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REVIEW

Morinda citrifolia (Noni): A comprehensive review on its industrial uses, pharmacological activities, and clinical trials

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Abstract Traditional medical practitioners in Hawaii and Polynesia have used *Morinda citrifolia* L. (Noni) for centuries to cure or prevent varieties of illnesses. The popularity of *M. citrifolia* as a dietary supplement, a food functional ingredient, or as a natural health enhancer is increasing throughout the world. *M. citrifolia* contains phytochemicals that own antibacterial, antiviral, anti-fungal, antitumor, anthelminthic, analgesic, hypotensive, anti-inflammatory and immune enhancing effects. Moreover, the increasing vogue of *M. citrifolia* has attracted industries to employ it as a part of various products and for wide applications such as a natural source of medicines and chemical reagents as well as a green insecticidal. The wide spread of *M. citrifolia* in tropical climate of the globe, from USA to Brazil reaching to Tahiti, Malaysia and Australia, contributed in enriching its uses and potentials due to the variation in harvest locations. *M. citrifolia* parts including fruits, seeds, barks, leaves, and flowers are utilized on their own for individual nutritional and therapeutical values, however, the fruit is considered to contain the most valuable chemical compounds. This review discusses in details the industrial uses and the pharmacological activities of *M. citrifolia* fruit, seed, leaf and root, along with their isolated phytochemical compounds, through describing the conducted *in vitro* and *in vivo* studies as well as clinical data.

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Contents

1. Introduction

Morinda citrifolia is the scientific name of the commercially known plant Noni. The name *Morinda citrifolia* is also referring to the botanical name which is originally derived from the two Latin words "morus" imputing to mulberry, and "indicus" imputing to Indian, it belongs to the Rubiaceae family (Nelson, 2006). In Hawaii *M. citrifolia* called Noni, whereas in India it is called Indian mulberry and nuna, or ach. Malaysians call it mengkudu and in Southeast Asia it is called nhaut, while in the Caribbean, it is called the painkiller bush or cheese fruit (Chan-Blanco et al., 2006).

Currently, there are two recognized varieties of *M. citrifolia* (*M. citrifolia* var. citrifolia and *M. citrifolia* var. bracteata) and one cultivar (*M. citrifolia* cultivar Potteri). The most commonly found variety is *M. citrifolia* var. citrifolia, with the greatest health and economic importance. Traditional healers can recognize these varieties by the leaf size and shape, in addition to the fruit odor; however, most research has not distinguished between the different *M. citrifolia* varieties yet (Pawlus and Kinghorn, 2007).

In the early 1990s, the first commercialized products derived from *M. citrifolia* fruit in USA were lunched (Santhosh Aruna et al., 2013). Later, in 1996, *M. citrifolia* juice was introduced as a wellness drink, due to numerous reports stating its therapeutic effects (Kamiya et al., 2009). In 2003, the fruit juice of *M. citrifolia* was approved as a novel food by the European commission; however, this approval was limited to the Tahitian fruit juice and not to other products (Potterat and Hamburger, 2007). Amazingly, even with the absence of specific mechanisms of action for the claimed *M. citrifolia* effects (Kamiya et al., 2009), yet the market annual sales of *M. citrifolia* products claimed to reach up to US $ 1.3 billion (Potterat and Hamburger, 2007).

2. Chemical constituents

Almost 200 phytochemicals were identified and isolated from different parts of *M. citrifolia* (Singh, 2012), however, up to date, the complete phytochemical composition of the *M. citrifolia* has not been fully reported. The chemical compositions and their concentrations are related significantly not only to

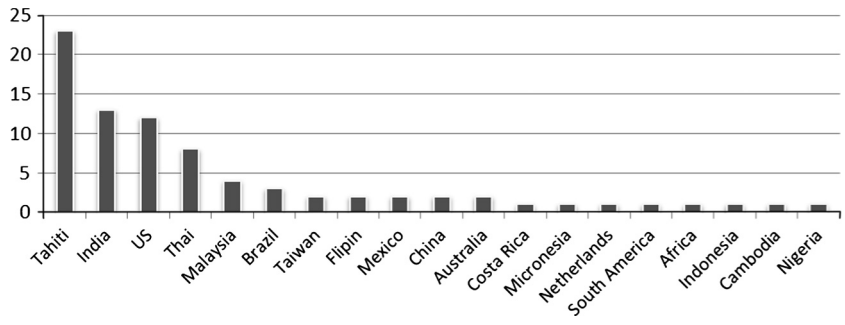

Figure 1 The most studied harvest locations and brands of *M. citrifolia* all over the world based on our review.

the part of the plant but also to its country of origin (Deng et al., 2010), and to the harvesting season (Iloki Assanga et al., 2013), however, the optimization of agricultural/post-harvest practices or processing technologies have been neglected (Chan-Blanco et al., 2006). Fig. 1 illustrates the most studied harvesting locations and brands of the *M. citrifolia* around the world.

Under favorable conditions, the plant can bear fruit about nine months to one year after planting, where *M. citrifolia* plots are usually harvested two or three times per month and one hectare of *M. citrifolia* can yield around 35 tons of juice. Fruits are usually harvested at different stages, but most processors buy them at the "hard white" stage for juice production (Chan-Blanco et al., 2006). The evolution of fruits phytochemical constituents, as well as isolation and identification of the bioactive compounds with their activity upon the different stages is not fully addressed yet. In one study, Mexican *M. citrifolia* fruit was assessed during its different maturity stages (1–4) for its phytochemical constituents, finding that it has high levels of soluble protein, carbohydrates, ascorbic acid, rutin and phenols, with an independent profile of season (Lewis Luján et al., 2014). It was suggested that the exposure of the fruits to light or high temperatures immediately after harvest does not affect their overall quality (Chan-Blanco et al., 2006), yet, precise studies are required to specify under which temperature and light conditions fruit quality remains stable.

According to a Malaysian medicinal plants book, *M. citrifolia* chemical constituents are: 5,7-Acacetin-7-*O*-β-*D*(+)-glycopyranoside, ajmalicine isomers, alizarin, asperuloside, asperulosidic acid, chrysophanol (1,8-dihydroxy-3-methylanthraquinone), damnacanthol, digoxin, 5,6-dihydroxylucidin, 5,6-dihydroxylucidin-3-β-primeveroside, 5,7-dimethylapigenin- 4′-*O*-β-*D*(+)-galacto pyranoside, lucidin, lucidin-3-β-primeveroside, 2-methyl-3,5,6-trihydroxy anthraquinone, 3-hydroxymorindone, 3-hydroxymorindone-6-β-primereroside, α-methoxyalizarin, 2-methyl-3,5,6-trihydroxyanthraquinone-6-β-primeveroside, mono-ethoxyrubiadin, morindadiol, morindin, morindone (1,5,6-trihydroxy-2-methylanthraquinone), morindone-6-β-primeveroside, nordamnacanthal, quinoline, rubiadin, rubiadin 1-methyl ether, saronjidiol, ursolic acid, alkaloids, anthraquinones and their glycosides, caproic acid, caprylic acid, fatty acids and alcohols (C5-9), flavones glycosides, flavonoids, glucose (β-D-glucopyranose), indoles, purines, and β-sitosterol (Krishnaiah et al., 2012).

Till now, 51 volatile compounds were identified in the *M. citrifolia* ripe fruit, without clear specification of the fruit harvest locations and stage conditions. These compounds include organic acids such as octanoic and hexanoic acids, alcohols including 3-methyl-3-butene-1-ol, and esters like methyl octanoate, and methyl decanoate, as well as ketones as 2-heptanone, and lactones (E)-6-dodeceno--lactone (Farine et al., 1996).

The lyophilized Tahitian *M. citrifolia* fruit juice contains trace elements including manganese (6.11 ± 0.21 g L^{-1}), copper (2.22 ± 0.31 g L^{-1}), molybdenum (0.160 ± 0.004 g L^{-1}), and cobalt (0.0474 ± 0.0006 g L^{-1}) (Rybak and Ruzik, 2013). Minerals including potassium, sulfur, calcium, phosphorus and traces of selenium were reported in the fruit juice of *M. citrifolia* from Cambodia (Chunhieng, 2003), while vitamins such as ascorbic acid and pro-vitamin A were detected in the Indian and Micronesian *M. citrifolia* fruit (Krishnaiah et al., 2012; Shovic and Whistler, 2001). Thai concentrated *M. citrifolia* fruit juice total fatty acid content reported to be 149 ± 8.735 mg/100 g, and its amino acids content was as follows: glutamate, alanine, arginine (range 20–26 mg/100 g); glycine, cysteine, methionine, tyrosine, phenylalanine, lysine (range 9.0–14.5 mg/100 g) and threonine, serine, valine, isoleucine, leucine (range 3–6.5 mg/100 g). The highest and lowest content was aspartate 34.9 (mg/100 g) and histidine (2.0 mg/100 g), respectively (Rawangban et al., 2011). Phenolic compounds are also dominating in the fruit of *M. citrifolia*, including damnacanthal, scopoletin, morindone, alizarin, aucubin, nordamnacanthal, rubiadin, rubiadin-1-methyl ether, and anthraquinone glycosides (Mahanthesh et al., 2013). A phytochemical screening for the presence of secondary metabolite was conducted on the Indian *M. citrifolia* fruit aqueous, ethanol and methanol extracts detecting steroids, cardiac glycosides, phenol, tannins, terpenoids, alkaloids, carbohydrates, flavonoids, reducing sugar, lipids and fats in all types of extracts, while saponins in aqueous and methanol extracts, as well as acidic compounds in aqueous extract only (Nagalingam et al., 2012), Brazilian *M. citrifolia* fresh fruit pulp showed the presence of reducing sugars mainly glucose, fructose and sucrose, and suggested large amount of minerals (Da Silva et al., 2012). Recently, phytochemical screenings of different commercial Nigerian *M. citrifolia* juice extracts confirmed the presence of secondary metabolites such as reducing sugars, phenols, tannins, flavonoids, saponins, glycosides, steroids, terpenoids, alkaloids, and acidic components, and the study also reported the absence of anthraquinones, phlobatannins and resins (Anugweje, 2015). Brazilian aqueous extracts from *M. citrifolia* leaves phytochemical screening showed the presence of alkaloids, coumarins, flavonoids, tannins, saponins, steroids, and triterpenoids (Serafini et al.,

2011). The phytochemical studies of Malaysian *M. citrifolia* roots dichloromethane extract have resulted in the isolation and characterization of ten anthraquinone including: I-hydroxy-2methylanthraquinone, nordamnacanthal, damnacanthal, morindone, rubiadin-I-methyl ether, soranjidiol, rubiadin and damnacanthol (Saidan, 2009). Furthermore screening led to the identification of twenty compounds from the Chinese dried *M. citrifolia* seeds ethanol extract including daucosterol, ursolic acid, 19-hydroxyl-ursolic acid, 1,5,15-trimethylmorindol, 5,15-dimethyl-morindol, scopoletin, 3,3′-bisdemethylpinoresinol, 3,4,3′4′-tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone, americanin D, americanin A, americanin, isoprincepin, deacetyl- asperulosidic acid, loganic acid, asperulosidic acid, rhodolatouside, quercetin-3-*O*-α-*L*-rhamnopyranosyl-(1→6)-β-*D*-glucopyranoside, 4-ethyl-2-hydroxyl-succinate, 5-hydroxymethyl-2-furancarboxaldehyde, 3-methylbut-3-enyl-6-*O*-β-*D*-glucopyranosyl-β-*D*-glucopyranoside (Yang et al., 2009). For a novel and accurate outcomes, *M. citrifolia* studies quality can be improved through developing identification markers for its chemical components and characterize their chemical structures on TLC, HPTLC, HPLC, NMR spectroscopy (Saminathan et al., 2014). Table 1 summarizes the major chemical components of *M. citrifolia* different organs and their phytochemical classification and proven activities.

3. Industrial uses

M. citrifolia is involved in various green industrial sectors, including the following:

3.1. Natural preservative

M. citrifolia is recognized as a novel food ingredient under the name of Noni fruit puree (Efsa, 2009), however, food industry is mainly interested in Tahitian *M. citrifolia* due to its leaf, fruit and root antioxidant properties which are similar to vitamin E, and they also contain butylated hydroxytoluene (a phenol derivative) which has a natural preservative activity (Zin et al., 2002), and was effective in blocking warmed-over flavor in formerly stewed beef pies, by reducing lipid oxidation, as well as enhancing color stability and the shelf life of the final aerobically wrapped pies (Nathan et al., 2012). Despite of the proven *in vivo* safety of Tahitian *M. citrifolia* as a food ingredient (West et al., 2011), yet, the unpleasant off-taste of its puree might restrict its use as a preservative (Nathan et al., 2012). Interestingly, the addition of maltodextrin to the *M. citrifolia* pulp powder (Fabra et al., 2011), as well as to the spray dried seedless *M. citrifolia* fruit powder, successfully eliminated *M. citrifolia* bad smell and unpleasant taste, and increased its resistance to humidity (Anwar and Arsyadi, 2007), yet no study has observed the effect of maltodextrin complexation with *M. citrifolia* on enhancing its preservative effects with less or no distasteful flavor and odor.

3.2. M. citrifolia juice

The *M. citrifolia* juice products are a corner stone within its industrial sector. Fresh Noni juice is obtained by compressing the fruits immediately after harvesting (Newton, 2002), whereas homemade juice is prepared by letting the fruits decompose naturally (Brown, 2012), and commercial juice is made by fruit fermentation (Nelson, 2006). The chemical composition of *M. citrifolia* juice depends majorly upon the method of juice extraction. The physiochemical screening of the fermented Indian *M. citrifolia* fruit showed that it contains anthraquinones, saponins, and scopoletin (Satwadhar et al., 2011), while the bioactive screening of the Thai *M. citrifolia* fermented fruit juice recorded a superior vitamins content (C, B1, B2, B3, B12) in comparison to the vitamin content of the American *M. citrifolia* fruit, it was also containing alkaloids, anthraquinones, antioxidants, essential oils, flavonoids, saponins, scopoletin and sugars, and these results were congruent to the content of the commercial Thai fruit juice content (Nandhasri et al., 2005). To overcome problems associated with transport and storage, *M. citrifolia* juice was concentrated (Valdés et al., 2009). However, its processing methods and storage conditions influence juice stability. For example, heat affects the organoleptic nature of the concentrated *M. citrifolia* juice (Valdés et al., 2009), while a fermentation process for 90 days caused about 90% reduction of its radical-scavenging activity (RSA), and a dryness at 50 °C reduced the RSA by 20%, as for freshly prepared *M. citrifolia* juice, the RSA is decreased by more than 90% if it is stored at 24 °C for 90 days, whereas the RSA of the juice or powder is reduced by 10–55% when stored for 90 days at −18 °C and 4 °C, respectively (Yang et al., 2007). *M. citrifolia* beverages taste was enhanced in an economic juice recipe which was prepared by mixing 10% of fermented juice extract of an Indian *M. citrifolia* ripe fruit with 14% total suspended solids (T.S.S.) and 2% ginger extract (Joshi et al., 2012). Only one published research has studied the stability of *M. citrifolia* final products where the concentrated Thai fruit juices and its dried powders showed stability for 451 days (Rawangban et al., 2011). This is indicating that stability factor should be considered more in future studies.

Many of *M. citrifolia* commercial juice parameters should be fixed including its concentrations variations, the prevalent bioactive component in the fermented products, pasteurization impact on these bioactive compounds, and the specification regarding the juice source for being fermented, and for how long, and pasteurized or unpasteurized (Brown, 2012).

3.3. M. citrifolia probiotic juice

Seedless fermented *M. citrifolia* fruit juice from Taiwan showed potentials for the production of probiotic which was produced by reacting *M. citrifolia* juice (as a raw substrate) with lactic acid bacteria (*Lactobacillus casei* and *Lactobacillus plantarum*) or Bifido-bacteria (*Bifidobacterium longum*). After 48 h. of fermentation, all tested strains grew well on *M. citrifolia* juice and colony-forming reached nearly 10^9 units/ml. *Lactobacillus casei* produced less lactic acid than *Bifidobacterium longum*, whereas *Lactobacillus plantarum*, *Bifidobacterium longum* and *Lactobacillus plantarum* survived under low-pH conditions in a cold storage at 4 °C for a period of 4 weeks. The results indicated that *Bifidobacterium longum* and *Lactobacillus plantarum* bacteria are selective for producing a probiotic *M. citrifolia* juice (Wang et al., 2009a).

Table 1 A list of identified compounds and their activities in fruit, leaf and root of *M. citrifolia*.

Plant part	Compound	Chemical classification	Activities/uses	Reference
Leaf	Americanin A	Lignan	Larvicidal, antioxidant	Kovendan et al. (2012) and Kovendana et al. (2014)
	Proline Leucine Cysteine Methionine Glycine Histidine Isolucine Glutamic acid Phenylalanine Serine Threonine Tryptophan Tyrosine Arginine Valine	Amino acid	A source of essential and conditional amino acids	Shovic and Whistler (2001), Elkins (1998) and Sang et al. (2001)
	Quercetin-3-*O*-*β*-*D*-glucopyranoside Quercetin-3-O-a-L-rhamnopyranosyl-(1-6)-*β*-*D*-glucopyranoside	Flavonoids	Antimicrobial	Chan-Blanco et al. (2006) and Sang et al. (2001)
	Ursolic acid	Triterpenoids	Anticancer	Elkins (1998), Sang et al. (2001) and Dittmar (1993)
	β-sitosterol	Sterols	Lowering blood cholesterol and stimulating immune system	Shovic and Whistler (2001) and Wang et al. (2002)
	Citrifolinoside B	Iridois	Suppressing UVB-induced Activator Protein-1 (AP-1) activity	Sang et al. (2001)
	Kaempferolm *3-O-β-D*-glucopyranosyl-(1-2)-a-Lrhamnopyranosyl-*(1-6)-β-D*-galactopyranoside	Chlorophyll derivatives	Might be involved in lowering blood glucose levels	Sang et al. (2001)
	Scopoletin	A coumarin derivative	Anti-proliferative effects on cancer	Kamiya et al. (2010) and Mohd Zin et al. (2007)
Fruit	Octanoic (caprylic) acid Hexanoic acid Caproic acid	Fatty acid	Antifungal Antifungal, Antioxidant Antifungal	Elkins (1998), Dittmar (1993), Wang et al. (1999, 2002), Mohd Zin et al. (2007), Jayaraman et al. (2008), Liu et al. (2001) and Zhang et al. (2014)
	Vitamin C Vitamin E Niacin	Vitamins	Antioxidant Nutritional Nutritional	Zin et al. (2002) and West et al. (2011)
	Manganese, Selenium	Trace elements	Nutritional	Zin et al. (2002) and West et al. (2011)
	Asperulosidic acid	Iridoid	Antibacterial	West et al. (2012)
	Quercetin	Flavonoids	Anti-inflammatory, Lipoxygenase inhibitor	Elkins (1998), Sang et al. (2001), Liu et al. (2001), Morton (1992), Yu (2004) and Deng et al. (2007b)
	2,6-di-*O*-*(β-D*-glucopyranosyl 1-O-octanoyl-*β-D* glucopyranose 6-*O*-*(β-D*-glucopyranosyl-1-O-octanoyl-*β-D* glucopyranose	Fatty acid ester	Melanogenesis suppression, antioxidant	Nelson (2006), Kamiya et al. (2010), Jayaraman et al. (2008) and Lin et al. (2013) Liu et al. (2001), Wang et al. (1999), Zhang et al. (2014) and Akihisa et al. (2012)
	Damnacanthal	Anthraquinones	Anti-cancer	Chan-Blanco et al. (2006) and Kamata et al. (2006)
	Americanin A	Lignan	Potent antioxidant	Su et al. (2005)
Root	8-hydroxy-8-methoxy-2-methyl-anthraquinone, rubiadin	Anthraquinone	Antiviral	Elkins (1998), Morton (1992) and Inoue et al. (1981)

(*continued on next page*)

Table 1 (*continued*)

Plant part	Compound	Chemical classification	Activities/uses	Reference
	1,3-dihydroxy-6-methyl anthraquinone			
	Morenone 1 Morenone 2		Anti-cancer	Elkins (1998) and Solomon (1999)
	Asperuloside (rubichloric acid)	Iridoid	Anti-bacterial	Bushnell et al. (1950)
	Quercetin	Flavonoids	Antioxidant, anti-dyslipidemic	Mohd Zin et al. (2007) and Mandukhail et al. (2010)
	Scopoletin	Coumarin derivative	Antibacterial	Sang et al. (2001) and Jensen et al. (2005)
	Damnacanthal	Anthraquinones	Anti-carcinogenic	Nualsanit et al. (2012)

3.4. Natural source of medicines

Scientists are looking at the *M. citrifolia* as a natural source for the medicinal production by using a bioreactor cultivation technology to produce specific medicinal compounds at a rate similar or superior to natural grown *M. citrifolia*. Data have shown that casual root cultures of *M. citrifolia* could be a useful way for the commercial production of biotechnology based chemicals such as rubiadin, flavonoids, phenolics and anthraquinones (Baque et al., 2012).

The aqueous root extract of Indian *M. citrifolia* was also used in nanobiotechnology field for the synthesis of ecological noble metal nanoparticles due to the presence of anthraquinones. Silver nanoparticles were prepared by the reduction of silver nitrate into silver ions upon adding *M. citrifolia* root aqueous extract and incubating for an overnight to yield particles between 30 and 55 nm with a cytotoxic activity against the HeLa cell lines (Suman et al., 2013). Gold nanoparticles were prepared by mixing *M. citrifolia* root aqueous extract with aqueous solution of chloroauric acid to produce gold nanoparticles. This preparation was predicted to have a higher anticancer activity due to its smaller size (12.17–38.26 nm) (Suman et al., 2014). However, before proceeding in this drug development program, a comprehensive phytochemical profiling of *M. citrifolia*, pharmaco-therapeutics, toxicity and clinical trials are needed (Singh, 2012).

3.5. Natural source of chemical reagents

Acetone extract of Thai *M. citrifolia* dried roots was reported as a source of natural reagents for the flow injection spectrophotometric technique in quantitative assays. Extract containing anthraquinones like alizarin was successfully detecting aluminum at a concentration range of 0.1–1.0 mg L^{-1} in instant tea samples. Anthraquinone compounds were acting as a complexing agent by reacting with aluminum and forming a reddish complex which could be measured at 499.0 nm (Tontrong et al., 2012). The potentials of *M. citrifolia* in being a green chemical reagent opened a new era of research in the analytical and biochemical fields.

3.6. Green insecticidal

The mosquitocidal activity of Indian *M. citrifolia* was successfully proved at various concentrations range (100–500 ppm). The activities of hexane, chloroform, acetone, methanol, and water leaf extracts were sequentially observed on the developing phases of malarial vector, *Anopheles stephensi*, Dengue vector, *Aedes aegypti* and Filarial vector culex quinquefasciatus. The studies were conducted for 24 and 48 h. showing that methanol extract had the highest larval and pupal mortality rate (Kovendan et al., 2012). The Indian *M. citrifolia* leaf ethanol extract was also reported for its larvicidal and pupicidal activities against the malarial vector *Anopheles stephensi* either alone at a range of 18.30–97.78 mg/L, or as a combination of *M. citrifolia* at a concentration range of 16.73–138.10 mg/L with *Metarhizium anisopliae* (an entomopathogenic fungi) at a concentration range of 150.15–806.67 mg/mL. The combination therapy showed the highest larval and pupal mortality rate (Kovendana et al., 2014).

4. Pharmacological activities

According to the European Commission 5th framework program quality of life, there are no systematic reviews or meta-analyses that have been published about the *M. citrifolia* wide ranges of therapeutical claims (Pilkington and The CAM-Cancer Consortium, 2015). In the next paragraph, the discussed therapeutic indications are linked to a clear scientific evidence of either *in vitro* and *in vivo* studies, or clinical trials, with a specification about the responsible phytochemical component of each activity, as well as the extracting solvent and the used part of the plant along with its country of origin and Fig. 2 summarizes the chemical structures of *M. citrifolia* most common pharmacologically active ingredients.

4.1. Antimicrobial and antiseptic activity

The anti-microbial activity of Tahitian *M. citrifolia* fruit in a methanol partitioned with n-butanol extract was assessed in an *in vitro* assay on *Escherichia coli*, *Candida albicans* and *Staphylococcus aureus*. *Candida albican* was the most sensitive to *M. citrifolia* antimicrobial activity, while *Staphylococcus aureus* sensitivity was the lowest. This activity was linked to the rich iridoid content of the fruit, particularly, deacetylasperulosidic acid and asperulosidic acid (West et al., 2012). Another anti-microbial *in vitro* assay was conducted on methanol, ethyl acetate and hexane Indian *M. citrifolia* fruit extracts against a wide range of organisms including the following: *Bacillus subtilis*, *Staphylococcus aureus*, *Lactococcus lactis*,

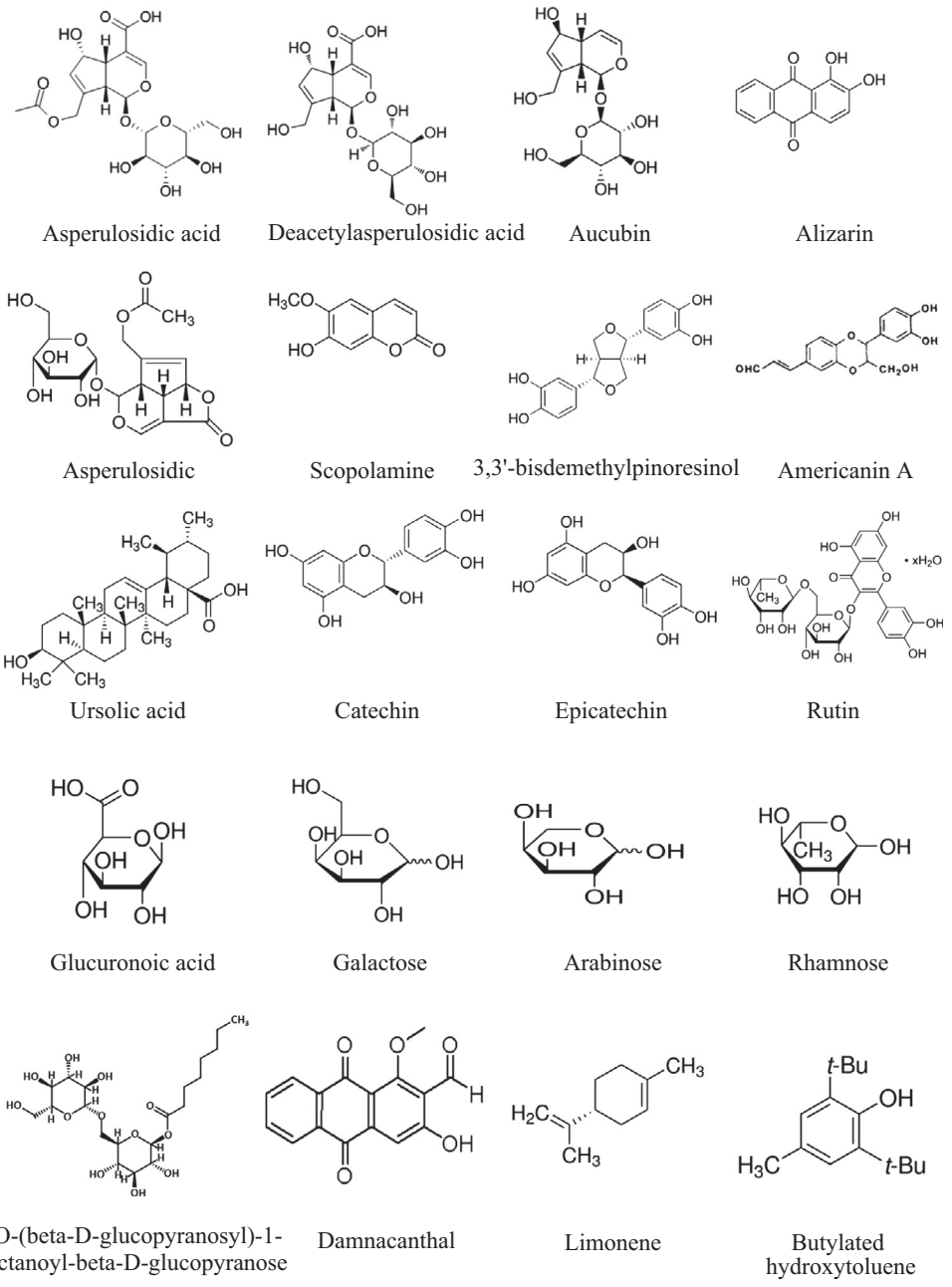

Figure 2 Summary of the chemical structures of *M. citrifolia* most common pharmacologically active ingredients.

Streptococcus thermophilus, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli*, *Vibrio harveyi*, *Klebsiella pneumonia*, *Shigella flexneri*, *Salmonella paratyphi* A, *Aeromonas hydrophila*, *Vibrio cholera*, *Chromobacterium violaceum*, and *Enterococcus faecalis*. Among the three tested extracts, methanol extract was the most effective, ethyl acetate was effective against all the tested micro-organisms except for *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, and hexane extract was ineffective against all tested microorganisms (Jayaraman et al., 2008). The antimicrobial activities of the Australian *M. citrifolia* leaf against Salmonella, Enterica serovar typhi (S76), *Staphylococcus aureus* (B313) and Myco. phlei CSL, were attributed to the presence of phenolic compounds such as acubin, l-asperuloside, alizarin and scopoletin (Atkinson, 1956). On the other hand, an *in vitro* study reported *M. citrifolia* as an oral antiseptic through teeth inoculation with *Enterococcus faecalis* at 37 °C in a CO_2 atmosphere for 30 days, and then treating them with Tahitian noni fruit juice (TNJ), NaOCl, chlorhexidine gluconate (CHX), and TNJ/CHX respectively, followed by a final flush with 17% ethylene diamine tetra acetic acid (EDTA). Upon scanning the teeth with electron microscopy, and examining the removed smear layer, TNJ efficacy found to be similar to NaOCl when it is used together with EDTA, authors recommended preclinical and clinical trials to evaluate TNJ biocompatibility and safety (Murray et al., 2008). The previous results

were confirmed with another study which additionally revealed TNJ safety on the micro-hardness property of root canal dentin (Saghiri et al., 2013).

4.2. Antifungal activity

The antifungal properties of Indian *M. citrifolia* fruit extract in three different solvents, methanol, ethyl acetate and hexane were tested in an *in vitro* assay on different fungi including *Candida albicans*, *Aspergillus niger*, *Trichophyton mentagrophytes*, *Penicillium* species, *Fusarium* species, *Aspergillus fumigates*, *Rhizopus* species, *Aspergillus flavus*, and *Mucor* species. The maximum inhibition was in the methanol and ethyl acetate extract of 79.3% and 62.06%, respectively against *Trichophyton mentagrophytes*, while almost 50% inhibition was recorded in the methanol extract against *Penicillium*, *Fusarium* and *Rhizopus* species, and none of the extracts were active against either *Candida albicans* or *Aspergillus* species (Jayaraman et al., 2008).

Despite the fact that *in vitro* results for anti-bacterial and anti-fungal studies are promising yet further *in vivo* and clinical research are highly recommended using different routes of administrations.

4.3. Antioxidant activity

Australian *M. citrifolia* fruit juice showed an anti-oxidant activity 2.8 and 1.4 times higher than vitamin C and pycnogenol, respectively. This antioxidant activity was similar to grape seed powder at the daily dose recommended by U.S. RDAs and manufacturers (Atkinson, 1956). Neolignan and americanin A were the potent antioxidant constituent of the American *M. citrifolia* fruit (Su et al., 2005). The optimum magnitudes of radical scavenging activity (RSA), and total phenolic content of Malaysian seedless *M. citrifolia* fruit methanol extract were 55.60% and 43.18 mg GAE/10 g, respectively (Krishnaiah et al., 2015). In other study, *M. citrifolia* anti-oxidant activity was evaluated as a natural anti-pigmentation agent by observing the effect of 50% ethanol extracts of Tahitian *M. citrifolia* fruit flesh, leaves, and seeds, on the tyrosinase enzyme responsible for controlling the production of melanin. The *in vitro* test was carried out using tyrosinase inhibitory assay, showing that seed extract had stronger tyrosinase inhibitory (from 20 to 500 μg/ml) and antioxidant activity than the fruit (500 μg/ml), while leaf extract did not have any tyrosinase inhibitory activity at any concentration. The tyrosinase inhibitory activity was linked to the presence of lignans in *M. citrifolia*, particularly 3,3′-bis demethylpinoresinol and americanin A (Masuda et al., 2009). The same seed extract was found to have anti-photoaging activity at concentrations ranging from 0.5 to 1.0 mg/ml (Matsuda et al., 2013), and also inhibited blood hemagglutination at concentrations ranging from 50 to 500 μg/ml (Matsuda et al., 2011); ursolic acid was the responsible chemical for the both activities.

M. citrifolia anti-oxidant property was also linked to other health enhancements activities. In an *in vitro* evaluation of methanol, chloroform, ethanol, butanol and aqueous extract of Indonesian *M. citrifolia* fruit, all extracts were able to inhibit Low-density lipoprotein (LDL) oxidation due to *M. citrifolia* lignans, such as americanol A, americanin A, americanoic acid A, morindolin, and isoprincepin (Kamiya et al., 2004). Other *in vitro* study suggested Malaysian *M. citrifolia* leaf ethanol extract was a highly effective natural anti-obesity supplement than its fruit. Leaf and fruit methanol extracts inhibited the lipoprotein lipase activity 66% ± 2.1 and 54.5% ± 2.5%, respectively. Both extracts contain high levels of phenolic constituents including catechin, epicatechin and rutin which acted synergistically to demonstrate this activity (Pak-Dek et al., 2008). Furthermore, Tahitian *M. citrifolia* juice was able to reduce obesity related to insulin resistance in an *in vitro* mouse muscle cells C2C12 culture, by inhibiting the reactive oxygen species and mitochondrial damage (Nerurkar and Eck, 2008).

A clinical study was carried out on twenty-two participants (16 women and 6 men), aged between 18 and 65 years old for 12 weeks trial of a weight-loss program with a fixed study factors including Tahitian *M. citrifolia* -based dietary supplements (US brand), daily calorie reduction, and exercise. All participants experienced weight loss with significant decrease in fat mass without side effects. However, the researchers suggested that further clinical studies should be carried out to include more male participants, and ethnic diversity (Palu et al., 2011). Antidyslipidemia activity was related to *M. citrifolia* antioxidant property in the aqueous-ethanol extracts of its Indian fruits, leaves, and roots in Sprague–Dawley rats and mice of either sex, all these different parts extracts caused significant reduction in total cholesterol, triglyceride (TC), low density lipoprotein-cholesterol, atherogenic index and TC/HDL ratio. There were no behavioral changes, toxicity or mortality occurred up to 10 g/kg of *M. citrifolia* intake, as compared to control group (Mandukhail et al., 2010). Hepato-protective effects *M. citrifolia* was also affined to anti-oxidant effects in its Taiwanese fermented fruit juice at a dose range of 3–9 mL NJ/kg BW on hamsters fed with a high-fat diet (Lin et al., 2013).

4.4. Anti-inflammatory activity

In an *in vitro* study, the anti-inflammatory activity was detected in the Costa Rican *M. citrifolia* fruit juice by measuring its direct inhibitory activities on cyclooxygenase (COX)-1 and -2 (Dussossoy et al., 2011). The *in vivo* study on Tahitian *M. citrifolia* fruit juice showed a reduction in the induced carrageenan paw edema in rats, revealing a strong anti-inflammatory effect comparable to that of non-steroidal inflammatory drugs, such as acetylsalicylic acid, indomethacin and celecoxib, without side effects (Su et al., 2001). Tahitian *M. citrifolia* seeds oil showed topical anti-inflammatory activity by inhibiting both COX-2 and 5-LOX enzymes in an *in vitro* assay at concentrations of 0.5 and 1 mg/ml (Palu et al., 2012). The topical safety of the *M. citrifolia* seed oil was evaluated on 49 adult volunteers using the patch test whereas topical comedogenic effect of the seed oil was studied on 23 Caucasian adolescent volunteers. Both studies were conducted for four weeks, and results indicated that the topical *M. citrifolia* seed oil was safe and non-comedogenic, in addition to showing a very little risk of causing allergic dermatitis which could be due to seed high fatty acids content, mainly linoleic acid (Palu et al., 2012).

A randomized double-blind placebo-controlled trial using a *M. citrifolia* dietary supplement (U.S brand) was first

performed on 100 women above 18 years old, however, only 80 women completed the study. The aim of the study was to find out the potential natural anti-inflammatory efficacy of *M. citrifolia*. This study included some variables such as age, parity, body mass index, pain, menstrual blood loss, hemoglobin, packed cell volume and erythrocyte sedimentation rate before and after treatment. Patients were observed for three menstrual cycles after being exposed to 400 mg of *M. citrifolia* capsules or placebo (38 in the placebo group and 42 in the *M. citrifolia* group) and there were no significant differences in any of the variables studied between treated and placebo group, further studies using higher doses of *M. citrifolia* with a larger sample size were recommended (Fletcher et al., 2013).

4.5. Anti-arthritic activity

An Indian brand of *M. citrifolia* fruit juice was orally administered to arthritic rats at doses 1.8 ml/kg and 3.6 ml/kg, and showed a dose dependent significant reduction in paw thickness, arthritic index, secondary lesions, mononuclear infiltration and pannus formation. Similar changes were also recorded by the administration of indomethacin except for the reduction of secondary lesions. The anti-arthritic activity could be due to the presence of flavonoids and phenols (Saraswathi et al., 2012). Precise investigations can add a therapeutical value by specifying the chemicals owning such activities and their effective and safe doses.

4.6. Anti-cancer activity

M. citrifolia natural components are mostly reported as a natural anticancer cure where sulphated polysaccharide stops metastasis by destabilizing the interaction between glycosaminoglycan and certain proteins (Liu et al., 2000) while damnacanthal inhibits the formation of tumors either by interfering with the growth of ras gene activation (Hiramatsu et al., 1993), or by increasing apoptosis in human colorectal cancer cell lines (Nualsanit et al., 2012). Alizarin has an antiangiogenic effect through blocking blood circulation to malignant tumors. Limonene prevents mammary, liver, and lung cancers by stimulating thymus gland to secrete more T cells which destroys the carcinoma cells. Last but not the least, ursolic acid inhibits the growth of cancerous cells and induces apoptosis by modulating the body immune process (Lv et al., 2011).

4.6.1. In vitro studies

Thai *M. citrifolia* fresh and dried leaf dichloromethane extracts were reported to be more effective and probably safer in treating cancer than *M. citrifolia* pure compounds such as damnacanthal, rutin, and scopoletin due to the extracts higher safety ratios. Four human cancer cell lines (epidermoid carcinoma, cervical carcinoma, breast carcinoma and hepatocellular carcinoma), and a Vero (African green monkey kidney) cell lines were used in the study. Both *M. citrifolia* extracts showed an inhibitory effect on epidermoid carcinoma and cervical carcinoma cells, while the pure compounds, rutin and scopoletin, showed lower anti-proliferative effects on all human cancer cell lines. However, only damnacanthal had potent cytotoxic effects against all human cancer cell lines as well as African green monkey kidney cell lines (Kamiya et al., 2010).

Furthermore, both pure polysaccharide, and aqueous extract from the root of Chinese *M. citrifolia* were cultured separately in a blood serum with osteoblasts (induced by trans-retinoic acid) to assess their cytotoxic role. The pure polysaccharides showed higher anticancer activity than the root aqueous extract (Li et al., 2008b), yet no specific screening was conducted on the type and structure of these polysaccharides. Furthermore, the damnacanthal which was isolated from the roots of Thai *M. citrifolia* had anticolorectal cancer activity as it showed a systematic cancer-suppressing capability in colorectal tumorigenesis (Nualsanit et al., 2012). Likewise, scientists extracted and scanned 18 different anthraquinones from the air dried powders of Hawaiian *M. citrifolia* roots for its anti-cancer activity using MTT cell proliferation assay. All the anthraquinones showed an anti-proliferation activity on both human lung cancer and colon cancer cells, specifically 1,3-dihydroxy-2-formylanthraquinone had the highest effects (Lv et al., 2011). Anthraquinone anti-cancer activity is not fully addressed, but it could be due to either aldehyde or methoxymethyl group at the C-2 position (Kamiya et al., 2010).

Anti-genotoxic potential of *M. citrifolia* juice was tested on human lymphocyte cultures at 200, 250, 300, 350 μl/ml per culture, showed a potent anti-genotoxic activity reflecting its possible anti-carcinogen effects at the initiation stage (Li et al., 2008b), however, further studies should specify the *M. citrifolia* juice ingredient(s) which is causing this effect, taking in consideration to evaluate wider concentrations range than the previously used ones on human lymphocyte cultures or even studying other models. *M. citrifolia* fruits ethanol extract from Kauai and Hawaii islands contains a polysaccharide rich substances (i.e. glucuronic acid, galactose, arabinose and rhamnose), which had immunomodulatory and anti-tumor effects on Lewis lung carcinoma cell lines (Hirazumi and Furusawa, 1999). Other two glycosides (6-O-(*β-D*-glucopyranosyl)-1-O-octanoyl-*β-D*-glucopyranose and asperulosidic acid) which were isolated from *M. citrifolia* fruit juice, showed an efficacy in suppressing the induced transformation in mouse epidermal JB6 cell line (Liu et al., 2001).

The crude extract of Hawaiian *M. citrifolia* fruit was reported to inhibit neuroblastoma (36%) and breast cancer (29%) cell lines effectively in comparison to hamster (6%) or human laryngeal (13%) cell lines, but it had no effects on green monkey kidney (0%) cell line (Arpornsuwan and Punjanon, 2006). In addition, the fermented Hawaiian *M. citrifolia* juice acted as an anti-proliferative for dendritic cells by stimulating both splenocytes, and B cells in order to produce IgG and IgM (Wong, 2004).

HeLa and SiHa cell lines were treated with either Indian *M. citrifolia* fruit juice, cisplatin (an anti-cervical cancer treatment), or their combination and showed that all the tested preparations were able to induce apoptosis in the examined cell lines. However, cisplatin showed slightly higher cell killing rate compared to *M. citrifolia* fruit juice, whereas their combination showed additive effects (Gupta et al., 2013). Furthermore, two lignans, 3,3′-bisdemethylpinoresinol (5 μM) and americanin A (200 μM), from the Tahitian *M. citrifolia* seed ethanol extract were evaluated for melanogenesis inhibitory properties, using B16 murine melanoma cells as a melanogenesis test model and α-melanocyte hormone (α-MSH) to stimulate the cells, before incubating them for 72 h. Both lignans were able to inhibit α-MSH-stimulated melanogenesis, however, 3,3′-bisdemethylpinoresinol effect

was superior, and the suggested mechanism of action was through tyrosinase suppression (Masuda et al., 2012).

4.6.2. In vivo studies

Rats with artificially induced cancer in specific organs were fed with 10% *M. citrifolia* juice in their drinking water. After one week DNA-adduct formation was reduced depending on sex and organ. The reduction rates in organs of female rats were heart 30%, liver 42%, lungs 41% and kidneys 80% whereas the reduction rates in organs of male rats were heart 60%, liver 70%, lungs 50% and kidneys 90% (Chan-Blanco et al., 2006). In other study, mice subjected to sarcoma tumor cells demonstrated synergistic beneficial effects after being treated with Hawaiian *M. citrifolia* fruit ethanol precipitate combined with some anti-cancer drugs including cisplatin, adriamycin, mitomycin-C, bleomycin, etoposide, 5-fluorouracil, vincristine or camptothecin. However, no beneficial effects were recorded when *M. citrifolia* combined with paclitaxel, cytosine arabinoside, or immunosuppressive anticancer drugs such as cyclophosphamide, methotrexate or 6-thioguanine. In contrast, mice treated with the fruit ethanol precipitate alone showed a cure rate of 25–45% (Furusawa et al., 2003). The freeze-dried Tahitian *M. citrifolia* fruit was also reported to prevent chemically induced tumorigenesis in rat esophagus (Stoner et al., 2010).

Li et al. (2008a,b) investigated antitumor effect of fermented Hawaiian Noni *M. citrifolia* exudate (500 μl/mouse/day) administered intraperitoneally to sarcoma 180 ascites mouse model. It was discovered that more than 85% of nude mice were tumor free in one and half months after tumor inoculation, versus 100% of the control mice died within 30 days of tumor inoculation (Li et al., 2008a). Another antitumor study was conducted on three groups of eight mice each was induced with Ehrlich ascites tumor. The first, second and third groups were given oral *M. citrifolia* juice (a commercial product from the Netherlands), doxorubicin (a potent anticancer drug), and a combination of both, respectively. The results suggested that oral *M. citrifolia* fruit juice may be useful in the treatment of breast cancer, either alone or in combination with doxorubicin (Taskin et al., 2009). Moreover, Tahitian *M. citrifolia* juice significantly reduced tumor weight and volume in mice, thus it might be useful in enhancing the treatment responses in women with the existing HER2/neu breast cancer (human epidermal growth factor receptor 2 gene) (Clafshenkel William et al., 2012). In contrast, Tahitian *M. citrifolia* fruit juice administered to MMTV-neu transgenic mice had no effect on mammary tumor latency, incidence, multiplicity, and metastatic, suggesting that the *M. citrifolia* juice did not increase or decrease breast cancer risk in women, but it could be taken as a dietary supplement for other benefits (Clafshenkel William et al., 2012). Thus, further work is highly recommended to clarify the role of Tahitian *M. citrifolia* juice and its other extracts in treating breast cancer.

4.6.3. Clinical trials

In one trial, Tahitian *M. citrifolia* fruit juice with a dose of 1 and 4 oz daily had reduced cancer risk among 203 heavy cigarette smokers. The data showed a significant reduction of aromatic DNA adducts levels in all participants by 44.9% after drinking the juice for 1 month. Dose-dependent analyses of aromatic DNA adduct levels revealed a reduction of 49.7% in the 1-oz dose group, and 37.6% in the 4-oz dose group. However, gender-specific analyses showed no significant differences in the 4-oz dose groups, while in the 1-oz dose group showed 43.1% reduction in females compared to 56.1% in males. The suggested mechanism of cancer reduction was by blocking carcinogen-DNA binding, or excising DNA adducts from genomic DNA (Wang et al., 2009b).

Only two cancer cases were reported to use *M. citrifolia*. Case 1 was about a 69 year old male with gastric cancer who was predicted to die within few months without surgical intervention. The patient chose to take homemade *M. citrifolia* fruit juice over the surgical operation and his condition improved within a month. After 6 months he stopped the self-treatment, and seven years later he did not have any gastric symptoms. However, a biopsy showed histological similarity to his original cancer and hence, he started taking *M. citrifolia* juice again but the outcome was not reported. Case 2 was about a 64 year old man with gastric cancer who underwent a gastrectomy. The cancer had spread to 17 out of 28 examined lymph nodes, and he was given 5 years to live. The patient consumed a homemade *M. citrifolia* juice and lived additional 16 years until he died at the age of 80 due to gastric cancer (Wong, 2004).

In a Phase I human clinical trial conducted at the Cancer Research Centre in Hawaii, 29 advanced cancer patients first started a daily dosage of 4 capsules (500 mg/capsule) from a freeze dried *M. citrifolia* fruit, and later it was increased up to 20 capsules (10 g) during a total 4 weeks trial which showed no tumor regression, but only a decrease in fatigue and pain interference, while the recorded maximum tolerated dose was six capsules four times daily (12 g) (Issell et al., 2009). The clinical trials' results are showing no clear role of *M. citrifolia* in either preventing or healing cancer disease, patients' number should be addressed on a larger scale, with wider parameters and specifications to ameliorate the understanding of applying *M. citrifolia* in therapeutic and prophylactic anti-cancer medicine.

4.7. Antidiabetic activity

Indian *M. citrifolia* commercial fruit juice was administered orally to induced steroid diabetic (diabetes type 2) female Wistar rats, at a dose of 1.8 and 3.6 ml/kg for 10 days. The blood glucose level was significantly decreased compared to control induced diabetic rats by dexamethasone. At higher oral dose (3.6 ml/kg, twice a day) *M. citrifolia* fruit juice had better results than rosiglitazone, but caused liver damage in rats (Puranik et al., 2013). On the other hand, fermented juice of South American *M. citrifolia* also controlled blood sugar induced diabetic rats by streptozotocin. Diabetic standard animals, treated with hypoglycemic drug, glibenclamide, while diabetic experimental animals treated with 2 ml/kg *M. citrifolia* twice a day for 20 days exhibited a significant reduction in blood glucose level of 125 mg/dl and 150 mg/dl, respectively, as compared to untreated diabetic rats with fasting blood sugar of 360.0 mg/dl (Shivananda Nayak et al., 2011). Hypoglycemic activity of Tahitian *M. citrifolia* fruit Juice was investigated by administering the juice to male Sprague–Dawley rats at a dose of 1 ml/150 g body weight, twice daily for 4 weeks prior to diabetic induction using alloxan. After induction, a rise in blood glucose levels occurred but followed by a steady decline due to *M. citrifolia* juice prophylaxis against the diabetogenic agent, alloxan (Horsfal et al., 2008).

Based on a microarray analysis data, hypoglycemic properties of Hawaiian fermented *M. citrifolia* fruit juice were associated with the ability to modulate transcription factors (FoxO1) in order to regulate the gluconeogenesis process. Fermented *M. citrifolia* juice supplement at a dose of 1.5 µl/g body weights, twice a day for 12 weeks improved glucose and insulin tolerance as well as fasting blood glucose level in male mice. Gluconeogenic genes which are regulated by insulin including phosphoenolpyruvate C kinase and glucose-6-phosphatase were also inhibited by more than 80% (Nerurkar et al., 2012). It was suggested that *M. citrifolia* antidiabetic effect might be due to the stimulatory effect on the remnant ß-cells to secrete more insulin (Mustaffa et al., 2011). Saponins as well as flavonoids in *M. citrifolia* fruit such as rutin may also act as a secretagogue by enhancing insulin secretion (Shivananda Nayak et al., 2011). *M. citrifolia* is showing promising *in vivo* results as a natural antidiabetic agent; however scientist should pay a great concern on its safety particularly liver. If the doses are adjusted within a safe range and a proven efficacy, preclinical studies will be recommended.

4.8. Wound healing activity

Fresh Tahitian *M. citrifolia* leaf juice (1 mg/ml), its leaf ethanol extract (10–200 µg/ml), and its methanol and hexane fractions (10–200 µg/ml), were investigated for their topical wound healing properties. Receptors involved in wound healing such as platelet-derived growth factor (PDGF) and adenosine A2A receptor were studied on male mice. All *M. citrifolia* extracts showed a wound healing activity at a concentration dependent manner; however, leaf methanol extract significantly increased wound closure and reduced the half closure time in treated mice compared to the control, suggesting that the probable mechanism underlying this effect was the ligand binding to PDGF/A2A receptor which promoted wound closure (Palu et al., 2010). The promising results in this study should be confirmed through further *in vivo* studies on various models to draw a sharp conclusion about the healing mechanism.

4.9. Memory enhancing activity

Observations in a scopolamine induced memory impairment mice model suggested that Indian *M. citrifolia* dry fruit may be useful in enhancing memory at concentration range of 5–400 µg/ml. The fruit ethanol extract and its ethyl acetate fraction were containing rutin, scopoletin and quercetin, while the chloroform fraction was containing rutin and scopoletin, have showed positive effects. However, butanol fraction containing rutin alone had no effect. The mechanism of action was thought to be by inhibiting acetylcholinesterase activity, and the enhancement of the cerebral circulation (Pachauri et al., 2012). Results should be confirmed by further research to justify *M. citrifolia* effects on different *in vivo* models with precise illustration of chemicals responsible of such activity and the precise mechanism of memory enhancement.

4.10. Anxiolytic and sedative activity

A preliminary *in vitro* study revealed that Tahitian *M. citrifolia* freeze dried fruit methanol extract had anxiolytic and sedative effects by showing an affinity to the gamma-aminobutyric acid A (GABAa) inhibitory neurotransmitter receptors at a concentration of 100 µg/ml. The action could be due to the presence of competitive ligand(s) bind to the GABAa receptor as an agonist that induced anxiolytic and sedative effects. However, *in vivo* studies and clinical trials were recommended by the authors to confirm the newly reported activity (Deng et al., 2007a). Furthermore, a US brand of Tahitian *M. citrifolia* fruit juice at 10 ml/kg/day showed to have an *in vivo* brain protection from the stress-induced impairment of cognitive function on male ICR mice. This beneficial effect may be partly mediated by the improvement in angiogenesis induced by *M. citrifolia* (Muto et al., 2010). In an *in vivo* study on the Swiss albino mice, Malaysian *M. citrifolia* unripe dried fruit methanol extract was also reported for its anti-dopaminergic effects at 1, 3, 5, 10 g/kg oral doses. The suggested mechanism of action was due to the possible inhibition of the Methamphetamine-induced stereotypy behavior in a dose dependent manner. Further studies to isolate and characterize the responsible compounds for anti-psychiatric disorders were recommended (Pandy et al., 2012).

4.11. Analgesic activity

Tahitian *M. citrifolia* fruit juice was reported for its analgesic effect in rats by using the hotplate assay. The rats tolerated more pain after feeding with 10% or 20% *M. citrifolia* juice (Wang et al., 2002). In another study, the lyophilized aqueous African *M. citrifolia* dry root extract had also demonstrated analgesic properties at dose of 800 mg/kg given intraperitoneal injections. The analgesic activity was observed using three methods, the antagonistic action of naloxone, the writhing test, and the hotplate assay (Younos et al., 1990).

4.12. Gastric ulcer healing activity

Thai dried mature unripe *M. citrifolia* fruit aqueous extract was reported for its *in vivo* gastro-esophageal anti-inflammatory effects in rats at a range of 0.63–2.50 g/kg, with possible mechanisms of reducing the formation of acute gastric lesions, blocking the esophagus reflux and acting as an antisecretory agent similar to ranitidine and lansoprazole (Mahattanadul et al., 2011). In an open-label, two-period crossover study, 20 healthy volunteers from 18 to 45 years old were given a single-dose of Thai *M. citrifolia* fruit aqueous extract containing 25.15 ± 0.11 µg/ml scopoletin. After 30 min the volunteer were given 1 tablet of ranitidine (300 mg) and blood samples were collected for 12 h. The results showed that *M. citrifolia* acted as a ranitidine absorbance inducer due to the presence of scopoletin which stimulated the 5-HT4 receptor. Further clinical trial using more patients having specific gastric motility defect or symptoms was recommended to provide stronger evidence (Nima et al., 2012).

4.13. Antiemetic activity

To study the antiemetic activity of *M. citrifolia*, a preliminary randomized double blinded, placebo-controlled clinical trial was done on 100 patients with a high risk of postoperative nausea and vomiting (PONV), their ages were 18–65 years old. In one group Thai *M. citrifolia* fruit was given 1 h. before the surgery at a dose of 600 mg, beside that the

patients were also received the standard general anesthesia as well as the post-operative analgesia. The results revealed that patients who received *M. citrifolia* experienced significantly less nausea during the first 6 h compared to the placebo group (Prapaitrakool and Itharat, 2010), to understand this activity further *in vitro*, *in vivo* and clinical trials should be conducted to specify by which mechanism(s) *M. citrifolia* is acting as an antiemetic, and what if it could be used in reducing emetic symptoms caused by different cases rather than PONV.

4.14. Gout and hyperuricemia healing activity

The *in vitro* bioassay of xanthine oxidase (XO) inhibiting effects revealed that the Tahitian noni juice (TNJ) is having a dose dependent natural anti-gout and anti-hyperuricemic effects. The half maximal inhibitory concentration (IC50) of *M. citrifolia* was 3.8 mg whereas IC50 of allopurinol was 2.4 μm. The concentrated methanol extract of this fruit juice at concentration of 0.1 mg/ml exhibited higher XO enzyme inhibition rate (64%) compared to XO enzyme inhibition rate

Table 2 The list of *M. citrifolia* pharmacological activities along with their *in vitro*, *in vivo* and clinical trials.

Plant part	Activity	*In vitro*	*In vivo*	Clinical trial	Reference
Fruit	Intracanal irrigant	X			Murray et al. (2008) and Saghiri et al. (2013)
Fruit	Anti-viral	X			Kamata et al. (2006)
Fruit, leaf	Anti-microbial	X			West et al. (2012), Jayaraman et al. (2008) and Atkinson (1956)
Fruit	Anti-fungal	X			Jayaraman et al. (2008)
Fruit, leaf, root	Anti-dyslipidemia		X		Mandukhail et al. (2010)
Fruit, leaf	Anti-oxidant	X			Su et al. (2005), Krishnaiah et al. (2015) and Nerurkar and Eck (2008)
Fruit	Memory dysfunction		X		Pachauri et al. (2012)
Fruit, root	Analgesic activity		X		Wang et al. (2002) and Younos et al. (1990)
Fruit, leaf, seed	Anti-inflammatory	X	X	X	Dussossoy et al. (2011), Su et al. (2001), Palu et al. (2012) and Fletcher et al. (2013)
Fruit	Anti-arthritic	X			Saraswathi et al. (2012)
Fruit, leaf, root	Anti-cancer	X	X	X	Chan-Blanco et al. (2006), Kamiya et al. (2010), Liu et al. (2001), Nualsanit et al. (2012), Lv et al. (2011), Li et al. (2008b), Hirazumi and Furusawa (1999), Arpornsuwan and Punjanon (2006), Wong (2004), Gupta et al. (2013), Masuda et al. (2012), Furusawa et al. (2003), Stoner et al. (2010), Li et al. (2008a), Taskin et al. (2009), Clafshenkel William et al. (2012), Wang et al. (2009b) and Issell et al. (2009)
Fruit, leaf	Anthelminthic activity	X	X		Brito et al. (2009)
Fruit	Source of trace elements	X			Rybak and Ruzik (2013)
Fruit	Stress reduction		X		Muto et al. (2010)
Fruit	Anxiolytic and Sedative	X			Deng et al. (2007a)
Fruit	Probiotic activity	X			Wang et al. (2009a)
Fruit, leaf	Anti-obesity	X		X	Pak-Dek et al. (2008) and Palu et al. (2011)
Fruit	Hepatoprotective agent		X		Lin et al. (2013)
Fruit	Immunological stimulator	X	X		Krishnaiah et al. (2012) and Palu et al. (2008)
Fruit	Antisecretory proton pump inhibitor		X		Mahattanadul et al. (2011) and Nima et al. (2012)
Seed	Antithrombotic effect		X		Masuda et al. (2009)
Seed	Anti photoaging agent	X			Masuda et al. (2009)
Seed	Anti-wrinkle formation	X			Masuda et al. (2009)
Seed, Fruit	Anti-pigmentation	X			Masuda et al. (2009)
Fruit	Anti-psoriasis			X	Okamoto (2012)
Fruit	Antidiabetic activity		X		Puranik et al. (2013), Shivananda Nayak et al. (2011), Horsfal et al. (2008) and Nerurkar et al. (2012)
Fruit	Antipsychotic activity		X		Pandy et al. (2012)
Fruit	Antiemetic activity			X	Prapaitrakool and Itharat (2010)
Fruit	Osteoporosis and hearing problems		X		Langford et al. (2004)
Leaf	Wound healing activity	X	X		Palu et al. (2010)
Fruit	Gout healing factor	X	X		Palu et al. (2009)
Leaf	Anti-tubercular activity	X			Saludes Jonel et al. (2002)

of TNJ itself (11%) at concentration of 1 mg/ml. However, the authors recommended further studies to isolate the active compounds, and to conduct clinical trials in an aim of supporting this hypothesis (Palu et al., 2009).

4.15. Anti-psoriasis healing activity

M. citrifolia was reported to act as an anti-psoriasis healing factor in a 31-year old man who received treatment of *M. citrifolia* fruit powder (4 g/day) and a weekly methotrexate. After one month treatment, his psoriatic skin lesions significantly improved. This could be due to the immune-modulation effect of both *M. citrifolia* and methotrexate on skin lesion (Okamoto, 2012). So far, this is the only case report about that activity, thus, such cases should be deeply investigated on *in vitro*, *in vivo* and clinical scales.

4.16. Immunity enhancing activity

The immunity enhancement activity of both Tahitian and commercial *M. citrifolia* fruit juices was reported in an *in vivo* study on mice, suggesting that *M. citrifolia* is modulating the immune system by activating the CB2 receptors, and suppressing the interleukin-4, as well as increasing the production of interferon gamma cytokines. However, authors recommended further *in vivo* and clinical research to illustrate the dosage and actual mode of action of *M. citrifolia* on the immune system (Palu et al., 2008).

4.17. Anti-viral activity

M. citrifolia fruit component damnacanthal showed to have an *in vitro* anti-viral activity via inhibiting one of the human immunodeficiency viruses type 1 (HIV-1) accessory proteins in a Hela cells through an unknown mechanism. Authors suggested further studies to elucidate the anti-viral mechanism of *M. citrifolia* that could be useful in assessing the treatment of HIV-1 and other viral diseases (Kamata et al., 2006).

4.18. Anti-parasitic activity

Brazilian *M. citrifolia* fruit aqueous extract at 50.1 mg/mL and ethanolic extract at 24.6 mg/mL were given for three days to chickens naturally infected by Ascardiagalli. The aqueous extract showed lower parasite mortality rate (27.08%) than ethanol extract (66.67%), and the authors recommended repeating the *in vivo* experiment using higher concentrations (Brito et al., 2009).

4.19. Anti-tuberculosis activity

The Filipino *M. citrifolia* leaves ethanol extract and hexane fractions at 100 μg/ml reported to have an anti-tubercular activity in Mycobacterium tuberculosis cultures, with inhibition rates of 89% and 95% respectively. It is suggested that the activity may come from E-Phytol compounds, which is a mixture of ketosteroids, and epidioxysterol (Saludes Jonel et al., 2002). Future studies should select a proper positive control to assess this activity.

4.20. Osteoporotic and otoscopic enhancer

Langford et al. (2004) investigated the ability of *M. citrifolia* fruit juice to enhance osteoporotic conditions and otoscopic deficiencies by conducting a pilot health survey using SF-36 measurements. Eight participants consumed 2 oz of either a placebo or a *M. citrifolia* juice (US brand), along with calcium supplement, two times a day for 3 months. The results showed an increase in bone reconstruction which is probably due to a slight increase in the mean value of the osteoclastic activity specific marker, the deoxypyridinoline crosslinks. The otoscopic evaluation showed a limited impact on hearing, with a possible prophylactic effect at the 8000 Hz sensorineural domains; however authors recommended further studies with a larger sample size and over longer time periods (Langford et al., 2004).

Table 2 shows the kinds of investigations (*in vivo*, *in vitro* and clinical trials) conducted on leaf, fruit seed and root of *M. citrifolia*.

5. Conclusion

M. citrifolia has been used as a medicine for the overall maintenance of a good health as well as the prevention of some diseases including skin, brain, GIT, heart, liver and cancer. Till date, the only information available for daily recommended oral dose of *M. citrifolia* is 2 g; however, there is no information on recommended doses range for topical preparations. It is important to understand that *M. citrifolia* properties require further extensive studies in terms of identification of the active compounds, their specific mechanism of action and safety. In addition, more *in vivo* and clinical studies are required with a significant number of subjects and a wider range of concentrations especially in the cancer field. Since further studies are recommended on *M. citrifolia* and its products, thus they should be used with caution particularly for customers with concomitant illness and medications. Companies which are producing *M. citrifolia* products should provide relevant information regarding the bioactive components of *M. citrifolia* and any extra nutritional elements added to the products, along with their concentrations in order to arouse a sense of awareness among consumers for the safe purchase.

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