westendorf, J., K. Effenberger, H. Iznaguen and S. Basar, 2007. Toxicological and analytical investigations of noni (*Morinda citrifolia*) fruit juice. J. Agric. Food Chem., 55: 529-537.

Wong, D.K., 2004. Are immune responses pivotal to cancer patient's long term survival? Two clinical case-study reports on the effects of *Morinda citrifolia* (Noni). Hawaii Med. J., 63: 182-184.

Yakout, S.M., S.H. Abd-Alrahman, A. Mostafa and M.M. Salem-Bekhit, 2013. Antimicrobial effect of seed ethanolic extract of Coriander. J. Pure Applied Microbiol., 7: 459-463.

Yamaguchi, S., J. Ohnishi, M. Sogawa, I. Maru, Y. Ohta and Y. Tsukada, 2002. Inhibition of angiotensin I converting enzyme by noni (*Morinda citrifolia*) juice. J. Jap. Soc. Food Sci. Technol., 49: 624-627.

Yarney, J., A. Donkor, S.Y. Opoku, L. Yarney, I. Agyeman-Duah, A.C. Abakah and E. Asampong, 2013. Characteristics of users and implications for the use of complementary and alternative medicine in Ghanaian cancer patients undergoing radiotherapy and chemotherapy: A cross-sectional study. BMC Complement. Altern. Med., Vol. 13 10.1186/1472-6882-13-16

Youngken, H.W., 1958. A study of the root of *Morinda citrifolia* Linn, I. J. Am. Pharm. Assoc., 47: 162-165.

Youngken, H.W., H.J. Jenkins and C.L. Butler, 1960. Studies on *Morinda citrifolia* L. II. J. Am. Pharm. Assoc., 49: 271-273.

Younos, C., A. Rolland, J. Fleurentin, M.C. Lanhers, R. Misslin and F. Mortier, 1990. Analgesic and behavioural effects of *Morinda citrifolia*. Planta Med., 56: 430-434.

Yuce, B., V. Gulberg, J. Diebold and A.L. Gerbes, 2006. Hepatitis induced by Noni juice from *Morinda citrifolia*: A rare cause of hepatotoxicity or the tip of the iceberg? Digestion, 73: 167-170.

Zhang, X., J. Li, D.K. Wong, T.E. Wagner and Y. Wei, 2009. Fermented noni exudate-treated dendritic cells directly stimulate B lymphocyte proliferation and differentiation. Oncol. Rep., 21: 1147-1152.

Zin, Z.M., A. Abdul-Hamid and A. Osman, 2002. Antioxidative activity of extracts from Mengkudu (*Morinda citrifolia* L.) root, fruit and leaf. Food Chem., 78: 227-231.