Moringa oleifera: a review of the medicinal potential

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Abstract

***Moringa oleifera*, or the horseradish tree, is a pan-tropical species that is known by such regional names as benzolive, drumstick tree, "miracle tree", kelor, marango, mlonge, mulangay, nébéday, saijhan, and sajna. Over the past two decades, many reports have appeared in mainstream scientific journals describing its nutritional and medicinal properties. Its utility as a non-food product has also been extensively described, but will not be discussed herein, (e.g., lumber, charcoal, fencing, water clarification, lubricating oil). As with many reports of the nutritional or medicinal value of a natural product, there are an alarming number of purveyors of "healthful" food who are now promoting *M. oleifera* as a panacea. While much of this recent enthusiasm indeed appears to be justified, it is critical to separate rigorous scientific evidence from anecdote. Those who charge a premium for products containing *Moringa* spp. must be held to a high standard. Those who promote the cultivation and use of *Moringa* spp. in regions where hope is in short supply, must be provided with the best available evidence, so as not to raise false hopes and to encourage the most fruitful use of scarce research capital. It is the purpose of this paper to: (a) critically evaluate the published scientific evidence on *M. oleifera*, (b) highlight claims from the traditional and tribal medicinal lore and from non-peer reviewed sources that would benefit from further, rigorous scientific evaluation, and (c) suggest directions for future clinical research that could be carried out by local investigators in developing regions.**

Keywords: phytochemistry, antibiotic, chronic disease, inflammation, nutrition, hypertension, diabetes, cancer, asthma

INTRODUCTION

The nutritional properties of moringa are now so well known that there seems to be little doubt of the substantial health benefit to be realized by consumption of moringa leaf powder in situations where starvation is imminent. Nonetheless, the outcomes of well controlled and well documented clinical studies are still clearly of great value. We have recently highlighted this need (Thurber and Fahey, 2009). *Moringa oleifera* is the most widely cultivated of the 13 species of a monogeneric family, the *Moringaceae* that is native to the sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan. This rapidly-growing tree, also known as the horseradish tree, drumstick tree, benzolive tree, kelor, marango, mlonge, moonga, mulangay, nébéday, saijhan, sajna or Ben oil tree, was utilized by the ancient Romans, Greeks and Egyptians.

Moringa is now widely cultivated and has become naturalized in many locations in the tropics. It is a perennial softwood tree with timber of low quality, but which for centuries has been advocated for traditional medicinal and industrial uses. It is already an important crop in India, Ethiopia, the Philippines and the Sudan, and is being grown in West, East and South Africa, tropical Asia, Latin America, the Caribbean, Florida (USA) and the Pacific islands.

All parts of the moringa tree are edible and have long been consumed by humans. According to Fuglie (1999) the many uses for moringa include: alley cropping (biomass

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production), animal forage (leaves and treated seed-cake), biogas (from leaves), domestic cleaning agent (crushed leaves), blue dye (wood), fencing (living trees), fertilizer (seed-cake), foliar nutrient (juice expressed from the leaves), green manure (from leaves), gum (from tree trunks), honey- and sugar cane juice-clarifier (powdered seeds), honey (flower nectar), medicine (all plant parts), ornamental plantings, biopesticide (soil incorporation of leaves to prevent seedling damping off), pulp (wood), rope (bark), tannin for tanning hides (bark and gum), water purification (powdered seeds).

Moringa seed oil (yield 30-40%, by weight), also known as Ben oil, is a sweet non-sticking, non-drying oil, that resists rancidity. It has been used as a food (in salads), for fine machine lubrication, and in the manufacture of perfume and hair care products (Tsaknis et al., 1999). In the West, one of the best known uses for moringa is the use of powdered seeds to flocculate contaminants and purify drinking water (Berger et al., 1984; Gassenschmidt et al., 1995; Olsen, 1987), but the seeds are also eaten green, roasted, powdered and steeped for tea and used in curries (Gassenschmidt et al., 1995). This tree has in recent times been advocated as an outstanding indigenous source of highly digestible protein, Ca, Fe, vitamin C, and carotenoids suitable for utilization in many of the so-called "developing" regions of the world where undernourishment is a major concern.

In many cultures throughout the tropics, differentiation between food and medicinal uses of plants (e.g., bark, fruit, leaves, nuts, seeds, tubers, roots, flowers), is very difficult since plant uses span both categories and this is deeply ingrained in the traditions and the fabric of the community (Lockett et al., 2000).

PHYTOCHEMISTRY

Phytochemicals are, in the strictest sense of the word, chemicals produced by plants. Commonly, though, the word refers to only those chemicals which may have an impact on health, or on flavor, texture, smell, or color of the plants, but are not required by humans as essential nutrients. An examination of the phytochemicals of moringa species affords the opportunity to examine a range of fairly unique compounds. We consider phytochemical content separately herein, because it also impacts taste, palatability, consumer acceptance, and bioavailability.

Moringa belongs to a family of plants that is exceptionally rich in phytochemicals that are involved in detoxification. Evolving from the primordial soup about a half billion years ago, land plants first started the evolutionary process to develop biochemical detoxication mechanisms for their own protection. One of the beauties, or symmetries of nature, is that we inherited most of our biochemical detoxification mechanisms, from the very plants upon which we depended for a food supply, and those phytochemicals are as effective as anything modern pharmacology has developed, in assisting us in our own protection.

Human beings, have not just recently developed the need to detoxify air and water pollutants like pesticides, plasticizers, and volatile organic hydrocarbons. From the moment we (and our predecessor mammals) started eating, our survival depended upon our ability to detoxify toxins from fungal and bacterial food contaminants, and from the plants and animals we ate. When *Homo sapiens* emerged from Neanderthal man and first tamed fire about 40,000 years ago, we started living in highly polluted microenvironments, and charring our steaks to produce carcinogenic heterocyclic amines. As stated so eloquently by the populist writer Michael Pollan in "The Botany of Desire" (Pollan, 2001),

> "While we animals were busy nailing down things like locomotion and consciousness, plants acquired an array of extraordinary and occasionally diabolical powers by discovering how to synthesize remarkably complicated molecules."

The phytochemical content of moringa has implications with respect to its utility as a nutritional plant and as a source of micronutrients, as well as its medicinal effects (the application with which phytochemicals are most often associated). In particular, this plant family is rich in compounds containing the simple sugar, rhamnose, and it is rich in a fairly unique group of phytochemicals called glucosinolates, which are enzymatically converted to isothiocyanates (reviewed by Fahey et al., 2001). The isothiocyanates in general, have

tremendous anti-inflammatory, detoxification, antibiotic, and neuroprotective properties, to name just a few. Moringa is replete with some very potent glucosinolates that we and others have documented are influenced by both environment and genetics (Doerr et al., 2009; Bennett et al., 2003).

In addition to their unique, rhamnosylated glucosinolates and isothiocyanates, moringa contains a variety of related carbamates, thiocarbamates and nitriles (Faizi et al., 1992, 1994a, b, 1995, 1998; Murakami et al., 1998). For example, specific components of moringa preparations that have been reported to have hypotensive, anti-cancer, and antibacterial activity are illustrated in Figure 1; they include 4-(α-L-rhamnopyranosyloxy)benzyl glucosinolate [1], 4-(α-L-rhamnopyranosyloxy)-benzyl isothiocyanate [2] (also known as glucomoringin), 4-[(4'-*O*-acetyl-α-L-rhamnopyranosyloxy) benzyl] isothiocyanate [3], benzyl isothiocyanate [4], niazimicin [5], niazirin [6], and niazimin [7]. While these compounds are relatively unique to the moringa family, it is also rich in a number of vitamins and minerals as well as other more commonly recognized phytochemicals such as the carotenoids (including β-carotene or pro-vitamin A). These attributes are all discussed extensively by Lowell Fuglie (1999) and others, and are the subject of this paper.

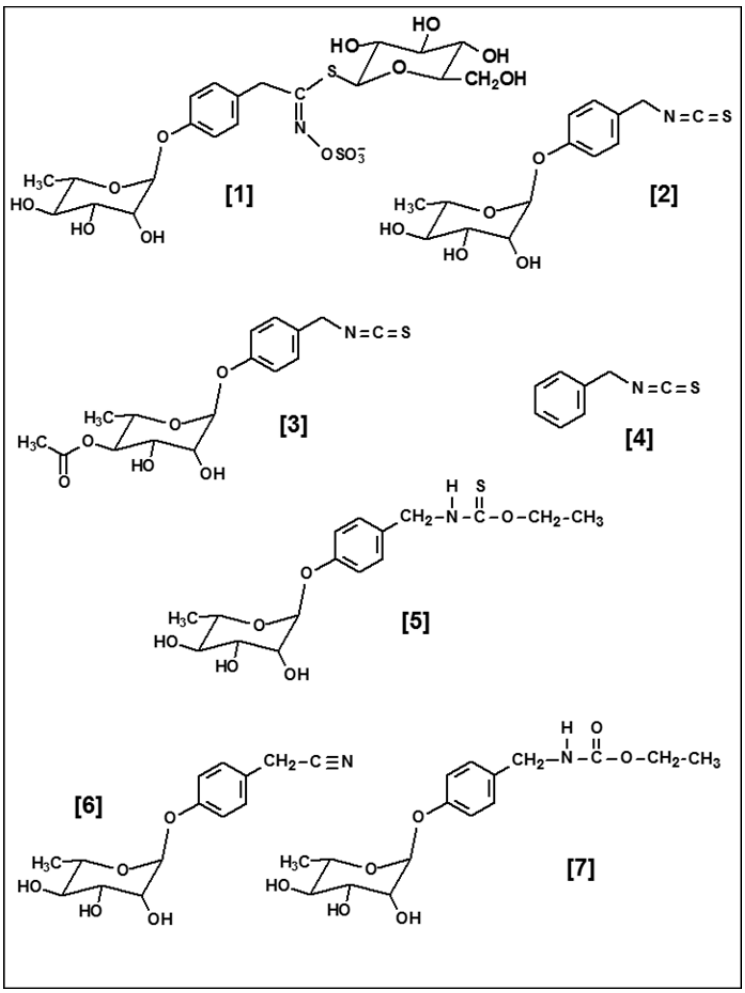

Figure 1. Structures of selected phytochemicals from *Moringa* spp.: 4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate [1], 4-(α-L-rhamnopyranosyloxy) benzyl isothiocyanate [2], 4-[4'-O-acetyl-α-L-rhamnopyranosyloxy)benzyl] isothiocyanate [3], benzyl isothiocyanate [4], niazimicin [5] (a thiocarbamate), niazirin [6] (a nitrile), and niazimin [7] (a carbamate).

DISEASE TREATMENT AND PREVENTION

Claims for medicinal uses are manifold, but are by-and-large less well documented than nutritional and micronutrient claims.

The following section was written 10 years ago (Fahey, 2005) and is paraphrased below. Unfortunately, whereas the volume of published work purporting medicinal benefits, and the number of papers repeating or newly reporting on in vitro and animal model tests has ballooned over the past decade, the number of peer-reviewed papers that describe well done studies in human beings can still be counted on the fingers of one hand.

> The benefits for the treatment or prevention of disease or infection that may accrue from either dietary or topical administration of moringa preparations (e.g., extracts, decoctions, poultices, creams, oils, emollients, salves, powders, porridges) are not quite so well known (Palada, 1996). Although the oral history here is also voluminous, it has been subject to much less intense scientific scrutiny, and it is useful to review the claims that have been made and to assess the quality of evidence available for the more well-documented claims. The readers of this review are encouraged to examine two recent papers that do an excellent job of contrasting the dilemma of balancing evidence from complementary and alternative medicine (e.g., traditional medicine, tribal lore, oral histories and anecdotes) with the burden of proof required in order to make sound scientific judgments on the efficacy of these traditional cures (Sampson, 2005; Talalay and Talalay, 2001). Clearly much more research is justified, but just as clearly this will be a highly fruitful field of endeavor for both basic and applied researchers over the next decade.
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> Widespread claims of the medicinal effectiveness of various moringa tree preparations have encouraged the author and his colleagues at The Johns Hopkins University to further investigate some of these possibilities. A plethora of traditional medicine references attest to its curative power, and scientific validation of these popular uses is developing to support at least some of the claims. Moringa preparations have been cited in the scientific literature as having antibiotic, antitrypanosomal, hypotensive, antispasmodic, antiulcer, anti-inflammatory, hypocholesterolemic, and hypoglycemic activities as well as having considerable efficacy in water purification by flocculation, sedimentation, antibiosis and even reduction of Schistosome cercariae titer (see Table 1).
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> Unfortunately, many of these reports of efficacy in human beings are not supported by placebo controlled, randomized clinical trials, nor have they been published in high visibility journals. For example, a report published almost 25 years ago (Shaw and Jana, 1982) appears on the surface to establish moringa as a powerful cure for urinary tract infection, but it provides the reader with no source of comparison (no control subjects). Thus, to the extent to which this is antithetical to Western medicine, moringa has not yet been, and will not be, embraced by Western-trained medical practitioners for either its medicinal or nutritional properties.
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> In many cases, published in-vitro (cultured cells) and in-vivo (animal) trials do provide a degree of mechanistic support for some of the claims that have sprung from the traditional medicine lore. For example, numerous studies now point to the elevation of a variety of detoxication and antioxidant enzymes and biomarkers as a result of treatment with moringa or with phytochemicals isolated from moringa (Fahey et al., 2004; Faizi et al., 1994a, b; Ashok Kumar and Pari, 2003; Rao et al., 1999). I shall briefly introduce antibiosis and cancer prevention as just two examples of areas of moringa research for which the existing scientific evidence appears to be particularly strong.

Table 1. Clinical evaluations of the anti-diabetic potential of *Moringa oleifera* leaf powder in 7 clinical studies.

Daily dose	Duration of intervention	No. of subjects taking moringa (M) or control (C)	Results[1]	Comments	Reference
100 g	3 months	20 – M 10 – C 20 – Other treatment	↓ FBG: (151 to 117.5)	"Control" group only measured once, but was just a baseline of non-diabetic patients; no control group of matched diabetic patients receiving placebo; dose regimen unclear	Sugunabai et al., 2014
50 g	40 days	15 – M	↓ BG: (132.5 to 120.3) ↓ LDL: (45.8 to 31.5)	No controls; dose regimen unclear ("All subjects were asked to use this (50 g) powder with their food regularly"); unclear how BG measured and whether it was fasting or post prandial	Kumar and Naga Subrahmanyam, 2013
?	?	45 – M	↓ 21.72 FBG ↓ 28.11 post-prandial	Other details not available	Kiranmayi and Babitha, 2011
?	3 months	30 – M 30 – C	↓ PPG (210 to 150) (M) & (179 to 163) (C)	Significant differences in the experimental BG (post vs. pre), but initial levels very different between the experimental and control (210 vs. 179); dose not specified	Giridhari et al., 2011
8 g	40 days	24 – M 9 – C 22 – Other treatment	↓ FBG (162 to 117); ↓ PPBG (219 to 163); ↓ SC (261 to 224); ↓ ST (130 to 112); ↓ LDL (171 to 122), & ↓ VLDL levels (26 to 22). No signif ↓ in any but ST in controls (138 to 133).	Randomization, masking and treatment allocation not indicated or specified	Kumari, 2010
4.68 g	50 days	20 – M 20 – C	Significant ↓ in LDL/HDL (3.27 to 2.99), TC/HDL (4.58 to 4.28), TC (187.14 to 184.00) and non-HDL (149.08 to 143.60)	Although directed at hyperlipidemic (not type 2 diabetes) subjects, there was no ↓ FBG in treatment, contrary to expectations	Nambiar et al., 2010
2.1 g	30 days	33 – M 35 – C	Both the experimental and control groups had ↓ BG, but no significant diff. between the two	Randomization, blinding and treatment allocation were all clearly stated, but study population was not type 2 diabetes and had normal glucose ranges at baseline	Sandoval and Jimeno, 2013

[1]FBG – fasting blood glucose; BG – blood glucose; LDL – low density lipoprotein; PPBG – post-prandial blood glucose; SC – serum cholesterol; HDL – high density lipoprotein; TC – total cholesterol; ST – serum triglycerides; VLDL – very low density lipoprotein.

In reviewing what has transpired in the scientific literature since the 2005 review was written, one comes up with the following metrics: A September, 2014 keyword search in the database Scopus (an Elsevier product that credits itself as the world's largest abstract and citation database of peer-reviewed literature) reveals that there are now 1643 peer-reviewed papers in which "Moringa" is a key word, 1332 of them since 2005, and now being published at a rate of one per day. It is instructive to sort through not only the titles and abstracts of these thousand or so post-2005 studies, but to examine how they are sorted and categorized (according to titles and keywords). After ruling out those studies that deal with plant anatomy and taxonomy, nutritional content, analytical methodology, biomass production, and water coagulation/purification by moringa, one can get a vision of how studies dealing with the biomedical or medicinal effects of moringa are clustered:

- Antioxidant activity (including lipid peroxidation) accounts for between 100 and 200 of the remaining papers.
- Drug screening, -isolation, and/or -efficacy accounts for another 75-100.
- Antibacterial activity, anti-inflammatory activity, anti-diabetic activity, anti-neoplastic activity ("anti-cancer" effects) account for about 50, 50, 40, 30, and 30 of the remaining publications, respectively.

At first glance it appears that there has been a lot of research activity on the latter categories and there have been reviews, both critical and otherwise (most recently: Hussain et al., 2014). However, a more critical evaluation of the publications shows that some are very poorly done studies that reach spurious and highly debatable conclusions about their data, and almost all are done on cell lines, in test-tube antibacterial assays, or in animal studies, and not in controlled human studies.

Although 383 of the 1643 papers identified are reported as "controlled studies", only three of them actually appear to be so. They are:

1. Agrawal, B., and Mehta, A. (2008). Anti-asthmatic activity of *Moringa oleifera* Lam: a clinical study. Indian J Pharmacol *40* (*1*), 28–31.
2. Ali, A., Akhtar, N., Khan, M.S., Khan, M.T., Ullah, A., and Shah, M.I. (2013). Effect of *Moringa oleifera* on undesirable skin sebum secretions of sebaceous glands observed during winter season in humans. Biomedical Research *24* (*1*), 127–130.
3. Sandoval, M.A.S., and Jimeno, C.A. (2013). Effect of malunggay (*Moringa oleifera*) capsules on lipid and glucose levels. Acta Medica Philippina *47* (*3*), 22–27. A fourth paper appears to be such a study but is actually carried out ex vivo, so would more properly be placed in the category of studies in cell culture (test-tube studies). However, it does provide encouraging results:
4. Arabshahi-Delouee, S., Aalami, M., Urooj, A., and Krishnakantha, T.P. (2009). *Moringa oleifera* leaves as an inhibitor of human platelet aggregation. Pharmaceutical Biology *47* (*8*), 734–739.

Furthermore, at the time this paper was written, there were three studies with human subjects listed on www.clinicaltrials.gov, in which moringa or a preparation containing moringa was to be administered orally:

1. NCT01410058; *Moringa oleifera* – Antiretroviral pharmacokinetic drug interaction. Sponsor: University of Zimbabwe; Status: Recruiting (Aug 2013).
2. NCT02021799; The effect of under-nutrition on the human microbiota. Sponsor: Western University, Canada; Status: Completed (Dec. 2013)
3. NCT02234206; A clinical trial to study the safety and efficacy of Chandrakanthi Choornam on patients with low sperm count. Sponsor: Tamil Nadu Dr. M.G.R. Medical University; Status: Completed (Aug 2014).

Thus, although the clinical studies highlighted above are commented upon herein, the fact remains that ten years further down the road, almost all studies of the biomedical or medicinal effects of moringa are still not the ultimate clinical trials that the Western medicine tradition requires for adoption of such therapies or preventive strategies. However, evaluating the overall quality of in vitro and animal study findings for the most promising applications of moringa, these studies can be highly informative. Understanding what they say should focus research strategy and help scientists to prioritize their research goals. In

particular, it should direct our attention to the clinical studies that have the highest likelihood of giving a definitive (e.g., Yes or No) answer rather than simply generating more studies because the data were inconclusive. Therefore we shall focus in the following sections, on the studies that address the areas of research which appear to have the most well-supported basis for further clinical efforts.

Anti-inflammatory and antioxidant

Anti-inflammatory and antioxidant effects will be discussed first. Antioxidant and anti-inflammatory studies by and large have been performed on cultured cells, and lead to general and overarching conclusions. Mechanistically, however, inflammation and oxidative stress are from a functional and pathophysiological perspective, at the very core of many chronic diseases (Fahey and Talalay, 1999; Fahey et al., 2012, 2013; Fahey and Kensler, 2013). These effects are absolutely central to many diseases, and these effects can be measured in vitro. Though traditional medicine has long observed this, the anti-inflammatory effects of *Moringa oleifera* roots were not well documented in the scientific literature until about two decades ago (Ezeamuzie et al., 1996). Most recently, for example, Waterman and colleagues (2014) showed the anti-inflammatory effects of isothiocyanate-rich extracts of *M. oleifera* in vitro, and Ndhlala et al. (2014) compared antioxidant variation between *M. oleifera* cultivars. However, associating antioxidative and anti-inflammatory measurements made in bodily fluids such as blood, urine, or sputum, with clinical symptoms of disease, are much more problematic. For example, Kushwaha et al. (2014) recently demonstrated changes in antioxidant profile and "oxidative status" upon monitoring blood/serum biomarkers in a trial in which 30 post-menopausal women were supplemented daily with 7 g of *M. oleifera* leaf powder for 3 months, but no symptom measurement was reported. Reports on the use of moringa in rodent models of disease have increased in recent years. For example Galuppo et al. (2014) have reported that the isothiocyanates of *M. oleifera* repress the inflammatory component of experimental autoimmune encephalomyelitis.

Though much has been written on the antioxidant activity of moringa extracts and leaves, as well as many other food and herbal medicinal ingredients, the real benefits of such antioxidant activity remains highly controversial. Whereas the lay public and the companies that market products to them appear to have resolved the controversy in favor of eating lots of antioxidants, the real value of such a strategy is still hotly debated in the scientific literature (Moyer, 2013; Bjelakovic et al., 2007; Guallar et al., 2013). Antioxidant effects will not be directly addressed herein from the perspective of moringa's medicinal value.

From the perspective of more specific medical indications, there are five areas that are now well supported within the moringa literature, and they hold strong promise for future and more definitive animal model and human clinical trials: antibiosis, chemoprevention (of cancer and other non-communicable diseases), diabetes, hypertension, and asthma.

Antibiotic activity

This is clearly an area in which the preponderance of evidence – both classical scientific and extensive anecdotal evidence – is overwhelming. The scientific evidence has now been available for over 60 years, although much of it is completely unknown to Western scientists. In the late 1940s and early 1950s a team from the University of Bombay (BR Das), Travancore University (P.A. Kurup), and the Department of Biochemistry at the Indian Institute of Science in Bangalore (P.L.N. Rao), identified a compound they called pterygospermin, a compound which they reported readily dissociated into two molecules of benzyl isothiocyanate [4] (Das et al., 1954, 1957a, b; Kurup and Narasimha Rao, 1952; Kurup and Rao, 1954a, b, c; Kurup et al., 1954; Narasimha Rao and Kurup, 1953).

Benzyl isothiocyanate was already understood at that time to have antimicrobial properties. This group not only identified pterygospermin, but performed extensive and elegant characterization of its mode of antimicrobial action in the mid-1950s. They identified the tree from which they isolated this substance as "*Moringa pterygosperma*", now regarded as an archaic designation for "*M. oleifera*". Although others were to show that

extracts of the moringa plants from which pterygospermin was reported to have been isolated, were antibacterial against a variety of microbes, the identity of pterygospermin was eventually challenged (Eilert et al., 1981) as an artifact of isolation or structural determination. Very recently, elegant computational chemistry and modeling performed by chemists at the University of Dayton (USA) concluded that pterygospermin would not be stable enough to exist in ambient conditions (Horwath and Benin, 2011). We must thus seek other phytochemicals to explain the very well documented antibiosis of moringa against certain environmental and clinical microbes.

Elegant and very thorough work, published in 1964 as a PhD thesis by Bennie Badgett (a student of the chemist Martin Ettlinger), identified a number of glyosylated derivatives of benzyl isothiocyanate [4] (e.g., compounds containing the 6-carbon simple sugar, rhamnose) (Badgett, 1964). The identity of these compounds was not available in the refereed scientific literature until "re-discovered" 15 years later by Kjaer et al. (1979). Seminal reports on the antibiotic activity of the primary rhamnosylated compound then followed, from Eilert and colleagues in Braunschweig, Germany (Eilert, 1978; Eilert et al., 1981). They re-isolated and confirmed the identity of 4-(α-L-rhamnopyranosyloxy)benzyl glucosinolate [1] and its cognate isothiocyanate [2] and verified the activity of the latter compound against a wide range of bacteria and fungi. Since then, we and others have done much work to isolate, purify, and identify the antibiotic compounds in moringa, as well as isolating and characterizing the enzyme (myrosinase; E.C. 3.2.1.147) that is responsible for converting precursor glucosinolates such as [1] above, to isothiocyanates such as [2] (Bennett et al., 2003; Fahey et al., 2003, 2004, 2013; Wade et al., 2007, 2015; Fisher et al., 2005; Haristoy et al., 2005; Waterman et al., 2014).

Extensive field reports and ecological studies (see Fahey, 2005) forming part of a rich traditional medicine history, claim efficacy of leaf, seed, root, bark, and flowers against a variety of dermal, internal, and parasitic infections including trypanosomiasis (Ayyari et al., 2014), dranunculaisis (Fabiyi et al., 1993) and mosquito-borne diseases (Pontual et al., 2014). Unfortunately, many of the reports of antibiotic efficacy in humans are not supported by placebo controlled, randomized clinical trials. Again, in keeping with Western medical prejudices, it would not be surprising if practitioners do not embrace moringa for its antibiotic properties. In this case, however, the in vitro (bacterial cultures) and observational studies provide a very plausible mechanistic underpinning for the plethora of efficacy claims that have accumulated over the years and were reviewed a decade ago (Fahey, 2005).

Aware of the reported antibiotic activity of [2-4], and other isothiocyanates and plants containing them, we undertook to determine whether some of them were also active as antibiotics against *Helicobacter pylori*. This bacterium was not discovered until the mid-1980s, a discovery for which the 2005 Nobel Prize in Medicine was awarded. *H. pylori* is an omnipresent pathogen of human beings in medically underserved areas of the world, and amongst the poorest of poor populations worldwide. It is a major cause of gastritis, and of gastric and duodenal ulcers, and it is a major risk factor for gastric cancer (having been classified as a carcinogen by the WHO in 1993). Cultures of *H. pylori*, it turned out, were extraordinarily susceptible to [2], and to a number of other isothiocyanates (Fahey et al., 2002; Haristoy et al., 2005). These compounds had antibiotic activity against *H. pylori* at concentrations up to 1000-fold lower than those which had been used in earlier studies against a wide range of bacteria and fungi. The extension of this finding to human *H. pylori* infection has been pursued in the clinic, and the prototypical isothiocyanate has already demonstrated some efficacy in pilot studies (Galan et al., 2004; Yanaka et al., 2005, 2009).

Cancer chemoprevention

Since *Moringa* species have long been recognized by folk medicine practitioners as having value in tumor therapy (Hartwell, 1971), we examined compounds [2] and [3] for their cancer preventive potential (Fahey et al., 2004). Recently, [3] and the related compound [4] were shown to be potent inhibitors of phorbol ester (TPA)-induced Epstein-Barr virus early antigen activation in lymphoblastoid (Burkitt's lymphoma) cells (Guevara et

al., 1999; Murakami et al., 1998). In one of these studies, [4] also inhibited tumor promotion in a mouse two-stage DMBA-TPA tumor model (Murakami et al., 1998). In a subsequent study, Bharali and colleagues examined skin tumor prevention following ingestion of drumstick (moringa seedpod) extracts (Bharali et al., 2003). In this mouse model, which included appropriate positive and negative controls, a dramatic reduction in skin papillomas was demonstrated.

Thus, traditional practice has long suggested that cancer prevention and therapy may be achievable with native plants. Modern practitioners have used crude extracts and isolated bioactive compounds. The proof required by modern medicine has not been realized because neither the prevention of cancer nor the modification of relevant biomarkers of the protected state has been adequately demonstrated in human subjects. Does this mean that it does not work? No. It may well work, but more rigorous study is required in order to achieve a level of proof required for full biomedical endorsement of moringa as, in this case, a cancer preventative plant.

Anti-diabetic activity

Diabetes is the most common metabolic disorder worldwide. It has become endemic in industrialized counties and it is a major public health problem. In much of sub-Saharan Africa, access to pharmaceuticals is minimal or absent, and people rely on medicinal plants to resolve their health problems. A cross sectional study in Senegal showed that out of 41 plants used for the treatment of diabetes, *Moringa oleifera* was the most common (Dièye et al., 2008). As indicated earlier, since reactive oxygen species are linked with the pathogenesis of chronic diseases such as hypertension and diabetes, plants with antioxidant properties are presumed to influence the etiology of these chronic diseases, and have been sought (Ogbunugafor et al., 2012).

Nine studies between 2003 and 2014 used moringa leaf extracts, in either aqueous or ethanolic solutions, to ameliorate glucose intolerance in rodent models of diabetes (Toma et al., 2012; Kar et al., 2003; Prakash et al., 2009; Momoh et al., 2013; Ndong et al., 2007; Jaiswal et al., 2009; Nardos et al., 2011; Divi et al., 2012; Yassa and Tohamy, 2014). In brief, these studies demonstrated reductions in fasting blood glucose, post prandial blood glucose, and oral glucose tolerance tests.

Seven studies have been conducted on humans, and six of these demonstrated an effect of moringa in reducing blood glucose in patients with type 2 diabetes (Table 1). Unfortunately, though, three of these six studies did not report including placebo controls (Sugunabai et al., 2014; Kumar and Naga Subrahmanyam, 2013; Kiranmayi and Babitha, 2011) thus reducing their potential impact and increasing the urgency for randomized controlled trials. Five of the seven studies enrolled type 2 diabetes patients as their study population, and the two that did not, report no reduction in blood glucose levels following treatment (Sandoval and Jimeno, 2013; Nambiar et al., 2010). Further, upon examining the three clinical studies in which placebo controls were used:

1. Giridhari et al. (2011) in Tamil Nadu, India, enrolled untreated controls, however, there was a large difference between the initial blood glucose of the controls (179) and the experimental group (210). Further, it was unclear precisely what the dose was (2 “tablets” of *M. oleifera* day^{-1}), how these groups were allocated, or whether there was randomization.
2. Kumari (2010), in Andhra Pradesh, India, was also not clear whether there was blinding, randomization, or how the treatments were allocated. However, in this study significant differences in fasting blood glucose, post prandial blood glucose, and lipid levels (LDL/HDL) were reported. Dose (8 g of dry *M. oleifera* leaf powder per day, for 40 d) was described, and the baseline glucose levels were similar for treated and control diabetic participants.
3. Vanisha Nambiar et al. (2010) in Gujurat, India, randomized 40 hyperlipidemic patients to either 4.68 g of dry *M. oleifera* leaves per day or a “no-supplementation” control. It was not made clear whether the study was blinded. Study subject allocation appeared reasonable (based on extensive baseline data), and

investigators reportedly observed the subjects eat half of their dose during dinner every day. In the experimental group there were significant decreases in the total cholesterol (TC), LDL/HDL ratio, TC/HDL ratio and non-HDL (total cholesterol minus HDL). There were no changes in any other parameters of the experimental group, including no change in fasting blood glucose. No significant differences were reported in the control group.

Anti-hypertensive activity

In the mid-1990s Faizi and colleagues in Karachi, Pakistan, followed up on moringa ethnobotanical observations of Cáceres et al. (1992), and on some of the early German phytochemical investigations (Eilert et al., 1981). They performed extensive isolation and characterization of both the 4-(α-L-rhamnosyloxy)benzyl isothiocyanate ([4]) and a series of related rhamnosyloxybenzyl compounds (partial list below), and demonstrated substantial hypotensive activity from many of these compounds using an anesthetized normotensive Wistar rat blood pressure bioassay (Faizi et al., 1992, 1994a, b, 1995, 1998). The compounds, named somewhat confusingly, include the following:

The first naturally occurring thiocarbamates (Faizi et al., 1992)

- Niaziminin A & B
- Niazinin A & B
- Niazimicin (e.g., [5] in Figure 1)

Nitrile glycosides (Faizi et al., 1994b):

- Niazirin (e.g., [6] in Figure 1)
- Niazirinin

The first naturally occurring carbamates (Faizi et al., 1994a):

- Niazimin A & B (e.g., [7] in Figure 1)
- Niazicin A & B

Certain of these anti-hypertensive rhamnosyloxybenzyl thiocarbamates and isothiocyanates were subsequently shown to be anti-trypanosomal (vs. *Trypanosoma brucei rhodesiense*), as well as cytotoxic against cultured rat skeletal myoblast (L6) cells (Ayyari et al., 2014). Aqueous and ethanolic leaf extracts containing a presumptive alkaloid have been used to demonstrate hypotensive effects on isolated frog hearts and guinea pig ilea, reducing chronotropic and ionotropic effects (Dangi et al., 2002). Similarly, studies with spontaneously hypertensive rats concluded that a *Moringa oleifera* leaf extract significantly reduced blood pressure (Kajihara et al., 2008; Chen et al., 2012), as did a similar study with normotensive guinea pigs (Mengistu et al., 2012). Although widely cited in the ethnobotanical and ethnopharmacologic literature as an anti-hypertensive, as of this writing, there are no relevant clinical studies for this indication.

Anti-asthmatic activity

One of the few published clinical trials with moringa was performed on patients with mild- to moderate bronchial asthma and it examined the effects of ingesting 3 g day^{-1} of finely powdered dried seeds for 3 weeks, in 20 patients (Agrawal and Mehta, 2008). The study was executed during visits to the outpatient hospital clinic in Gujurat, India. This open-label, non-comparative study reported significant improvement in lung volume (33% increase in forced vital capacity [FVC], and a 30% increase in forced expiratory volume in one second [FEV_1]), pulmonary function (32% increase in peak expiratory flow rate [PEFR], 20% increase in forced expiratory flow rate [FEF], and 35% increase in maximum ventilator volume [MVV]), as well as significant reduction of symptoms (reduced dyspnea, wheezing, chest tightness, and cough). In addition, ethanolic extracts of *M. oleifera* seeds reduced ovalbumin-induced airway inflammation in a Guinea pig model of asthma (Mahajan and Mehta, 2008; Mahajan et al., 2009). Possible mechanisms of action have been suggested to include inhibition of the immediate hypersensitive reaction, of histamine release, and of inflammatory cell infiltration into the airways (Goyal et al., 2009).

Other activity

As suggested at the beginning of this paper, other medical indications for moringa abound in the literature. One of the more interesting suggestions that is now supported by two powerful and apparently well-done animal studies, is the concept that some of the rhamnopyranosyl compounds may actually serve cardio- and cerebro-protective functions.

In the first of these studies, using a focal cerebral ischemia Wistar rat model in Thailand, Kirisattayakul et al. (2012) measured reduced oxidative damage, significantly decreased brain infarct volume at cortical and subcortical structures, elevated SOD activity in the hippocampus and striatum, and increased GSHPx activity in the hippocampus. Neither neuroprotective mechanism nor active ingredient were identified.

The second study, performed in India, demonstrated robust cardioprotection by a rhamnopyranosyl vincosamide (an indole alkaloid) from *M. oleifera* leaves, using an isoproterenol induced cardiotoxin model in rats (Panda et al., 2013). They provided evidence that cardioprotection involved preventing the disruption in cardiac myofibrils by reduction of oxidative stress, leading to improved cardiac contractile function.

CONCLUSIONS

There are thus a plethora of studies that have been published in the decade or so since this author's last review. However, there is still a dearth of well-designed and executed clinical trials in the Western medical tradition. Anecdotes continue to abound, and in the last ten years the popularity of moringa as a "miracle tree" has skyrocketed. The sheer volume of information on nutritional benefits – coming from all over the world – has indeed given credence to claims of proponents, silenced some critics, and likely saved lives or improved healthspan of many people who otherwise might not have ingested moringa. The same case cannot, and probably should not be made for moringa's medicinal benefits. Preclinical investigations, and a few small clinical trials are now beginning to support a short list of claims (anti-diabetic, anti-hypertensive, cardioprotective, anti-asthmatic, anti-inflammatory, antioxidant, chemoprotective). The antibiotic claims and studies stand alone, in that many such indications do NOT have an absolute requirement for clinical trials, although modification of clinical outcomes is at the root of many such claims. The author's erstwhile appeal to commercial purveyors of all things moringa NOT to raise false hope in regions and situations where hope is in short supply, still stands. No new evidence suggests anything but positive effects which, if applied in moderation will support overall healthy living. All recent evidence supports the need for further well-designed and rigorous clinical experiments to validate the most promising claims in human beings.

ACKNOWLEDGEMENTS

Portions of this paper are excerpted from a peer reviewed, copyrighted, open-access paper by the author that appeared in Trees for Life Journal 2005, 1:5 (http://www.tfljournal.org/article.php/20051201124931586) (Fahey, 2005), which contains a more comprehensive citation of the earlier references.

The author gratefully acknowledges: Robin Megill for valuable assistance in gathering and analyzing background literature; Gwen Chodur, Mark Olson, Katherine Stephenson, Paul Talalay, and Kristina Wade for ongoing support, enthusiasm, and encouragement in our past work with moringa; the Lewis B. and Dorothy Cullman Foundation for providing unrestricted research funds that have facilitated the preparation of this review and the author's work on antibiosis against *H. pylori*; NCI Grant # R01 CA93780 and funding from the American Institute for Cancer Research that helped to support work with moringa in the author's laboratory.

This paper is dedicated to Balbir Mathur, visionary founder of Trees for Life International.

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