Peer-reviewed version available at *Nutrients* **2017**, *9*, , 525; doi:10.3390/nu9050525

Review

Multifaceted Healthy Benefits of *Mangifera Indica* L. (Mango): The Inestimable Value of an Orchard Recently Rooted in Sicilian Rural Areas

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Abstract: Historically, *Mangifera indica* L. cultivations have been widely rooted in tropical areas of India, Africa, Asia and Central America. However, at least 20 years ago its spreading allowed the development of some cultivars, also in Sicily, the South of Italy, where the favorable subtropical climate and adapted soils represent the perfect field to create new sources of production for Sicilian agricultural supply chain. Currently, cultivations of Kensington Pride, Keitt, Klenn, Maya and Tommy Atkins varieties are active in Sicilian island and their products meet the requirements of local and European markets. Mango plants produce fleshy stone fruits rich in phytochemicals with an undisputed nutritional value for its high content of flavonoids, vitamins, micro- and macro-elements, vital for maintaining health. This review provides an overview of the antioxidant, anti-inflammatory and anticancer properties of Mango, a fruit that should be included in everyone's diet for its multifaceted biochemical actions and nutraceutical potential.

Keywords: *Mangifera indica* L. fruit; phytochemicals; nutraceutical properties; mangiferin.

1. Introduction

Nowadays, the use of medicinal plants and bioactive phytocompounds has seen a more growing interest. The importance of a diet rich in polyphenols has been long sponsored and underlined because of their radical scavenging action as well as anti-carcinogenetic properties [1]. Fruit and vegetables are a rich source of many different bioactive phytocompounds including phenolic components, anthocyanins, carotenoids, vitamin E and vitamin C, which exhibit good antioxidant properties and are therefore regarded as an unquestionable component that should be present in everyone's diet [1]. Epidemiologic studies have consistently shown that consumption of fruits and vegetables reduces the incidence of chronic diseases such as cancer, diabetes and cardiovascular disease [2- 4].

Fruits of tropical and subtropical regions are appreciated for their nutritional value as well as for the presence of health-enhancing compounds. *Mangifera indica* L. (mango) is known as "*the king of fruits*" because it is the most popular fruit in tropical regions. It is the national fruit of India and Philippines and the national tree of Bangladesh. The mango belongs to genus Mangifera, which consists of numerous species of tropical fruits in the family of *Anacardiaceae*. *Mangifera indica* L. is native to India and Southeast Asia where it has been cultivated for over 4,000 years for the good qualities of the fruits. Mango is now also grown in Central America, Africa, Asia, Australia, and from a few years in Europe. Over one hundred mango varieties are available worldwide, although only a few are grown on commercial scales. In the Mediterranean area Spain and Israel are the major

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producing countries. In Italy, particularly in Sicily, mango began to have an initial controversial departure in early '80s, but it was only 20 years later (2000) that its spreading took off, meeting the farmers enthusiasm to cover abandoned soils, previously dedicated to citrus groves and not more profitable for Sicilian rural market.

2. Plant

Mango tree is an evergreen, fast-growing and long-lived. It is very vigorous with a large canopy and a projection almost circular. The leaves are perennial, deep green, pointed and shiny, while the inflorescence occurs in panicles consisting of about 3,000 whitish-red or yellowish–green flowers. In tropical regions the trees can reach heights of 30-40 meters, while in subtropical areas the growth rate is significantly reduced. The mango fruit has hundreds of varieties, each having its own characteristic taste, shape and size. Each fruit measures from 5 to 15 cm in length and about 4 to 10 cm in width and its weight ranges from 150 g to around 750 g. Outer skin (exocarp) is smooth and is green in unripe mangoes, but it turns into golden yellow, crimson red, yellow or orange-red in ripe fruits, depending upon the cultivar type. The endocarp is a big core of ovoid-oblong, which contains a single seed. The pulp (mesocarp) is orange-yellow in color with numerous soft fibrils radiating from its centrally placed flat (Figure 1). Its flavor is pleasant and rich, and tastes sweet with mild tartness. Mangoes are consumed fresh or are processed for chutney, pickles, curries, dried products, puree, nectar and canned or frozen slices that are popular worldwide. The growing interest for *Mangifera indica* L. cultivations, that has been the focus of attention of many researchers around the tropical and subtropical areas, has to be searched in its phytochemical content that qualified mango fruit as a *superfruit model* [5].

Figure 1 Mango is native to India and Southeast Asia. (**A**). The fruit has a thin and colorful peel. (**B**). A yellowish-orange flesh represents the edible part. (**C**). Details of different mango fractions are reported, illustrating the outer peel (exocarp), the edible pulp (mesocarp) and the stony pit (endocarp) enclosing a big seed inside.

The chemical composition of mango pulp varies with the location of cultivation, variety and stage of ripeness. Chemical analysis of the fruit provided evidence that it has a relatively high content in calories (70 Kcal/100 g fresh weight) and is an important source of nutrients, such as carbohydrates, proteins, essential fatty acids, minerals (potassium, magnesium, calcium, phosphorus), fibers and vitamins. Nutritive value of mango fruits is listed in Table 1.

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Table1. Profile of *M. indica* nutrients, vitamins, minerals and carotenoid contents.

Mangifera indica* L.** ***Nutrition value per 100 g	
Energy	70 Kcal
Fruit composition	**Quantity**
Carbohydrates	14.96 g
Proteins	0.82 g
Fats	0.38 g
Fibers	1.6 g
Vitamins	
Vitamin C	36.4 mg
Vitamin E	1.12 mg
Vitamin A	1082 IU
Niacin (vit B3)	669 µg
Pantothenic acid (vit B5)	160 µg
Pyridoxine (vit B6)	119 µg
Riboflavin (vit B2)	38 µg
Thiamin (vit B1)	28 µg
Folates	43 µg
Vitamin K	4.2 µg
Minerals	
Potassium	168 mg
Phosphorus	14 mg
Calcium	11 mg
Magnesium	10 mg
Sodium	1 mg
Copper	110 µg
Iron	160 µg
Manganese	27 µg
Zinc	90 µg
Carotenoids	
Carotene-β	445 µg
Carotene-α	17 µg

Up to 25 diverse carotenoids have been identified in pulp fraction such as provitamin A, lutein, alpha-carotene and beta-carotene that account for the yellowish color of the pulp. Mango is also a particularly rich source of polyphenols, a diverse group of organic micronutrients found in plants which exert specific health benefits for their ability to scavenge free radicals via hydrogen or electron donation [6]. Polyphenols identified in mango mesocarp (pulp) include mangiferin, gallic acid, gallotannins, quercetin, isoquercetin, ellagic acid, and β-glucogallin [7, 8]. Gallic acid has been identified as the major polyphenol present in this fraction. During processing of mango, exocarp (peel) and seed are discarded. However, several studies reported that these mango by-products also

contain high levels of health-enhancing compounds. Mango exocarp has been found to be a good source of polyphenols, carotenoids, dietary fibers and vitamin E [9]. Polyphenols present in mango exocarp include mangiferin, quercetin, rhamnentin, ellagic acid and kaempferol [7, 8]. The analysis of exocarp polyphenolic content of different mango cultivars unveiled the highest level in Josè, Tommy Athkins, Ngowe, Haden and Heidi varieties [8]. Generally, ripe peels contain higher total polyphenols than raw peels [10]. Like mango pulp and peel, also mango seed kernels are equally rich in polyphenols with potent antioxidant activity. As reported by Jahurul et al. [9] mango seed kernels contain tannin, gallic acid, coumarin, caffeic acid, vanillin, mangiferin, ferulic acid and cinnamic acid. Finally, polyphenols are also present in mango leaves, flowers and stem bark.

Mango is one of the widely consumed tropical fruits in the world. Moreover, different parts of mango tree (fruit pulp, extracts of fruit kernel, leaves and stem bark) are used in traditional medicine for their health properties [11]. Mango kernel decoction is used as vermifuge and as astringent in diarrhea, hemorrhages and bleeding hemorrhoids. Extracts of unripe fruit, bark and leaves showed antibiotic activity. An aqueous stem bark extract from *Mangifera indica* L. is used in Cuba under the brand name of Vimang® as a remedy for diarrhea, fever, gastritis and ulcers.

The reason why mango should be included in everyone's diet lies in its content of phytochemical compounds and essential nutrients that brings undebated benefits to human health for its antioxidant, antitumor and anti-inflammatory properties. However, the nutraceutical properties of *Mangifera indica* change depending on which part of mango tree or fruit or which specific cultivar is considered.

3. Antioxidant properties of *Mangifera indica* L.

Nowadays, particular attention is paid to nutrients capable of counteracting oxidative stress. A certain number of reactive oxygen species, or ROS, including superoxide anion, hydroxyl and hydrogen peroxide, are produced in the human body by several enzyme systems. Some of them, as superoxide anion and hydrogen peroxide are physiologically generated during the electron transfer in the mitochondrial respiratory chain. Other species, as the hydroxyl radical, one of the more dangerous ROS, is produced by Fenton reaction causing the oxidation of Fe2+ to Fe3+.

These derivatives of oxygen, highly unstable and particularly reactive, oxidize atoms or organic molecules, especially cell components such as proteins, lipids and nucleic acids (DNA and RNA).

A specific group of enzymatic systems (catalase, superoxide dismutase, glutathione peroxidase, etc.) have been developed by cells to remove ROS and many of them are transcriptionally regulated by Nrf-2 (Nuclear factor erythroid 2–related factor 2), the master regulator of antioxidant response. Nrf2 is a transcription factor that in normal conditions is inhibited by Keap-1 (Kelch-like ECH-associated protein 1) that targets Nrf2 for ubiquitination and proteasomal degradation [12]. Under stress conditions, Nrf2 is stabilized and allows survival and stress adaptation upregulating the expression of some cytoprotective molecules, the antioxidant responses and the stress-mediated detoxification enzymes (NAD(P)H quinina reductase, glutathione S-transferase, superoxide dismutase, heme oxygenase, catalase and glutathione peroxidase) [13].

On the contrary, if ROS are not removed, their accumulation overcomes the cellular reparative abilities, causing the collapse of cellular functions and can concur to the generation of pathological states related to aging, cancer, atherosclerosis, heart stroke and diabetes.

It is well known that phytochemical compounds of phenolic nature commonly found in fruits display a free radical scavenging activity, due to the reactivity of the phenol moiety and via hydrogen or electron donation. Mango is a real functional food containing a large variety of antioxidants, pigments and vitamins that are present in any part of the plant and are endowed with antioxidant and free radical scavenging activity.

A plethora of carotenoids and polyphenols has been found in both pulp and peel fractions, although the highest content is present in the peel, where its phytochemical profile significantly differs in polyphenol composition, than in fruit pulp. Divergences in the polyphenolic content have been also found along the examined varieties. Studies performed on many different Mango cultivars to characterize their health beneficiary profiles provided evidence that biochemical properties of the fruit also change in relationship to the analyzed plant variety as well as to the ripening stage of the fruit. The analysis of different commercially ripe mangoes (*Mangifera indica* L.) from Bangladesh such as Fazli, Langra, Ashwina, Himsagor and Amrupali demonstrated, for example, the existence of differences in functional factors and antioxidant constituents (ascorbic acid and total phenol contents) present in the pulp which change from a cultivar to another [14]. Among all analyzed cultivars, Langra was found to have the higher phenol content as well as antioxidant properties compared to those of other four mango varieties, whereas Ashwina variety showed the highest content in ascorbic acid. The anti-scavenging activity of these cultivars was positively correlated with both ascorbic acid and total polyphenol contents.

4. Anti-inflammatory effects of mango

Several studies showed that phytochemicals contained in mango play anti-inflammatory role in several chronic pathological disorders associated with inflammatory responses. Inflammatory bowel disease, primarily including ulcerative colitis, is a chronic disease that is characterized by chronic inflammation and mucosal damage in the large intestine. This is associated with an increased risk of cancer of the colon and rectum [15]. Although the exact etiology of this disease is not fully known, the mucosa of patients has been shown to produce large quantities of pro-inflammatory cytokines, such as IL-1, IL-6, IL-12 and TNFα [16, 17]. These, in turn, induce the expression of enzymes associated with inflammation, such as iNOS and COX-2. The expression of pro-inflammatory cytokines is regulated by the nuclear factor kappa-B (NF-κB), a transcriptional factor whose level has been found increased in mucosa of inflammatory bowel disease patients [18]. Mango extracts have been shown to exert anti-inflammatory activity in experimental murine models of ulcerative colitis. In dextran sulfate sodium (DSS)-induced colitis model in mice, treatment with an aqueous stem bark extract from *Mangifera indica*, containing a mixture of polyphenols and flavonoids, attenuated the colitis symptoms, like body weight loss, colon shortening and diarrhea [19]. Moreover, mango extracts reduced the levels of iNOS, COX-2, TNF-α and TNFR-2 expression in colonic tissue, as well as decreased IL-6 and TNF-α serum levels [19]. These effects can be related to the ability of mango stem bark extract to inhibit NF-κB [20]. Furthermore, Kim et al. [21] reported that mango beverage, a mango pulp extract rich in polyphenols (475.90 mg/L gallic acid equivalent), reduced the inflammatory response associated with DSS-induced colitis in mice by inhibiting the IGF1R/AKT/mTOR pathway. Such an effect was attributed to gallic acid, the most prevalent polyphenol of mango pulp, which showed in silico modeling the ability to bind and inhibit the catalytic domain of IGF-1R [21]. In another study the same authors also showed that inhibition of mTOR pathway by mango polyphenols is in part due to the increased expression of miR-126, an inhibitor of the phosphatidylinositol 3-kinase (PI3K), an upstream activator of mTOR [22]. Many evidence support that mango also possesses gastro-protective effects. To this purpose, Severi et al. [23] showed that a *Mangifera indica* leaf decoction attenuated in mice the gastric damage induced by HCl/ethanol. This effect seems to be related to mangiferin and benzophenone glycoside, the main bioactive molecules present in leaf decoction. In this regard, Mahmoud-Awny et al. [24] reported that mangiferin mitigates gastric ulcer in ischemia/reperfused rats via inducing the expression of Nrf2, heme oxygenase (HO-1) and PPAR-γ (Peroxisome Proliferator-Activated Receptor gamma).

Bioactive compounds of mango have been also reported to exert anti-diabetic effects. Diabetes mellitus is a group of metabolic disorders associated with hyperglycemia and caused by defects in insulin secretion and/or action. Hyperglycemia induced advanced glycation end products (AGEs) which activate their receptors (RAGEs) resulting in NF-κB mediated release of pro-inflammatory cytokines. Activation of AGE-RAGE axis is associated with diabetic compliances, as cardiomyopathy and nephropathy. Pulp and leaf extracts of mango produced a significant

hypoglycemic effect in streptozotocin (STZ)-induced diabetic rats [25-27]. Furthermore, Gondi et al. [28] showed that also mango peel extracts have the ability to ameliorate diabetes. In fact, administration of different doses of peel extracts to STZ-induced diabetic rats resulted in significant decline in blood glucose levels, increased plasma insulin level as well as decreased levels of fructosamine and glycated hemoglobin, two diabetes status indicators. The anti-diabetic effect of mango peel extracts can be partially attributed to their ability to inhibit α-amylase and α-glucosidase, the carbohydrate hydrolyzing enzymes. This effect may be due to the presence of polyphenolic acids, like gallic acid, chlorogenic acid and ferulic acid, which have been shown to inhibit α-amylase and α-glucosidase activities [28]. Subclinical low-grade inflammation plays an important role in the pathogenesis of insulin resistance. Insulin-resistance and type II diabetes have been associated with obesity. Enlarged adipocytes and monocyte-derived macrophages alter the expression and secretion of adipokines favoring a pro-inflammatory state, where the production of inflammatory cytokines such as TNF-α and IL-6 is enhanced, while the production of adiponectin, an anti-inflammatory adipokine, is reduced. In this contest, evidence has been provided that in diabetic insulin-resistant rat model mangiferin caused a reduction of serum TNF-α and an elevation of serum adiponectin production as a consequence to PPAR-γ activation [29]. Moreover, mangiferin has also been shown to ameliorate diabetic compliances as cardiomyopathy and nephropathy. In this connection, Hou et al. [30] showed that in diabetic rat model chronic treatment with mangiferin decreased the levels of myocardial enzymes (CK-MB, LDH-1) and inflammatory mediators (TNF-α, IL-1β), as well as reduced the production of AGEs and their receptor RAGE.

Another study shows that chronic treatment with mangiferin significantly ameliorated renal dysfunction and reduced levels of AGEs and RAGEs in the renal cortex of diabetic rats. This last effect seems to be related to the ability of mangiferin to induce glyoxalase 1 (Glo-1), a detoxifying enzyme of methylglyoxal [31].

5. Anticancer effect of mango

Bioactive components contained in the different part of mango have also shown anticancer activity in different tumor cell lines. Nguyen et al. [32] showed that a methanol bark extract of *Mangifera indica* L. exerts cytotoxic effects in pancreatic cancer cells that correlated, among the isolated bioactive compounds, with mangiferolate and isoambolic acid. Ethanolic extract of mango peel induced apoptosis in human cervix adenocarcinoma HeLa cells by down-regulating the anti-apoptotic factor Bcl-2 and activating caspase proteases [33]. The presence of quercetin 3-O-galactoside, mangiferin gallate, isomangiferin gallate, quercetin-3-O-arabinopyranoside and mangiferin in these extracts can be responsible for this effect. An acqueous extract of mango pulp has been reported to exert antitumor activity in a human colon adenocarcinoma cell line as well as in a rodent model of colorectal cancer [34]. Moreover, Abdullah et al. [35] reported that an ethanolic extract of mango kernel is able to induce cell death in both estrogen positive and negative breast cancer cell lines, but not in normal breast cells. The cytotoxic effect of mango kernel extract in estrogen-negative breast tumor cells has been correlated with the production of ROS, which promotes apoptosis through Bax activation and cytochrome c release. In this contest it has also been reported that gallic acid and gallotannin-rich mango extracts exert antitumor effects in BT474 breast cancer cells and athymic mice bearing BT474 cells as xenografts through suppression of the PI3K/Akt/mTOR pathway [36].

6. Mangiferin: an unusual natural plant polyphenol by pleotropic nutraceutical features

Many studies, performed in order to analyze in details the chemical profiles and the mechanistic action of *Mangifera indica* fruit components, provided evidence that many of their anti-scavenging properties can be ascribed to mangiferin. Mangiferin is a plant natural polyphenol of xanthone structure with C-glucosyl linkage and four aromatic hydroxyl groups that have been considered crucial for its antiradical and antioxidant effect as well as for its pharmacological activity [37]. This polyphenolic xanthonoid is one of the most potent antioxidants known, mainly found in many Anacardiaceae and Gentianaceae plant families [38].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 April 2017 doi:10.20944/preprints201704.0161.v1

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This molecule has also been highlighted in some medicinal herbs, influencing their therapeutic and preventive properties, and in honeybush (Cyclopia sp.), a popular herbal tea widely spread in South African areas. Mangiferin is well soluble in water and can be easily extracted by infusion or in decoction preparations.

Mangiferin is differently distributed in many parts of mango plant and fruit. It has been found in the bark of plant (18.33 g/kg dry weight), in leaves and roots [39], in pulp, where its content can significantly vary depending on plant variety and fruit ripening stage (from 0.2 to 2.65 mg/kg dry weight) and in fruit peel (4.94 g/kg dry weight) which is the richest part of fruit in mangiferin [40].

The anti free-radical action of mangiferin relies in its ability to directly neutralize reactive oxygen species as hydroxyl radical [41], superoxide anion, hydrogen peroxide [42], 2,2-diphenyl-1-picrylhydrazyl (DPPH), as well as in the scavenging property of lipid peroxides, peroxynitrite free radicals and reactive oxygen species induced by heavy metal exposure [37].

Compelling evidence demonstrated that mangiferin displays an efficient iron chelating potential (Figure 2), counteracting the hydroxyl radical generation in Fenton reactions [43]. Moreover, the anti-scavenging activity of mangiferin seems to be related to its ability to modulate the Nrf2/ARE (antioxidant response element) signaling detoxification pathway or promote the activation of key detoxifying enzymes [44].

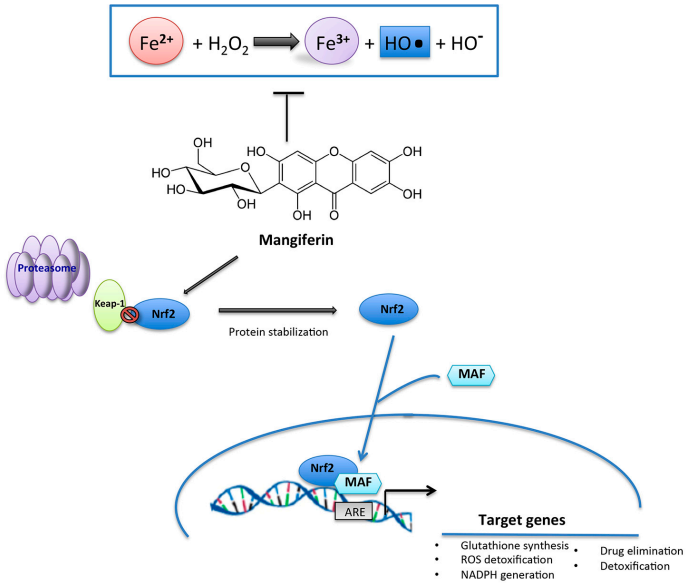

Figure 2 Schematic representation of the antioxidant actions of the xanthonoid Mangiferin.

Mangiferin has been proved to modulate Nrf2/ARE signaling pathway in healthy cells by increasing the Nrf2 half-life, the nuclear accumulation and the downstream production of NAD(P)H quinina reductase [44, 45].

Many published studies also indicated mangiferin as a new promising anticancer bioactive compound [46] able to inhibit cancerogenesis and cancer cell growth by apoptosis induction both in vitro and in vivo systems [47]. It has also found application in cosmetics [48], due to both antioxidant and UV-protection action [49].

7. Vimang®: the Cuban mango plant extract with antioxidant potential and beneficial effect for human health

Beyond the nutraceutical activities observed with Mango fruit extract, a significant antiradical action has also been observed by other parts of the plant. An example of the nutraceutical potential

of this plant is provided by an aqueous stem bark extract obtained from selected species of *Mangifera indica* L. and that is used as nutritional supplement in Cuba [50].

This extract has been recently employed in the preparation of some pharmaceutical formulations and is, currently, commercialized under the brand name of Vimang®. More than 217 cultivars of *Mangifera indica* L. exist, but only 17 of them are endowed with the right requirements for Vimang® extract preparation.

In some studies it provided health benefits to patients suffering from elevated stress also improving their quality of life and showed a potent anti-inflammatory activity both *in vivo* and *in vitro*. When administered in animals, Vimang® exhibited a potent and dose-dependent anti-nociceptive and anti-inflammatory action against acetic acid exposure in mice [50]. Such an effect was attributed to the presence of micronutrients as selenium and different polyphenols (amounted to 34g/100g gallic acid equivalents) such as phenolic acids, phenolic esters, flavan-3-ols and mangiferin, the most abundant component (up to 20% of all Vimang®), that could account for its powerful scavenger activity against hydroxyl radicals (OH·) and hypochlorous acid [51, 52]. This extract has been proved to be effective also against phospholipidic peroxidation in rat brains, counteracting DNA damages caused by iron/bleomycin or copper phenantroline exposure [53].

Vimang® has been registered in more than 21 countries where it has been introduced as dietary supplement and currently it is also available in Italy. For its anti-inflammatory and analgesics properties, it represents an important support to numerous pathological processes, such as chronical disorders as tumors, brain diseases and diabetes, especially to prevent complications as diabetic retinopathy, arteriopathy and diabetic neuropathy.

In some studies it has also been demonstrated that Vimang® exerts a neuroprotective and cognitive enhancing action for mild cognitive impairment (MCI), a prodromal phase of dementia, by increasing the activity of some scavenger enzymes such as superoxide dismutase, glutathione peroxidase, catalase and lowering malondialdehyde levels [54].

8. Diffusion of *Mangifera indica* cultivations in mediterranean Sicilian area

In the last years, the presence of specific and favorable pedoclimatic conditions allowed the rimodulation of rural areas of Sicily (southern Italy), through a strategic pathway of growth and valorization. This intervention strongly promoted in Sicily the introduction of subtropical orchards of Mango (*Mangifera indica* L.), Avocado (*Persea americana* Mill), Papaya (*Carica papaya* L.) and Lychees (*Litchi chinensis* S.) that could be more profitable than the arboreal cultivations of citrus or olive trees, historically rooted in Mediterranean area. These subtropical cultivations are able to conjugate the needs of territorial productive realities and the requirements expressed by different players of supply chain consumers for nutritional and organoleptic properties.

Fruits imported by Africa and Latin America are usually harvested unripe to finally reach European market, often resulting lacking in taste, scent and bioactive components that are so attractive for consumers. Differently, the Sicilian production offers quality, commercial ripe and consumption coinciding with market requirements and providing a fruit ripped in the tree that can easily reach European market within 24-48 h.

Many different Sicilian mango-growing provinces have been identified as particularly prone areas for the cultivation of Klenn, Maya, Tommy Atkins, Kensington Pride and Keitt varieties, which are preferentially distributed in Balestrate, regions between Caronia and Milazzo, Acireale and Fiumefreddo (Figure 3).

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Figure 3 Sicilian Mango plants and fruits. (**A**). Kensington Pride tree plantation in the province of Palermo (Balestrate). (**B**). Typical panicle inflorescence that stems at the apex of the branches carrying leaves and flowers. (**C**). Details of mango fruits growing on terminal shaped panicles inflorescences. (**D**). Mango fruits of Kensington Pride variety from Balestrate cultivated land. (**E**). Sicilian mango fruits ready for the market. All pictures in the Figure were gently provided by Ing. Luigi Martino.

The evaluation of organoleptic and sensory properties provided evidence that Sicilian mango fruit results better respect to those imported by extra-EU countries such as China and Madagascar [55, 56].

The interest for mango fruit also relies in the well-known benefits on health and its nutraceutical properties. In this scenario, considering our know-how in the study of oxidative stress and in the induction of cell death in tumor systems [57-63], we started some time ago to explore the antioxidant and anti-age properties of Sicilian mango extracts. Our preliminary results, using fruit extract from Kensington Pride cultivar grown and widely spread in Balestrate and other Sicilian rural areas, provided evidence that exocarp, mesocarp and endocarp of *Mangifera indica* L. can efficaciously counteract oxidative damage caused by reactive oxygen species modulating the enzyme based scavenger systems (*unpublished data*). A better understanding of the different healthy properties of this fruit could promote its consumption and make Sicily, also for its favorable climate, one of the most important exporters of mango, not only for Mediterranean area, but also for European consumers which have shown a growing interest for this flavored fruit enriched in bioactive healthy phytochemicals.

9. Conclusions

In modern society there is a growing interest in finding new bioactive molecules contained in the plants and fruits to be used both in food and pharmaceutical industry. Fruit and vegetables are

excellent sources of essential nutrients because of their high content in phytochemicals, such as phenolic compounds and flavonoids, which help to keep the consumer in good health. Great attention has been paid to phytochemicals present in different fractions of mango that can exert their beneficial potential counteracting either the action of pro-inflammatory molecules or reactive oxygen species associated to human pathologies such as cancer, cardiovascular diseases, aging and neurodegenerative diseases. A better characterization of phytocompounds found in Mango and a broader analysis of their properties could favor the production of phytopharmaceuticals to associate to the most common therapies for some human diseases treatment.

Acknowledgments: This work has been carried out with the financial support from Gruppo Azione Locale (GAL) of Golfo di Castellammare, Italy.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Liu, R.H. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am. J. Clin. Nutr.* **2003**, *78*:517S–520S.
2. Micha, R.; Peñalvo, J.L.; Cudhea, F.; Imamura, F.; Rehm, C.D.; Mozaffarian, D. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. *JAMA* **2017**, *317*:912-924.
3. Willett, W.C. Diet, nutrition, and avoidable cancer. *Environ. Health Perspect.* **1995**, *103*:165–170.
4. Temple, N.J. Antioxidants and disease: more questions than answers. *Nutr. Res.* **2000**, *20*:449–459.
5. Masud Parvez, G.M. Pharmacological Activities of Mango (Mangifera Indica): A Review *J. Pharmac. Phytochem.* **2016**, *5*: 01-07.
6. Shahidi, F.; Janitha, P.K.; Wanasundara, P.D. Phenolic antioxidants. *Crit. Rev. Food Sci. Nutr.* **1992**, *32*:67–103.
7. Berardini, N.; Carle, R.; Schieber, A. Characterization of gallotannins and benzophenone derivatives from mango (Mangifera indica L. cv. 'Tommy Atkins') peels, pulp and kernels by high-performance liquid chromatography/electrospray ionization mass spectrometry. *Rapid Commun. Mass Spectrom.* **2004**, *18*:2208-2216.
8. Berardini, N.; Fezer, R.; Conrad, J.; Beifuss, U.; Carle, R.; Schieber, A. Screening of mango (Mangifera indica L.) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins, and pectin. *J. Agric. Food Chem.* **2005**, *53*:1563-1570.
9. Jahurul, M.H.; Zaidul, I.S.; Ghafoor, K.; Al-Juhaimi, F.Y.; Nyam, K.L.; Norulaini, N.A.; Sahena, F.; Mohd Omar, A.K. Mango (Mangifera indica L.) by-products and their valuable components: a review. *Food Chem.* **2015**,*183*:173-180.
10. Ajila, C.M.; Bhat, S.G.; Prasada Rao, U.J.S. Valuable components of raw and ripe peels from two Indian mango varieties. *Food Chem.* **2007**, *102*:1006–1011.
11. Guevara Garcia, M.; Gonzalez Laime, S.; Alvarez Leon, A.; Riano Montalvo, A.; Garrido, G.G.; Nunez Selles, A.J. Ethnomedical uses of Mangifera indica L. stem bark extract in Cuba (spanish). *Rev. Cub Plant Med.* **2004**, *9*:27–32.
12. Ahmed, S.M.; Luo, L.; Namani, A.; Wang, X.J.; Tang, X. Nrf2 signaling pathway: Pivotal roles in inflammation. *Biochim. Biophys. Acta* **2017**, *1863*:585-597.
13. Done, A.J.; Traustadóttir, T. Nrf2 mediates redox adaptations to exercise. *Redox Biol.* **2016**, *10*:191-199.
14. Afifa, K.; Kamruzzaman, M.; Mahfuza, I.; Afzal, H.; Arzina, H.; Roksana, H. A comparison with antioxidant and functional properties among five mango (Mangifera indica L.) varieties in Bangladesh. *Int. Food Res. Journal* **2014**, *21*:1501-1506.
15. Duricova, D. What Can We Learn from Epidemiological Studies in Inflammatory Bowel Disease? *Dig. Dis.* **2017**, *35*:69-73.

16. Papadakis, K.A.; Targan, S.R. Role of cytokines in the pathogenesis of inflammatory bowel disease. *Ann. Rev. Med.* **2000**, *51*:289–298.
17. Rogler, G.; Andus, T. Cytokines in inflammatory bowel disease. *World J. Surg.* **1998**, *22*:382–389.
18. Andresen, L.; Jørgensen, V.; Perner, A.; Hansen, A.; Eugen-Olsen, J.; Rask-Madsen, J. Activation of nuclear factor kB in colonic mucosa from patients with collagenous and ulcerative colitis. *Gut* ***2005***, *54*:503–509.
19. Márquez, L.; Pérez-Nievas, B.G.; Gárate, I.; García-Bueno, B.; Madrigal, J.L.; Menchén, L.; Garrido, G.; Leza, J.C. Anti-inflammatory effects of Mangifera indica L. extract in a model of colitis. *World J. Gastroenterol.* **2010**, *16*:4922-4931.
20. Garrido, G.; Blanco-Molina, M.; Sancho, R.; Macho, A.; Delgado, R.; Muñoz, E. An aqueous stem bark extract of Mangifera indica (Vimang) inhibits T cell proliferation and TNF-induced activation of nuclear transcription factor NF-kappaB. *Phytother. Res.* **2005**, *19*:211-215.
21. Kim, H.; Banerjee, N.; Ivanov, I.; Pfent, C.M.; Prudhomme, K.R.; Bisson, W.H.; Dashwood, R.H.; Talcott, S.T.; Mertens-Talcott, S.U. Comparison of anti-inflammatory mechanisms of mango (Mangifera Indica L.) and pomegranate (Punica Granatum L.) in a preclinical model of colitis. *Mol. Nutr. Food Res.* **2016**, *60*:1912-1923.
22. Kim, H.; Banerjee, N.; Barnes, R.C.; Pfent, C.M.; Talcott, S.T.; Dashwood, R.H.; Mertens-Talcott, S.U. Mango polyphenolics reduce inflammation in intestinal colitis-involvement of the miR-126/PI3K/AKT/mTOR axis in vitro and in vivo. *Mol. Carcinog.* **2017**, *56*:197-207.
23. Severi, J.A.; Pinheiro Lima, Z.P.; Kushima, H.; Brito, A.R.; dos Santos, L.C.; Vilegas, W.; Hiruma Lima, C.A. Polyphenols with antiulcerogenic action from aqueous decoction of mango leaves (Mangifera indica L.). *Molecules* **2009**, *14*:1098-1110.
24. Mahmoud-Awny, M.; Attia, A.S.; Abd-Ellah, M.F.; El-Abhar, H.S. Mangiferin Mitigates Gastric Ulcer in Ischemia/Reperfused Rats: Involvement of PPAR-γ, NF-κB and Nrf2/HO-1 Signaling Pathways. *PLoS One* **2015**, *10*:e0132497.
25. Sharma, S.R.; Dwivedi, S.K.; Swarup, D. Hypoglycemic potential of Mangifera indica leaves in rats. *Int. J. Pharmacol.* **1997**, *35*:130-133.
26. Aderibigbe, A.O.; Emudianughe, T.S.; Lawal, B.A. Antihyperglycaemic effect of Mangifera indica in rat. *Phytother. Res.* **1999**,*13*:504–507.
27. Perpetuo, G.F.; Salgado, J.M. Effect of mango (Mangifera indica, L.) ingestion on blood glucose levels of normal and diabetic rats. *J. Plant Foods Hum. Nutr.* **2003**, *58*:1–12.
28. Gondi, M.; Prasada Rao, U.J.S. Ethanol extract of mango (Mangifera indica L.) peel inhibits α-amylase and α-glucosidase activities, and ameliorates diabetes related biochemical parameters in streptozotocin (STZ)-induced diabetic rats. *J. Food Sci. Technol*. **2015**, *52*:7883–7889.
29. Saleh, S.; El-Maraghy, N.; Reda, E.; Baraka, W. Modulation of Diabetes and Dyslipidemia in Diabetic Insulin-Resistant Rats by Mangiferin: Role of Adiponectin and TNF-α. *Ann. Brazilian Acad. Sci.* **2014**, *86*:1935-1948.
30. Hou, J.; Zheng, D.; Fung, G.; Deng, H.; Chen, L.; Liang, J.; Jiang, Y.; Hu, Y. Mangiferin suppressed advanced glycation end products (AGEs) through NF-κB deactivation and displayed anti-inflammatory effects in streptozotocin and high fat diet-diabetic cardiomyopathy rats. *Can. J. Physiol. Pharmacol.* **2016**,*94*:332-340.
31. Liu, Y.W.; Zhu, X.; Zhang, L.; Lu, Q.; Wang, J.Y.; Zhang, F.; Guo, H.; Yin, J.L.; Yin, X.X. Up-regulation of glyoxalase 1 by mangiferin prevents diabetic nephropathy progression in streptozotocin-induced diabetic rats. *Eur. J. Pharmacol.* **2013**, *721*:355-364.

32. Nguyen, H.X.; Do, T.N.; Le, T.H.; Nguyen, M.T.; Nguyen, N.T.; Esumi, H.; Awale, S. Chemical Constituents of Mangifera indica and Their Antiausterity Activity against the PANC-1 Human Pancreatic Cancer Cell Line. *J. Nat. Prod*. **2016**, 79:2053-2059.
33. Kim, H.; Kim, H.; Mosaddik, A.; Gyawali, R.; Ahn, K.S.; Cho, S.K. Induction of apoptosis by ethanolic extract of mango peel and comparative analysis of the chemical constitutes of mango peel and flesh. *Food Chem.* **2012**, *133*:416-422.
34. Corrales-Bernal, A.; Amparo Urango, L.; Rojano, B.; Maldonado, M.E. In vitro and in vivo effects of mango pulp (Mangifera indica cv. Azucar) in colon carcinogenesis. *Arch.Latinoam. Nutr.* **2014**, *64*:16-23.
35. Abdullah, A.S.; Mohammed, A.S.; Rasedee, A.; Mirghani, M.E.; Al-Qubaisi, M.S. Induction of apoptosis and oxidative stress in estrogen receptor-negative breast cancer, MDA-MB231 cells, by ethanolic mango seed extract. *BMC Complement Altern. Med.* **2015**,*15*:45-51.
36. Banerjee, N.; Kim, H.; Krenek, K.; Talcott, S.T.; Mertens-Talcott, S.U. Mango polyphenolics suppressed tumor growth in breast cancer xenografts in mice: role of the PI3K/AKT pathway and associated microRNAs. *Nutr. Res.* **2015**, *35*:744-751.
37. Matkowski, A.; Kuś, P.; Góralska, E.; Woźniak, D. Mangiferin—A bioactive xanthonoid, not only from mango and not just antioxidant. *Mini Rev. Med. Chem.* **2013**, *13*: 439–455.
38. Andreu, G.P.; Delgado, R.; Velho, J.A.; Curti, C.; Vercesi, A.E. Iron complexing activity of mangiferin, a naturally occurring glucosylxanthone, inhibits mitochondrial lipid peroxidation induced by Fe2+-citrate. *Eur. J. Pharmacol.* **2005**, *513*:47-55.
39. Barreto, J.C.; Trevisan, M.T.; Hull, W.E.; Erben, G.; de Brito, E.S.; Pfundstein, B.; Würtele, G.; Spiegelhalder, B.; Owen, R.W. Characterization and quantitation of polyphenolic compounds in bark, kernel, leaves, and peel of mango (Mangifera indica L.). *J. Agric. Food Chem.* **2008**, *56:*5599-5610.
40. Hewavitharana, A.K.; Tan, Z.W.; Shimada, R.; Shaw, P.N.; Flanagan, B.M. Between fruit variability of the bioactive compounds, β-carotene and mangiferin, in mango (Mangifera indica). *Nutr. Diet* **2013**, *70*:158–163.
41. Lei, J.; Zhou, C.; Hu, H.; Hu, L.; Zhao, M.; Yang, Y.; Chuai, Y.; Ni, J.; Cai, J. Mangiferin aglycone attenuates radiation-induced damage on human intestinal epithelial cells. *J. Cell Biochem.* **2012**, *113*: 2633–2642.
42. Kawpoomhae, K.; Sukma, M.; Ngawhirunpat, T.; Opanasopit, P.; Sripattanaporn, A. Antioxidant and neuroprotective effects of standardized extracts of Mangifera indica leaf. *Thai J. Pharm. Sci.* **2010**, *34*, 32–43.
43. Gold-Smith, F.; Fernandez, A.; Bishop, K. Mangiferin and Cancer: Mechanisms of Action. *Nutrients* **2016**, *28*:396-421.
44. Zhang, B-P.; Zhao, J.; Li, S-S.; Yang, L-J.; Zeng, L-L.; Chen, Y.; Fang, J. Mangiferin activates Nrf2-antioxidant response element signaling without reducing the sensitivity to etoposide of human myeloid leukemia cells in vitro. *Acta Pharmacol. Sin.* **2014,** *35*:257–266.
45. Zhao, J.; Zhang, B.; Li, S.; Zeng, L.; Chen, Y.; Fang, J. Mangiferin increases Nrf2 protein stability by inhibiting its ubiquitination and degradation in human HL60 myeloid leukemia cells. *Int. J. Mol. Med.* **2014**, *33*:1348–1354.
46. Khurana, R.K.; Kaur, R.; Lohan, S.; Singh, K.K.; Singh, B. Mangiferin: a promising anticancer bioactive. *Pharm. Pat. Anal.* **2016**, *5*:169-181.

47. Núñez Selles, A.J.; Daglia, M.; Rastrelli, L. The potential role of mangiferin in cancer treatment through its immunomodulatory, anti-angiogenic, apoptopic, and gene regulatory effects. *Biofactors* **2016**, *42*:475-491.
48. Telang, M.; Dhulap, S.; Mandhare, A.; Hirwani, R. Therapeutic and cosmetic applications of mangiferin: a patent review. *Expert Opin. Ther. Pat.* **2013**, *23*:1561-1580.
49. Kawakami, C.M.; Gaspar, L.R. Mangiferin and naringenin affect the photostability and phototoxicity of sunscreens containing avobenzone. *J. Photochem. Photobiol. B.* **2015**, *151*:239-247.
50. Garrido, G.; Rodeiro, I.; Hernández, I.; García, G.; Pérez, G.; Merino, N.; Núñez-Sellés, A.; Delgado, R. In vivo acute toxicological studies of an antioxidant extract from Mangifera indica L. (Vimang). *Drug Chem. Toxicol.* **2009**, *32*:53-58.
51. Pardo-Andreu, G.L.; Dorta, D.J.; Delgado, R.; Cavalheiro, R.A.; Santos, A.C.; Vercesi, A.E.; Curti, C. Vimang (Mangifera indica L. extract) induces permeability transition in isolated mitochondria, closely reproducing the effect of mangiferin, Vimang's main component. *Chem. Biol. Interact.* **2006**,*159*:141-148.
52. Pardo-Andreu, G.L.; Paim, B.A.; Castilho, R.F.; Velho, J.A.; Delgado, R.; Vercesi, A.E.; Oliveira, H.C. Mangifera indica L. extract (Vimang) and its main polyphenol mangiferin prevent mitochondrial oxidative stress in atherosclerosis-prone hypercholesterolemic mouse. *Pharmacol. Res.* **2008**, *57*:332-338.
53. Martinez, G.; Delgado, R.; Pérez, G.; Garrido, G.; Núñez Sellés, A.J.; León, O.S. Evaluation of the in vitro antioxidant activity of Mangifera indica L. extract (Vimang). *Phytother. Res*. **2000**, *4*:424-427.
54. Wattanathorn, J.; Muchimapura, S.; Thukham-Mee, W.; Ingkaninan, K.; Wittaya-Areekul, S. Mangifera indica fruit extract improves memory impairment, cholinergic dysfunction, and oxidative stress damage in animal model of mild cognitive impairment. *Oxid. Med. Cell. Longev.* **2014**, *2014*:132097-132104.
55. Farina, V.; Mazzaglia, A.; Padoan, D.; Barone, F. Caratterizzazione chimico-fisica e sensoriale di frutti di mango (Mangifera indica L.) coltivati in Sicilia. *Acta Italus Hortus* **2013**, *12*:113.
56. Mazzaglia, A.; Farina, V.; Barone, F.; Lanza, C.M. Studio preliminare sulle caratteristiche sensoriali di frutti di mango prodotti in Sicilia. *Atti III Convegno Nazionale SISS* ***2010,*** Portici (NA), 1-2 dicembre, *1*:123-126.
57. Carlisi, D.; D'Anneo, A.; Martinez, R.; Emanuele, S.; Buttitta, G.; Di Fiore, R.; Vento, R.; Tesoriere, G.; Lauricella, M. The oxygen radicals involved in the toxicity induced by parthenolide in MDA-MB-231 cells. *Oncol. Rep.* **2014**, *32*:167-172.
58. Lauricella, M.; Carlisi, D.; Giuliano, M.; Calvaruso, G.; Cernigliaro, C.; Vento, R.; D'Anneo, A. The analysis of estrogen receptor-α positive breast cancer stem-like cells unveils a high expression of the serpin proteinase inhibitor PI-9: Possible regulatory mechanisms. *Int. J. Oncol.* **2016,** *49*:352-360.
59. Notaro, A.; Sabella, S.; Pellerito, O.; Vento, R.; Calvaruso, G.; Giuliano, M. The secreted protein acidic and rich in cysteine is a critical mediator of cell death program induced by WIN/TRAIL combined treatment in osteosarcoma cells. *Int. J. Oncol*. **2016,** *48*:1039-1044.
60. Campanella, C.; D'Anneo, A.; Marino Gammazza A.; Caruso Bavisotto, C.; Barone, R.; Emanuele, S.; Lo Cascio, F; Mocciaro, E; Fais, S.; Conway De Macario, E.; Macario; A.J.; Cappello, F.; Lauricella, M. The histone deacetylase inhibitor SAHA induces HSP60 nitration and its

extracellular release by exosomal vesicles in human lung-derived carcinoma cells. *Oncotarget* **2016**, *7*:28849-28867.

61. D'Anneo, A.; Carlisi, D.; Lauricella, M.; Puleio, R.; Martinez, R.; Di Bella, S.; Di Marco, P.; Emanuele, S.; Di Fiore, R.; Guercio, A.; Vento, R.; Tesoriere G. Parthenolide generates reactive oxygen species and autophagy in MDA-MB231 cells. A soluble parthenolide analogue inhibits tumour growth and metastasis in a xenograft model of breast cancer. *Cell Death Dis*. **2013**, *4*:e891.
62. Pellerito, O.; Notaro, A.; Sabella, S.; De Blasio, A.; Vento, R.; Calvaruso G.; Giuliano, M. WIN induces apoptotic cell death in human colon cancer cells through a block of autophagic flux dependent on PPARγ down-regulation. *Apoptosis* **2014**, *19*:1029-1042.
63. Marino Gammazza, A.; Campanella, C.; Barone, R.; Caruso Bavisotto, C.; Gorska, M.; Wozniak, M.; Carini, F.; Cappello, F.; D'Anneo, A.; Lauricella, M.; Zummo, G.; Conway de Macario, E.; Macario, A.J.; Di Felice, V. Doxorubicin anti-tumor mechanisms include Hsp60 post-translational modifications leading to the Hsp60/p53 complex dissociation and instauration of replicative senescence. *Cancer Lett*. **2017**, *385*:75-86.