Mangos and their bioactive components: Adding variety to the fruit plate of health.

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Abstract

Diet is an essential factor affecting the risk for the development and progression of modern day chronic diseases, particularly those with pathophysiological roots in inflammation and oxidative stress-induced damage. The potential impact of certain foods and their bioactive compounds to reverse or prevent destructive dysregulated processes leading to disease has attracted intense research attention. The mango (*Mangifera indica* Linn.) is a tropical fruit with distinctive nutritional and phytochemical composition. Notably, the mango contains several essential water- and lipid- soluble micronutrients along with the distinguishing phytochemicals gallotannins and mangiferin. *In vitro* and *in vivo* studies reveal various mechanisms through which mangos or their associated compounds reduce risk or reverse metabolic- and inflammation- associated diseases. Health benefits of isolated individual mango compounds and extracts from mango by-products are well described in the literature with less attention on the whole fruit. Here, we review and summarize the available literature assessing the health promoting potential of mango flesh, the edible portion contributing to the fruit plate of the diet, focusing specifically on modern day health issues of obesity and the risk factors and diseases it precipitates, including diabetes and cardiovascular disease. Additionally, the review explores new insights on the benefits of mango in brain, skin and intestinal health. Overall, the foundation of research is growing and supporting the potential role for mangos in reducing risk for inflammation- and metabolically- based chronic diseases.

KEY WORDS: mangiferin, gallotannin, polyphenols, gallic acid, diabetes, cardiovascular disease, inflammation, oxidative stress, insulin resistance, obesity

Introduction

Consuming a diet rich in fruits and vegetables is associated with a number of health benefits, including maintaining physiological function and reducing risk of a number of age and lifestyle related diseases, including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), Alzheimer's disease, cancers, among others [1]. In addition to contributing essential vitamins and minerals, fruits and vegetables also provide health promoting phytochemical components. The role of these components in health and disease risk reduction has been the subject of intense study in recent years. Risk factor reduction may occur through the action of these components' ability to impact cellular processes to maintain "normal" tissue function and or their ability to reestablish normal homeostasis when pathological shifts are underway. Recent hypotheses have focused on characterizing various health promoting attributes of fruits, including defining their phytochemical content and composition, their bioavailability and metabolite profiles, and determining their effects on health/disease risk endpoints. The focus of the present paper is on mango fruit and their bioactive components relative to health promoting properties.

Prior reviews on the health benefits of mango have focused on the bark, leaves, peel, and seed/kernel due to their high content of pharmacologically-active compounds and health promoting effects. In contrast, very little information is available on the flesh/pulp, the part which is mainly consumed as fresh produce or processed for juice or ingredients, such as purees and dried fruits. Mangos represent a fruit with distinctive nutritional and phytochemical interests for researchers, consumers and health professionals. Research is unveiling new insights about mangos and their role in adding variety to the fruit plate of health. The present review discusses these findings providing a brief background about the mango followed by a review of the

nutritional and phytochemical composition of mango fruit flesh/pulp, bioavailability of major compounds and current knowledge associated with body weight control, diabetes development and management, and related metabolic disturbances. Additionally, the paper will briefly explore new areas of opportunity for mango pulp delivering benefits for brain, skin and intestinal health. Information on mango peel, kernels, bark, and leaves or individual compounds are the topic of many other reviews, including many that have focused on cancer [2-5] and will not be discussed in any length here, although reference to fruit by-products or individual compounds are included for context, as appropriate. Research was identified primarily in Medline with PubMed searches on the following keywords: "mango", "mangos", "mango pulp", "mango flesh", "polyphenols", "mangiferin", "gallic acid", "gallotannin", "carotenoids" in association with "cardiovascular disease", "heart disease", "diabetes", "inflammation", "intestine", "oxidative stress", "oxidation", "body weight", "obesity", "Alzheimer's disease", "skin", "metabolism", "pharmacokinetics", "bioaccessibility" and "bioavailability". Searches were also conducted in Web of Science and by cross-reference reviewing of published papers.

Mango background

Mango (*Mangifera indica* Linn.) is a commercially important tropical fruit in the family *Anacardiaceae*. Mangos are stone fruits (drupe) containing one large seed surrounded by yellow-orange flesh. They have a rich cultivation history starting thousands of years ago in Southeast Asia. Today, mangos rank 4th in total production among major fruit crops worldwide contributing over 45,000,000 tons per year to the global fruit market [6]. Mango producing countries are manly tropical and sub-tropical, including India, China, Thailand, Indonesia, Philippines, Pakistan, and Mexico. However, since the 1970's mango production has increased

dramatically owing to increased production in non-traditional growing regions such as southeast United States of America (USA), Central and South America, Australia, Hawaii among other locations.

There are several hundred cultivars of mango; however, the world market is currently dominated by the cultivar "Tommy Atkins" due to its long shelf life and excellent ratings in handling and transport tolerance. In addition to Tommy Atkins, consumers in the USA may also find Ataulfos, Francis, Haden, Keitt, Kent, and Palmer cultivars [7]. Each mango cultivar varies in size, shape, color, texture and flavor. The pulp (edible part) of mango constitutes around 40-65% of total fruit weight depending upon variety [3] while the remaining portion is peel and seed, which is discarded as waste. Mangos are a climacteric fruit, which means they will ripen off the tree. The period of ripening is characterized by a series of endogenous biochemical changes, including enhanced production of ethylene and increased respiration rate [8]. With ripening, mango cultivars achieve their characteristic color, taste, aroma and desired softening. During this period nutritional and phytochemical composition will also change. Mangos are one of the few fruits that are utilized at different stages of growth and maturation. For example, "green" fruit may be used for products like pickles, chutney or sauces or beverages (*panna*), whereas ripe fruits may be eaten as fresh products, sliced for frozen or canned applications or made into fruit leathers, purees, nectar, or juices among other processed products. Besides commercial processing, their use is increasing in culinary applications such as in the preparation of salsas, fruit salads, chutneys, ice-creams and other mango flavored desserts [8].

Nutritional and Phytochemical Content of Mangos

Mangos contain various nutrients including carbohydrates, organic acids, dietary fiber, and vitamins C along with other vitamins and minerals (**Table 1**). The major soluble sugars in mango are sucrose, fructose and glucose, while citric and malic acid are the predominant organic acids [9]. The fruit taste is dependent upon the balance between these two components and their content varies from 40-77% depending upon stage of maturity [10]. Apart from the essential nutrients, mangos contain considerable amounts of non-essential components known as phytochemicals. Mangos consist of both simple and complex phytochemicals, most notably phenolic acids, mangiferin, carotenoids and gallotannins [11].

Phenolic acids: Mango flesh contains both hydroxybenzoic and hydroxycinnamic acid derivatives, the two major categories of phenolic acids in plants. These phenolic acids are present in free or conjugated forms, commonly as simple esters with quinic acid or glucose [12, 13]. Among the hydroxybenzoic acids, gallic acid, vanillic, syringic, protocatechuic acid, p-hydroxybenzoic acid have been reported in flesh while hydroxycinnamic acid derivatives include p-coumaric acid, chlorogenic acid, ferulic acid and caffeic acid [14, 15]. The phenolic acid type and content varies with variety, geographical location and ripening stage. Abbasi et al., 2015 [14] compared the phenolic acid content in the pulp and peel of nine mango cultivars grown in China. Ferulic acid was reported to be highest in mango pulp measuring up to 33.75±1.44 mg/100 g fresh weight ((FW)), followed by protocatechuic (0.77±0.01- 6.83±0.53 mg/100 g FW), chlorogenic (0.96±0.06- 6.20±0.41 mg/100 g FW), gallic (0.93±0.08- 2.98±0.23 mg/100 g FW), vanillic (0.57±0.09- 1.63±0.09 mg/100 g FW) and caffeic acids (0.25±0.04- 1.12±0.10 mg/100 g FW). Similarly, the major phenolic acids in Ataulfo mango pulp were identified and quantified at four ripening stages [15]. Chlorogenic acid was most abundant in Ataulfo mango pulp, followed by

gallic, vanillic and protocatechuic acids showing an increase of 90%, 4%, 30% and 56% at the final ripening stage, respectively.

Contrary to these studies, Kim et al., 2009 [16] reported gallic acid as the major phenolic acid in mango pulp (Tommy Atkins cultivar) since they were unable to quantify the other identified phenolic acids (p-hydroxy benzoic, p-coumaric, and ferulic acids) due to low concentration. Compared to other fruits like banana, guava and orange, mango showed the highest content of total (soluble and insoluble fraction) phenolic acids, with gallic acid reported in the highest content [17]. Likewise, in another study comparing phenolic acid content of mango, durian and avocado fruits, mangos had the highest content of gallic acid and total phenolic acids [18].

Carotenoids: Carotenoids are lipid soluble pigments responsible for yellow, orange and red color of the skin and flesh of mangos, although the reddish color of skin in some cultivars is contributed by anthocyanins as well [11]. Mangos contain two classes of carotenoids i. e., hydrocarbon carotenoids (such as α-carotene, β –carotene and γ-carotene), and oxygenated derivatives known as xanthophyll's (such as auraxanthin, antheraxanthin, neoxanthin, lutein, violaxanthin and zeaxanthin) [19, 20]. Apart from compositional variation among different mango cultivars due to factors such as genetic, environmental, stage of maturity, production practices, postharvest handling, processing, and storage [21], the major discrepancies in qualitative and quantitative data reported by different authors could be due to analytical procedures employed and the unstable nature of carotenoids. More than 25 different carotenoids (free form, butyrates and esterified compounds) have been identified [22, 23], however, the most abundant carotenoids in mango flesh appear to be *all-trans-β*-carotene, and *all-trans*- and 9-*cis*-violaxanthin [22, 24, 25]. A

study on seven Mexican mango cultivars reported the highest content of carotenoids was contributed by *all-trans-β*-carotene (ranging from 0.4-2.8 mg/100 g FW), *all-trans*-violaxanthin (0.5-2.8 mg/100 g FW) and 9-*cis*-violaxanthin (0.4-2.0 mg/100 g FW). Among different cultivars, Haden mangos had the highest content of all the three carotenoids [22]. Mango cultivar Keitt from Brazil showed the highest content of *all-trans*-violaxanthin (2.1±0.3 mg/100 g FW), followed by *all-trans-β*-carotene (1.5±0.2 mg/100 g FW), and 9-*cis*-violaxanthin (1.0±0.0 mg/100 g FW) [24]. *β*-carotene content in five different mango cultivars (Tommy Atkins, Haden, Keitt, Kent, and Ataulfo) obtained from four countries with multiple harvests over a year varied between 5-30 mg/kg FW puree (ie., 0.5-3.0 mg/100 g FW puree). The results showed that fruit cultivar had a greater influence on the *β*-carotene content than the country of origin or harvest date [26]. Another study compared the total carotenoid levels in 12 mango cultivars from Bangladesh at various stages of maturity (green, semi-ripe and ripe stages). The carotenoid content increased from green (0.003 mg/100 g edible portion) to semi-ripe (0.07 mg/100 g edible portion) and ripe stage (0.25 mg/100 g edible portion) [27].

Xanthones/Xanthonoids: These are bioactive compounds with C6-C3-C6 backbone structure with hydroxyl, methoxyl and isoprene units attached on A and B rings resulting in wide array of compounds, but mostly occur as ethers or glycosides [28]. They are found in a few higher plant families, fungi and lichen [29]. Six xanthone derivatives have been identified in Mango pulp namely mangiferin, dimethylmangiferin, homomangiferin, mangiferin gallate, isomangiferin and isomangiferin gallate [30-32]. The content of mangiferin and derivatives is very low in pulp compared to peel and seed. Mangiferin content in the pulp of Pica and Tommy Atkin cultivars from Chile was reported to be 4.24±0.10 mg/100 g FW and 3.25±0.10 mg/100 g FW, respectively [31]. Out of 11 Chinese mango cultivars studied, mangiferin was only detected in the

158 pulp of 5 cultivars with values ranging from 0.002-0.20 mg/g dry matter (0.032-3.20 mg/100 g
159 FW, values converted to fresh weight assuming 84 % moisture content in mangos) [30]. Among
160 four Brazilian mango cultivars the mangiferin content was highest in Uba cultivar 12.4±0.3
161 mg/kg dry matter (0.2±0.0 mg/100 g FW, values converted to fresh weight assuming 84 %
162 moisture content in mangos) and was not detectable in the pulp of Palmer cultivar [32]. Harvest
163 date and geographical location can also impact the mangiferin content. Ataulfo mango showed
164 increases in mangiferin content depending on harvest dates of early and late ranging from 22.7-
165 99.6 mg/100 g puree. Kent cultivar from Peru showed the highest mangiferin content at
166 11.0±11.6 mg/100 g puree while it was present only in trace amounts in Kent cultivar from
167 Ecuador [26]. Two studies reported significant variation among cultivars in the content of
168 mangiferin derivatives in the pulp. For example, Ramirez et al., 2013 [31] quantified mangiferin
169 gallate in the pulp of Pica cultivar at 2.35±0.03 mg/100 g FW; however, it was not detected in
170 the pulp of Tommy Atkins cultivar. Similarly, mangiferin gallate was not detectable in 3
171 Brazilian mango cultivars and only a small amount was present in Uba cultivar (1.3±0.00 mg/kg
172 dry matter, 0.02±0.00 mg/100 g FW, values converted to fresh weight assuming 84 % moisture
173 content in mangos) [32]. The content of homomangiferin varied between 1.71-1.96 mg/100 g FW
174 in Tommy Atkins and Pica mango pulp. A small amount of dimethylmangiferin was also
175 detected in the pulp of Pica mango cultivar [31]. In some Brazilian mango cultivars, isomangiferin
176 ranged from not detected to 1.1 mg/kg dry matter (or on FW basis: not detected to 0.02 mg/100 g
177 FW) and isomangiferin gallate was only present in Uba cultivar (4.5 mg/kg dry matter or 0.07
178 mg/100g FW) [32].

179 ***Flavonols***: Flavonols are flavonoid compounds and consists of the characteristic C6-C3-C6
180 backbone structure and double bonds between C-2 and C-3 of the C ring. They are commonly

present as *O*-glycosides but methylated, malonated and acetylated derivatives have also been reported [33-35]. The predominant flavonols in mango pulp are quercetin glycosides (glucose, galactose, rhamnose, xylose and arabinose) with kaempferol, isorhamnetin, fisetin and myricetin also reported in small quantities [18, 31, 36, 37]. Quercetin-3-*O*-glucoside is the major flavonol in mango pulp with values varying from 1.70±0.04 mg/100 g FW to 2.66±0.08 mg/100 g in Pica and Tommy Atkins cultivars, respectively[31].

Flavan-3-ols and condensed tannins: Flavan-3-ols and condensed tannins are monomeric and oligomeric compounds, respectively. They are flavonoid compounds formed from the characteristic C6-C3-C6 backbone structure, but without oxygenation at C4 and lack double bonds between C2-C3 of the C ring. Catechin and epicatechin are the monomeric units of condensed tannins, also known as proanthocyanidins [38]. Mango pulp contain monomeric units and catechin appears to be most abundant (1.72±1.57 mg/100 g FW) [39] and epicatechin is present in very low amounts, approximately 0.15±0.0 mg/100 g FW [40]. Ramirez et al., 2014 [31] identified procyanidin A dimers and its galloylated form in mango pulp. A comprehensive study on the proanthocyanidin content of some common foods reported that mango pulp contains monomers (2.3±0.1 mg/100 g FW), dimers (1.8±0.0 mg/100 g FW), trimers (1.4±0.0 mg/100 g FW) and tetra-hexamers (7.2±0.5 mg/100 g FW) [41].

Gallotannins and derivatives: Gallotannins are classified as hydrolysable tannins and consist of galloyl groups completely or partially substituting the hydroxyl groups of glucose (as a core molecule) resulting in a wide array of gallotannin derivatives. However, other polyols such as glucitol, hammamelose, shikimic acid, quinic acid and quercitol have also been reported as core molecules in some species [42]. In mango pulp, 11 gallotannins and their isomers have been

identified in different cultivars, including mono, di, tri, tetra, penta, hexa and hepta galloyl glycosides [43-45]. Apart from the aforementioned, several other gallic acid derivatives including conjugated forms with methyl groups have also been reported [45].

Recognizing that mangos are a climacteric fruit, they are generally harvested while still green and stored until ready for distribution. It is not possible to harvest all mangos at the same maturity stage which could be one of the factors affecting the homogeneity of batches, thus affecting the overall quality and nutrient composition [46]. In addition, the variability in phytochemical composition of mangos could be affected by several pre- and post-harvest factors such as environmental conditions (light, temperature, carbon and water availabilities), genetic factors, cultural practices, maturity at harvest, postharvest handling, storage and processing [46, 47]. Therefore, a certain amount of variability in values might always be expected making it important that fruit interventions in health research are chemically characterized. This chemical characterization, including content of components aid in reproducing findings across labs and contribute to the science-base for making dietary recommendations. Likewise, when expected biological effects are not observed, knowing the chemistry of fruit may be critically insightful in explaining results.

Bioavailability and metabolism of mango phytochemicals

Bioactive components (phytochemicals) from different dietary sources require being bio-accessible and to some degree bioavailable, depending on target organ system, to exert beneficial health effects. Bioaccessibility and bioavailability are two different terms used in pharmacokinetic analysis. For example, bioaccessibility is defined as the release of bioactive components from food matrix for absorption in the gastrointestinal tract (GI) [48] while

bioavailability is defined as the fraction of ingested compound or its metabolite that reaches the systemic circulation to exert a biological effect [49]. Bioavailability has a much broader meaning and includes digestion, absorption, metabolism, distribution and elimination of bioactive components/metabolites from the body. Phytochemical metabolism involves partial or complete degradation of compounds, changes in the functional groups (e.g., methylation, sulphation, etc.) and or conjugation with other molecules (e.g., glucuronidation, plasma proteins).

Mangos contain fat soluble (carotenoids) and water soluble (polyphenols) phytochemicals, both having different pathways of absorption and metabolism. In general, polyphenols are absorbed in the body in their aglycone form with the exception of some compounds such as anthocyanins. Their metabolism occurs throughout the GI tract beginning in the mouth by action of salivary enzymes and resident microflora where only limited hydrolysis of glycosides takes place. The structural modification of polyphenols (deglycosylation, hydrolysis) occurs in the stomach and small intestine (pH effects) along with the action of resident enzymes. Compounds that escape absorption from the upper GI tract pass to the large intestine where they undergo extensive breakdown by endogenous and microbial enzymes to phenolic acids and various other small molecules. The absorbed compounds can be further metabolized (glucuronidated, methylated and sulphated) by phase I and II enzymes in the small intestine, liver, kidney and various body tissues. While most of the absorbed compounds/metabolites will enter general circulation, some compounds will be excreted back into the small intestine via bile and be re-absorbed via entero-hepatic circulation. The kidney is the primary clearance pathway for absorbed compounds via excretion in urine. Unabsorbed phenolic compounds and microbial metabolites are excreted in feces.

Carotenoids, which are fat soluble phytochemicals undergo a different metabolic pathway than water soluble polyphenols. They are released from the food matrix by mastication, gastric action and digestive enzymes [50]. After being incorporated into micelles formed by dietary fat and bile acids, carotenoids are absorbed in the intestinal lumen (enterocytes) by passive diffusion and active uptake by apical membrane transporters [51]. Carotenoids like β-carotene are cleaved by enzymes within the enterocytes producing Vitamin A, and corresponding esters and oxidized forms which are incorporated into triglyceride rich lipoproteins called chylomicrons. The chylomicrons are metabolized forming chylomicron remnants. Chylomicrons and their remnants deliver carotenoids to extrahepatic tissue, but most will return to the liver where they are stored or re-secreted into blood with the very low density lipoproteins [50].

The bioaccessibility and bioavailability of mango phytochemicals has been studied *in vitro* and in animal models. Most of the bioavailability studies used isolated compounds (mangiferin) or extracts from mango leaf and mango seed kernels, which does not represent the delivery/absorption of phytochemicals from a complex food matrix such as mango pulp. However, there are a few in vitro, animal, and human studies assessing the bioavailability of phytochemicals from mango pulp (**Table 2**). In an *in vitro* digestion and absorption model, Epriliati et al., 2009 [52] found that dried mango and fresh fruit released lower levels of nutriome components (sugars, organic acids and β-carotene) than juices. The same group conducted another study using Caco-2 cell monolayers as human intestinal absorption model to investigate nutriome passages (sugars, organic acids and phytochemicals) from fruit digest solutions of fresh, dried and juiced mango, and concluded that phytochemical constituents, including carotenoids were not absorbed from the small intestine based on this model [53]. They also predicted that pectin might play a role in determining the rate of nutriome release and absorption.

In a simulated *in vitro* digestion model, the micellarization of β-carotene from Ataulfo mango pulp at different ripening stages in the absence or presence of chicken baby food was evaluated and uptake by Caco 2 cells was studied [54]. The micellarization of β-carotene from mango pulp increased with fruit ripening and in the presence of chicken baby food. However, the uptake of micellarized β-carotene by Caco 2 cells was only 17%. Low and co-workers conducted a series of studies on the effects of mastication on bioaccesibility of mango pulp phytochemicals followed by *in vitro* digestion and fermentation to mimic the effects of the GI tract [55, 56]. Mastication influences particle size and surface area of food. After *in vitro* digestion, smaller particles showed a greater % release of carotenoids, however bioaccessibility of xanthophylls was higher than β-carotene irrespective of particle size [55] . *In vitro* fermentation of chewed mango resulted in the formation of catabolites such as 4-hydroxyphenylacetic acid (within 4-8 h), while other compounds such as catechin derivative and 3-(4-hydroxyphenyl) propanoic acid were apparent at 48 h [56]. Blancas-Benitez et al., 2015 [57] studied the bioaccessibility of polyphenols associated with dietary fiber and the kinetics of release of polyphenols in mango (Ataulfo) paste and peel. The results showed that polyphenols associated with soluble fiber were higher than insoluble fiber in mango paste and the bioaccessibility of polyphenols from mango paste was around 39%. Gallic acid and hydroxybenzoic acids were the major polyphenols released after digestion reaching maximum concentration at 180 min. In a recent study aimed to increase the bioaccessibility of phenolics and carotenoids from mangos, oil-in-water excipient nanoemulsions were prepared, mixed with pureed mango and passed through a simulated GI tract. An increase in lipophilic bioactives was observed in nanoemulsions made with long chain triglycerides vs medium chain triglycerides; however, bioaccessibility of phenolics remained unaltered [58] (**Table 2**). There is only one animal model study conducted to study the effect of

293 food matrix (mango and carrots) on bioconversion efficiency of β carotene to Vitamin A [54, 59]. In
294 this study, Vitamin A depleted rats were fed with the same daily dose of β carotene from Ataulfo
295 mango, carrots and synthetic β carotene with and without soy bean oil. The results showed that
296 rats fed with carrots accumulated 37% less retinol than those fed mango without oil. A human
297 clinical trial assessing the bioavailability of carotenoids from mango (fresh, juice and dried)
298 showed an increase in plasma carotenoid content after all mango treatments, but was highest
299 after volunteers consumed the fresh mango followed by juice and then dried mango [60]. The most
300 recent clinical study was published by Barnes and co-workers [61] in which they evaluated the
301 urinary excretion of galloyl metabolites after 10 day consumption of mango fruit. They
302 characterized and quantified seven galloyl metabolites in urine; however, nothing was detected
303 in plasma. This could be due to limited bioavailability of polyphenols from mango pulp which
304 could be affected by several factors including food matrix, dose, inter-individual variations,
305 study design, or interactions of polyphenols and other food components during digestion and
306 absorption. Instrumentation sensitivity and analytical challenges could also result in undetectable
307 polyphenols and their metabolites.

308 Overall, the phytochemicals of mango are accessible for absorption; however, the site and
309 mechanism of absorption differs depending on the characteristics of the phytochemical and to
310 some degree the composition of co-ingested nutrients (i.e., lipids enhance carotenoid absorption).
311 Much less is known about the bioavailability and pharmacokinetic characteristics of polyphenol
312 constituents of mango fruit, yet the field is advancing to help understand the relationship
313 between these component and their health benefits.

314 **Obesity and Diabetes: Pathophysiology and Diet, general**

315 The prevalence of obesity and type 2 diabetes has increased sharply around the world
316 over the last two decades. The growth in both has presented health care challenges aimed toward
317 managing complications and reducing incidences. Obesity is characterized by excess adiposity,
318 although it is defined more routinely by a body mass index (BMI) of ≥ 30 kg/m^2. In Asia, obesity
319 may be defined at a lower BMI based on associated health risks [62]. Obesity is a major risk factor
320 for type 2 diabetes and a number of other diseases, including cardiovascular diseases (CVD),
321 osteoarthritis, non-alcoholic liver disease and some cancers. Obesity is typically characterized by
322 a state of chronic low grade inflammation, oxidative stress, hyperglycemia, hyperlipidemia and
323 insulin resistance, which serves to promote a number tissue and organ disturbances and
324 complications, from diabetes and CVD to Alzheimer's disease and cancer. Even in the absence
325 of obesity modern day eating patterns comprised of excess calories, readily available
326 carbohydrates and fats induce acute increases in glycemia, insulinemia, lipemia and markers of
327 inflammation and oxidative stress. Considering that people eat multiple times a day, every meal
328 becomes an opportunity for metabolic and inflammatory stress; or alternatively, an opportunity
329 for maintaining balance and protecting cells from the discourse of metabolic-oxidative-immuno-
330 disruption [63]. Therefore, the diet is a critical preventive and therapeutic tool to combat the
331 processes underlying obesity and diabetes and the aforementioned non-communicable diseases
332 apparent today.

333 Among the most consistent advice for promoting health and reducing disease risk is
334 regular consumption of fruits and vegetables. Unlike vegetables, the recommendations for fruit
335 intake are general and there is interest in the role individual fruit types can play in health,
336 particularly tropical fruits.

Mangos and Obesity and Diabetes

Mangos are a source of phytochemicals with a number of health attributes assigned to them, including anti-inflammatory, antioxidant, anti-diabetic, anti-obesity, anti-cancer, among others. The literature is dense in studies examining these effects using extracts from mango leaves, seeds, peels, bark and individual compounds such as mangiferin; however, very little of this work has been conducted after consuming the mango fruit. Reviewing the literature, we found only four articles studying obesity and or diabetes outcomes in animal models [64-67] (**Table 3**) and seven reports in humans [68-74] (**Table 4**). Much of the *in vivo* work on inflammation was captured as secondary measures in the aforementioned investigations or in models of colitis [75, 76]. *In vivo* evaluation of antioxidant properties of the mango flesh are few, captured in studies discussed in this paper or in animal models studying cancer [77, 78]. Much of the antioxidant work is conducted in cell culture and with extracts of individual compounds: mangiferin, gallotannins, gallic acid and are difficult to translate into in vivo effects [11, 79, 80]. The concentration at which compounds are used for in vitro studies may not relate to their concentration in vivo.

Apart from the few investigations available for review, important findings have been revealed about mangos relative to obesity and diabetes. The *in vivo* animal data using the high fat fed diet-induced obesity model suggests that mango and its associated constituents may have a role in reducing risk for obesity and diabetes. In this model, high fat diets increase weight gain and fat accumulation that leads to metabolic- oxidative- and immune- disruption that manifests in pre-disease states similar to those observed in humans, such as pre-diabetes and metabolic syndrome characterized by insulin resistance, glucose intolerance, dyslipidemia, elevated markers of inflammation, endothelial dysfunction, among others. Studies in rodents

supplemented with mango juice or freeze-dried mango fruit (1-10% of diet) reduced the high fat diet-induced increases in weight gain [64], increases in fat mass [64, 65] and impairments in metabolic endpoints, including reducing insulin resistance, total cholesterol (TC), TC to high density cholesterol (HDL) ratio, triglycerides (TG) and glucose concentrations [64, 65]. The data from these studies suggest that the action(s) of mango constituents may be due to changes in inflammatory status and adipose morphology possibly due to changes in fatty acid metabolism (i.e., peroxisome proliferator-activated receptor gamma (PPAR-γ), lipoprotein lipase (LPL) and fatty acid synthase (FAS) expression [64]. Another study using the same high fat diet-induced obesity model in mice found a dose of 10% mango in the diet (w/w) increased body weight and fat accumulation in mice compared to high fat diet alone or the 1% mango supplemented mouse diet, however, the 10% mango diet was the most effective in modulating gut bacteria in favor of *Bifidobacteria* and *Akkermansia* [66], bacteria that have been associated with reduced obesity and improved metabolic outcomes [81]. The study also found increased short chain fatty acid production and modulation of gut inflammatory cytokines, of which mango (at 1% or 10% of the diet) significantly increased the expression of anti-inflammatory cytokine interleukin 10.

In addition to diet-induced obesity, alloxan treatment induces type 1 and type 2 diabetes. Alloxan is toxic to the insulin secreting beta cells of the pancreas diminishing or fully ablating beta cell function. In an alloxan-induced diabetes model, mango pulp flour made from the Tommy Atkins cultivar was tested for effects on weight gain, energy intake, glycemia and hepatic glycogen content in a 30 day and 90 day protocol [67]. The 90 day protocol was designed to further test the lowest effective dose (5% mango flour) determined in the 30 day trial. Blood glucose concentrations at the end of 90 days was 66% lower than that in the diabetic controls and hepatic glycogen levels of the animals fed mango flour was 64% greater than in the controls. In

addition, the animals fed mango had a higher serum insulin level ($p < 0.05$) than those in the control group, which indicated restoration of beta cell function damaged by the alloxan treatment. Results also suggested animals were healthier and more metabolically stable on the mango diet as suggested by increased food intake and body weight gain, since the processes of uncontrolled diabetes induce accelerated catabolism of proteins, carbohydrates and fats and weight loss. The effects of the mango treatment on hepatic glycogen content are important and indicate restoration of glycogen metabolism shown to be diminished in poorly controlled type 1 and type 2 diabetes [82, 83]. Stimulation of net hepatic glycogen synthesis is relevant in glycemic control in general, and may be another mechanism by which mangos exert their anti-diabetes effects. Small amounts of fructose can have a catalytic effect in stimulating hepatic glycogen synthesis in humans augmenting hepatic glucose uptake and lowering the glycemic response to dietary carbohydrate. This may explain why lower doses of mango (1% of diet) performed better than higher doses in glucose tolerance test [65].

In humans, seven trials were identified that fed mango fruit or puree to individuals and measured obesity or diabetes endpoints. Among these, five were conducted in individuals diagnosed with type 2 diabetes and two were in people without diabetes who were obese [71] or generally healthy [70]. Among the non-disease groups, mango supplementation (10 g freeze-dried powder/d, Tommy Atkins) reduced glucose concentrations after 12 weeks compared to baseline measures (no control arm studied). The glucose-lowering effect of mango was observed in both male [-4.5 mg/dL (-0.25 mmol/L), $P = 0.018$] and female [-3.6 mg/dL (-0.20 mmol/L), $P = 0.003$] participants and was not associated with changes in body weight or body composition, although men were reported to have reduced waist circumference [71]. In a three-arm randomized controlled crossover design in healthy Mexican adults (n=38, 19 male, 19 female) fresh mango

puree (Tommy Atkins) resulted in a lower glucose response over 2 h compared to an equivalent amount of glucose (control); and purees that were hydrostatic high pressure processed resulted in lower glycemia than unprocessed puree, suggesting an opportunity for the food industry to consider technologies in their product development strategies that can deliver enhanced health promoting foods for people concerned about glucose control.

Studies conducted in people diagnosed with type 2 diabetes assessed the effects of mango on glycemic endpoints compared to glucose control [69], white/wheat bread controls [72, 73] and or other fruits [68, 69, 72-74]. Available carbohydrate was matched at either 50 g or 25 g equivalents and testing was performed over 2 or 3 h (**Table 4**). In three of the five studies in people with diabetes, mango reduced acute glucose excursions compared to 50 g glucose control [69] and 25 g carbohydrate equivalent wheat bread or alternative fruit control [73, 74]. Two other studies in people with diabetes reported either no difference in glycemia between mango and banana [68, 74] or increased glucose compared to white bread control [72]. The reason for the discrepancy in findings may be related to the diversity of the population being studied, since people can be at different stages of disease and be using different forms of medication for disease management. Additionally, sample sizes were relatively small (n=10-13) for the between subject variance expected in these trials. Two studies also measured postprandial insulin with no difference between mango and white bread control treatments [72] or other tropical fruits [74], except when compared to durian fruit, where the area under the insulin concentration curve was lower after mango compared to 25 g carbohydrate equivalent of durian fruit [74]. Collectively, the research suggests that people with diabetes mellitus do not experience heightened glycemic responses when consuming mango fruit; and moreover, there may be indication for therapeutic benefits specific to certain fractions of mango, including fractions rich in gallotannins and mangiferin [84,

[85]. Less well understood is the role mango consumption plays in the population *at risk* for type 2 diabetes. This is an area rich for investigation especially with animal and cell culture studies indicating effects on insulin resistance [65, 84], glycogen metabolism and a potential benefit for beta-cell pancreatic function [67, 86]. Future investigations with mango that focus on well-characterized populations of people with pre-diabetes will be important for revealing the health value of mangos in diabetes control.

Mangos and Cardiovascular disease

Cardiovascular diseases account for approximately 17.5 million deaths per year, representing 31% of all deaths globally. Obesity and diabetes contribute significantly to CVD risk. Diabetes increases the risk of a cardiovascular event by 3-4 times. Therefore, achieving a healthy body weight and managing cardio-metabolic risk factors is top priority for reducing risk for a cardiac event. The role of different fruits is emerging in helping to manage CVD risk factors; however less is known about mangos.

Reports testing mangiferin, mangiferin-rich extracts, gallotannins, or gallic acid supplementation on traditional risk factors such as lipid endpoints (ie., TC, TG, HDL) or blood pressure control have revealed improvements in lipid profiles in rat models [87-90] and reduced blood pressure elevation in spontaneously hypertensive rats [91], suggesting that mango fruit consumption may have similar effects, albeit these compounds are supplied in the flesh in lower amounts. Nonetheless, lower amounts of these compounds may still be important, considering additivity or synergistic effects when delivered with the full complement of mango phytochemicals and other fruit components, such as fibers and organic acids. No data in humans are available at present, however, feeding animals mango juice (Ubá mango, 35 mL/d) for 8

450 weeks resulted in reduced fasting TC, TC:HDL ratio, and TG [64] and 2 months of 1% or 10%
451 mango supplementation attenuated high fat diet induced increases in total cholesterol and fasting
452 free fatty acid in mice [65]. Although blood pressure has not been assessed after mango fruit
453 supplementation in either animals or humans, a study was recently published assessing effects of
454 a pure unripe mango fruit powder marketed as Careless™ on cutaneous blood flow and
455 endothelial function in ten relatively healthy women (mean age 55 ± 10 y and BMI 25 ± 3
456 kg/m^2). The study tested two doses (100 and 300 mg, no control intervention) and compared
457 results to baseline over a 6 h period [92] (**Table 3**). Endothelial dependent relaxation as measured
458 by EndoPAT™ was not different at 3h from pre-measurement values (baseline) or between doses
459 in this study. However, blood flow increased approximately 54% at 6 h over baseline in the
460 100 mg group and 35% over pre-measurement in the 300 mg group, which implies biological
461 activity resulting in micro-vascular dilation. For context, the intake of cocoa, known for its
462 microvascular effects, increased blood flow approximately 70% at 2 h in ten healthy women [93].
463 Cutaneous microcirculation influences thermoregulation, nutrient and oxygen delivery and
464 impacts skin health and appearance [94]. These data are preliminary but provide insight to the
465 potential of mangos in vascular function, since stimulation of endothelial nitric oxide synthase
466 and endothelial cell migration has been reported in cell culture [92, 95] and vaso-relaxation has
467 been demonstrated with mangiferin and gallotannin in rats and rabbits, respectively, albeit
468 compounds were not extracted from mango [96, 97].
469 Risk for thrombotic complications is increased in patients with diabetes and is a main
470 contributor to higher incidence of CVD and mortality due to ischemic heart disease. Increased
471 adhesion and aggregation of platelets are characteristic processes promoting thrombosis. Work
472 with mangos has not concentrated on platelets or a potential for anti-thrombotic actions per se;

however, administration of gallotannin (20 mg/kg) to wild type mice blocked ex vivo platelet aggregation induced by ADP or collagen [98]. The same study reported that pre-treating platelets with gallotannin (1,2,3,4,6-penta-O-galloyl-α-D-glucopyranose) blocked thrombin-induced release of P-selectin, secretion of ATP and aggregation along with significantly attenuating ADP- or thrombin- induced decrease in platelet cyclic AMP levels without altering basal or PGE-1 induced increase in cAMP levels. Interactions of mango with warfarin have also been reported increasing its anticoagulant effect, which could be due to mangos' high vitamin A content increasing blood levels of warfarin or due to other components of mango, such as gallotannin, adding to the effect of warfarin [99].

Underlying processes fueling CVD risk factors are suggested to be oxidative stress and chronic low grade inflammation, both which can lead to cellular and tissue damage and dysfunction. Addressing these imbalances is considered an important part of disease risk reduction and health. Animal and cell culture studies with mangos, including extracts from all parts i.e., flesh, leaf, peel, bark, seed, and individual compounds such as mangiferin and gallic acid and gallotannins show improved oxidative and inflammatory balance as measured by reduced reactive oxygen species, enhanced endogenous defenses and or reduced cytokine production. Collectively, the data suggest several potential targets for which mangos may have a role in reducing CVD risk factors. The data at present suggest exploring in greater detail the effects of mango fruit consumption on lipid and lipoprotein metabolism and endothelial and platelet function.

Emerging areas for Mango fruit Health Benefits

Brain: Addressing processes underlying disease can have benefits on many systems. Risk factors for Alzheimer's disease, for example, are shared with other common chronic diseases. With the exception of rare cases caused by known genetic mutations, Alzheimer's develops as a result of multiple factors rather than a single cause; and develops over several decades. Advancing age is the greatest risk factor, but Alzheimer's disease is not part of normal aging. Other risk factors include family history, apo E genotype, mild cognitive impairment, and cardio-metabolic risk factors [100]. Several studies in cell culture and animal models suggest mangiferin [101-103]and gallotannin [104, 105] have potent neuroprotective activity due to their antioxidant (scavenging ROS and increasing endogenous defenses) and anti-inflammatory effects, and ability to restore mitochondrial membrane potential in neuronal cells. Favorable behavioral outcomes have also been documented in accordance with the biochemical improvements after treatment with the individual compounds [104-106]. These data aid in understanding the potential active compounds in mango flesh. In an *in vitro* model of isolated rat brain mitochondria, mango fruit extract inhibited amyloid beta peptide-induced mitochondrial toxicity as measured decreased ROS formation, mitochondrial membrane potential collapse, mitochondrial swelling, and cytochrome c release [107]. In an animal model studying cognitive performance using step down passive avoidance task and elevated plus maze tasks, seven days treatment with mango fruit extract reversed aging- and scopolamine- induced memory deficits as assessed in both paradigms [108] (**Table 5**). Likewise, in a model of mild cognitive impairment, two weeks pre-treatment and one week post-bilateral injection with AF64A, mango fruit extract (12.5-200 mg/kg) improved memory and oxidative stress / defense status; and at the 50 and 200 mg/kg doses, increased cholinergic neurons density in the hippocampus [109]. Collectively, the data support actions of mango fruit in brain health with insight to the potentially active components. Further research is essential to elucidate active

ingredients in the flesh, including active metabolites relative to mechanism of action; notwithstanding, the need to demonstrate behavioral outcomes in humans, in which no data are available currently.

***Skin*:** The role of ROS producing oxidative stress and damage in skin aging has become increasingly appreciated over the last several decades. ROS are generated in normal physiological processes and increased under exaggerated or stressed physiological conditions, such as during mitochondria-catalyzed electron transport reactions and by neutrophils and macrophages during inflammation, respectively. ROS are also generated during environmental exposures such as to irradiation by UV light (sun light). The skin is a major environmental interface for the body placing it at continual risk for accumulated ROS, particularly from excessive UV exposure that can overwhelm endogenous defenses and damage cellular components than lead to "photo-aged" skin, skin cancer and other cutaneous inflammatory conditions [110]. The skin contains various mechanisms for oxidative defense; however, enhancing protection through the intake of antioxidant-rich foods has attracted attention in recent years.

Mangos contain both hydrophilic and lipophilic compounds with antioxidant properties ideal for protecting lipid-rich membranes and aqueous cellular components. Few studies have been published on mangos and skin health; however, the data look promising warranting further research. In a UVB-induced skin aging model, mango extract (100 mg/kg/d) inhibited increases in epidermal thickness and epidermal hypertrophy, and protected against UVB-induced collagen fiber damage as well as increased collagen bundles [111] (**Table 5**). Collagen is an important component of skin tissue providing stability and structural integrity. Degradation of collagen is considered a major contributor to wrinkle formation and skin appearance. Therefore, reducing

collagen damage and loss and or stimulating synthesis would be advantageous in maintaining healthy, younger looking skin. The protective effects of mango is thought to be due to its antioxidant capability and reducing damaging ROS [112, 113], and this effect appears to be associated with ethanol fractions of the mango fruit [113]. Likewise, studies with mangiferin alone indicate reduced oxidative stress, decreased activation of cellular stress pathways ie., ERK, MEK, JNK, AP-1, and decreased synthesis of matrix metalloproteinases MMP [112, 114], which is involved in collagen degradation.

***Intestinal health*:** Ulcerative colitis is a form inflammatory bowel disease characterized by overproduction of ROS relative to endogenous defenses and pro-inflammatory cytokines leading to chronic inflammation and mucosal damage in the large intestine [115]. Ulcerative colitis development is influenced by a number of factors including genetic predisposition, immune dysregulation, the composition of the microbiome and various environmental factors, including the diet [116, 117]. As described in various parts of this paper, a variety of cell culture and animal models of disease, including models of colitis and gastritis, have shown that mangiferin, neomangiferin and gallotannin as well as extracts rich in these compounds from non-edible, by-products of mango, reduce ROS, in part by inducing the expression of Nrf2 and HO-1 along with downregulating NF-κB via suppression of stress response pathways that would otherwise lead to a robust inflammatory response characterized by marked increases inflammatory cytokines, chemokines and iNOS, COX-2 among others [118-125]. Extending this research to better understand the role of mango fruit actions in inflammation-based intestinal diseases, mango fruit (Keitt cv) beverages were prepared from homogenized flesh and fed to dextran sodium sulfate (DSS) treated rats to induce chronic colitis. Extracts from the same fruit were prepared and molecular mechanisms investigated in lipopolysaccharide (LPS) stimulated non-cancer colon cells [75, 76]

(**Table 5**). In two studies, each studying mango in cells and animals, reported mango beverages or extracts from the fruit beverages significantly attenuated gene and protein expression of pro-inflammatory cytokines as well as reduced expression of upstream signaling proteins including PI3K, AKT, and mTOR, whereas, miR-126 was upregulated by the mango treatment. Proliferation indexes were reduced compared to control; however, ulceration scores were not reduced. In silico docking studies suggested mango extracts and gallic acid docked favorably into the IGF-1R ATP binding pocket; results that were corroborated by cell studies showing reduced expression of IGF-1R mRNA by 29% (10 mg/L GAE of mango extract) and by 39% with 4 mg/L of gallic acid. IGF-1R is involved in mTOR and MAPK pathways influencing inflammation and proliferation endpoints.

The DSS-induced colitis rodent model is a standard model that mimics changes in epithelial cell permeability and acute inflammation in the colon of humans with colitis. Different levels of severity can be induced making it a useful pre-clinical model for testing the therapeutic potential of agents to prevent or treat human ulcerative colitis. While much of the earlier work focused on the efficacy of individual compounds (ie., gallic acid, mangiferin), the results of this recent work demonstrates biologically relevant activity with mango fruit beverages. The results are promising and support further work, particularly related to understanding the relationship between mangos' effects on intestinal inflammation and improvements in the proliferation index but not ulceration scores. It may be that dose and treatment duration may be influencing results or the role of mango maybe more preventative and best used for managing disease process rather than wound healing. Continued research in the area will undoubtedly uncover these details.

Summary and Conclusions

Mangos contribute a number of valuable essential nutrients and exclusive bioactive components to the diet. However, bioavailability, metabolism and pharmacokinetic parameters of mango polyphenols have not been studied in detail and future studies can fill gaps in this area, which can guide clinical study design and support evidence associated with mango health benefits. Epidemiology indicates mango consumption is associated with better nutrients intake and diet quality [126]. *In vitro* and *in vivo* animal studies have indicated that mangos and their various extracts and individual components have anti-inflammatory and anti-oxidative properties, which serve as major targets for controlling the dysfunction and damage that these imbalances create leading to disease. Concerns about mango as a tropical fruit contributing to obesity and diabetes are outdated. The current research suggests otherwise, with human studies reporting benefits in glycemic control, possibly through improvements in insulin action and or glycogen synthesis bringing to bare the importance of dose (amount of mango consumed) and role of fructose. Newer work in mice has revealed benefits on the microbiome which future studies in humans may uncover as a critical factor in mango associated inflammation- and metabolic- benefits; locally in the bowel and systemically. Work on blood flow indicate potential benefits for vascular health and skin health, increasing cutaneous flow bringing protective nutrients to skin for fighting excess ROS. Likewise, eating mangos for systemic and gut health may also be important for brain health and deserves more investigation to reveal the benefits. **Figure 2** depicts the role mangos may play in human health. The review of the science provides insight for future directions and warrants follow up research in humans.

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Table 1: Nutritional Content of the Mango Fruit

Value/100g	Mangos, edible fruit flesh
Water (g)	83.46
Energy (kcal)	60
Protein (g)	0.82
Total lipid (fat) (g)	0.38
Carbohydrate, by difference (g)	14.98
Fiber, total dietary (g)	1.6
Sugars, total (g)	13.66
Minerals	
Calcium, Ca (mg)	11
Iron, Fe (mg)	0.16
Magnesium, Mg (mg)	10
Phosphorus, P (mg)	14
Potassium, K (mg)	168
Sodium, Na (mg)	1
Zinc, Zn (mg)	0.09
Vitamins	
Vitamin C, total ascorbic acid (mg)	36.4
Thiamin (mg)	0.028
Riboflavin (mg)	0.038
Niacin (mg)	0.669
Pantothenic acid (mg)	0.119
Folate, DFE (µg)	43
Vitamin A, RAE (µg)	54
Vitamin A, IU	1082

Vitamin E (alpha-tocopherol) (mg)	0.90
Vitamin K (phylloquinone) (µg)	4.2
Lipids	
Fatty acids, total saturated (g)	0.092
Fatty acids, total monounsaturated (g)	0.14
Fatty acids, total polyunsaturated (g)	0.071
Fatty acids, total trans (g)	0
Cholesterol (g)	0
Carotenoids	
Beta-carotene (µg)	640
Alpha-carotene (µg)	9
Beta cryptoxanthin (µg)	10
Lycopene (µg)	3
Lutein and zeaxanthin (ug)	23
Polyphenols	
Cyanidin (mg)	0.10
Catechin (mg)	1.7
Kaempferol (mg)	0.1
Myricetin (mg)	0.1
Proanthocyanidin dimers (mg)	1.8
Proanthocyanidin trimers (mg)	1.4
Proanthocyanidin 4-6mers (mg)	7.2

Source: National Nutrient Database for Standard Reference Service Release 28 Agricultural Research Services, United States Department of Agriculture, slightly revised May 2016. RAE-retinol activity equivalent; DFE-dietary folate equivalent

Table 2: Mango Bioaccessibility and Bioavailability

		STUDY DETAILS			RESULTS
Ref #	**First Author Date**	**Bio-Accessibility Availability Model**	**Methods, generally**	**Treatment**	**Analytical Chemistry**
52	Epriliati I 2009	*in vivo* Human mastication *in vitro* digestion and absorption	Effects of processing and in vitro digestion steps on carotenoid, sugar, and organic acid release from mango products were comprehensively studied. *In vivo* chewing experiments using 24 healthy adult volunteers was carried out prior to chewing simulation.	Mango Fresh Mango Juice Mango Dried	Dried and fresh fruits released lower levels of nutriome components than juices. Pectin may play a role in determining the rate of nutriome release and absorption
53	Epriliati I 2009	*in vitro* Cells Caco-2	Caco-2 cell monolayers as human intestinal absorption models were used to investigate nutriome passages from fruit digest solutions. Passage of sugars, organic acids, major phytochemicals (disappearances of apical carotenoids and phenolics).	Mango Fresh Mango Juice Mango Dried	Phytochemical constituents, including carotenoids suspected to NOT be absorbed from small intestine based on this model
54	Ornelas-Paz Jde 2010	*in vivo* Animal Vitamin A depleted rats	Vitamin A depleted rats were fed with vitamin A and carotenoid deficient diet and one of 5 the test foods for 2 weeks (Mango fruit cubes, carrot slices, synthetic β carotene ± soybean oil. The rats were sacrificed to measure liver retinol.	Mango flesh Carrot β carotene 2 weeks	↑ retinol accumulation was found in rats feeding the β carotene + oil. Rats fed with carrots accumulated 37% less retinol than those feeding mango without oil.

55	Low DY 2015	*in vivo* Human Mastication simulated gastrointestinal digestion	To investigate effect of mastication on carotenoid bioaccessibility from mango fruit tissue. After *In vivo* human mastication of mango pulp (coarse and fine chewer), collected chewed boluses were fractionated by wet sieving followed by gastrointestinal digestion.	Mango cubes	Small particle size ↑ % release of carotenoids after digestion Large particle size ↑ content of total carotenoids Bioaccessible = Xanthophylls > β-carotene irrespective of particle sizes Chewing reduced release of β-carotene (34%) and xanthophylls (by 18%).
56	Low DY 2016	*in vivo* Human Mastication *in vitro* digestion and colonic fermentation	To study the microbial biotransformation of polyphenols during in vitro colonic fermentation (48 h) of masticated mango and banana.	Mango cubes	Microbial metabolism-ring fission, dihydroxylation and decarboxylation Formation of catabolites 4-hydroxyphenylacetic acid (4-8 h) Catechin derivative and 3-(4-hydroxyphenyl)propanoic acid (up to 48 h)
57	Blancas-Benitez FJ 2015	*in vitro* Assay	Study to test the bioaccessibility of polyphenols associated with dietary fiber (DF) and the kinetics release of polyphenols in mango (Ataulfo) paste and peel.	Mango Pulp Paste Mango Peel	Polyphenols association with fiber Soluble DF > Insoluble DF ~40% bioaccessible Gallic acid & hydroxybenzoic acid released (paste, max ~180 min)
58	Liu X 2016	*in vitro* Assay simulated GIT	To investigate ways to increase the bioaccessibility of phenolics and carotenoids in mangoes. Oil-in-water excipient nanoemulsions using medium chain triglycerides (MCT) and long-chain triglycerides (LCT) were prepared, mixed with pureed mango and passed through a simulated gastrointestinal tract (GIT).	Mango Puree	↑ Lipophilic bioactives (eg., carotenes) LCT>MCT>Buffer ↔ Phenolics

59	Ornelas-Paz Jde 2010	*in vitro* Assay Caco 2 cells	To study the impact of stage of ripening of mango and dietary fat on micellarization during digestion of β-carotene (BC) and uptake by Caco 2 cells. Mango (Ataulfo) pulp with varied ripeness (slightly ripe, SR; moderately ripe, MR; fully ripe, FR) with or without chicken baby food (CBF)	Mango pulp Varied ripeness (SR, MR, FR) ± CBF	↑ micellarization of β carotene with ripening stage and when fruit mixed with CBF. Uptake of β carotene was 17% by Caco 2 cells.
60	Gouado I 2007	*in vivo* Human Healthy	Two groups (n=7 each) of healthy weight young adults (mid-20s y, BMI ~ 21.5 kg/m^2) were fed fresh, dried or juice of mango or papaya with bread and yogurt for breakfast. Blood collected at 0, 4, 8 h. Plasma carotenoids (lutein, alpha-carotene, beta-carotene, lycopene, cryptoxanthin) and bioavailability measured.	Mango Fresh (568 g) Mango Juice (565 g) Mango Dried (100 g) acute 8 h	↑ carotenoids in plasma Juice, Fresh > Dried for Bioavailability
61	Barnes RC 2016	*in vivo* Human Healthy	One-arm human pilot trial, healthy volunteers (age = 21-38 y, n = 11) consumed 400 g/day of mango-pulp (Keitt cultivar) for 10 days. Urine (12 h) and plasma analyzed for metabolites of gallotannins (GT), gallic acid, mangiferin.	Mango Pulp 400 g / day 10 days	7 metabolites of GA identified (urine) ↑ 2 metabolites after 10 d feed metabolites not detected in plasma

Arrows: ↑(increase)

Table 3: *In vivo* animal research on the anti- Obesity and anti-Diabetes effects of consuming Mango flesh.

STUDY DETAILS					RESULTS		
Ref #	**First Author Date**	**Disease area and Model**	**Methods, generally**	**Treatments Duration**	**Risk factors/ Biomarkers** ↓, ↔, ↑	**Oxidative & Inflammation Biomarkers** ↓, ↔, ↑	**Other data of interest** ↓, ↔, ↑
64	Gomes Natal DI 2016	Obesity Rats High Fat (HF) diet-induced Obesity	The effect of Ubá mango juice with and without peel extract (PE) on metabolic indices and adipose tissue and inflammation modulation in HF diet-induced obese Wistar rats. Control diet (AIN-93M).	Mango Juice (MJ) Diets: Control HF HF+MJ HF+MJ+PE 8 week MJ = 35 mL/d	HF+MJ vs HF ↓ BW, FM (visceral) ↓ Glucose, TG, TC, TC/HDL, ALT, AST HF+MJ ≥ benefit to HF+MJ+PE	HF+MJ vs HF ↑ PPAR-γ, LPL ↓ FAS, TNF-α ↔ Interleukin 10	HF+MJ vs HF ↓ adipose hypertrophy
65	Lucas EA 2011	Obesity Mice High Fat (HF) diet-induced Obesity	The effects of freeze-dried mango pulp (Tommy Atkins) in comparison with the hypolipidaemic drug, fenofibrate, and the hypoglycaemic drug, rosiglitazone, in reducing adiposity and alterations in glucose metabolism and lipid profile in mice fed a high fat (HF, 60% fat energy) diet. Control diet (AIN-93M).	Mango Pulp (M) Diets: Control HF+0% M HF+1% M HF+10% M HF+Fenofibrate (500 mg/kg diet) HF+Rosiglitazone (50 mg/kg diet) 8 week	HF+M vs HF ↔ BW ↓ Fat Mass ↑ Lean Mass ↓ Insulin Resistance ↑ Glucose Tolerance (1% Mango)		Mango results not different from Rosiglitazone

					↓ Lipids		
66	Ojo B 2016	Obesity Mice High Fat (HF) diet-induced Obesity	The effects of freeze-dried mango pulp in a high fat (HF, 60% fat energy) diet on body weight (BW), body composition, lipids, glucose, cecal microbial population (16S rDNA sequencing), short-chain fatty acid production, and gut inflammatory markers (mRNA abundance) in ileum and colonic lamina propria in C57BL/6 mice. Control diet (AIN-93M).	Mango Pulp (M) Diets: Control HF + 0% M HF + 1% M HF + 10% M 12 week	HF+10% M vs HF ↑ BW, FM, Insulin, non-HDL-c ↔ Glucose, TG, TC, HDL, PAI-1	HF+10% M vs HF ↑ Interleukin 10 (colon)	HF+10% M prevented HF-induced ↓ in Bifidobacteria, Akkermansia HF+10% M vs HF ↑ fecal acetic and butyric acids
67	Perpetuo GF 2003	Diabetes Rats Diabetic alloxan-induced	The effects of the intake of flour obtained from mango pulp (Tommy Atkins) in normal and diabetic (DM) rats. No effect in normal rats. Results shown for DM rats only.	Mango Pulp Flour (MPF) Diets: Control (0% MPF) 5% MPF 10% MPF 15% MPF 30 days (all diets) and 90 days (0%, 5%)	30 day study: 5,10,15% MPF ↓ Glucose 90 day study: 5% MPF ↓ glucose ↑ liver glycogen ↑ Insulin		30 day study: ↔ FI, BW 90 day study: ↑ FI, BW on 5%* * likely due to better control of diabetes

Arrows: ↓(decrease); ↔ (no effect); ↑(increase)

ALT: AST: BW: body weight; FAS: fatty acid synthase; FI: food intake; FM: fat mass; HDL: high density lipoprotein; LPL: lipoprotein lipase; non-HDL-c: non high density lipoprotein cholesterol; PAI 1: plasminogen activator inhibitor 1; PPAR-γ: peroxisome proliferator-activated receptor gamma; TC: total cholesterol; TG: triglycerides

Table 4: Biological Effects of Consuming Mango Fruit: *In vivo* Human Research

		STUDY DETAILS			RESULTS	
Ref #	**First Author Date**	**Disease area and Model**	**Methods, generally**	**Treatment Duration**	**Risk factors/ Biomarkers** ↓, ↔, ↑	**Other data of interest** ↓, ↔, ↑
68	Contractor Z 1999	Diabetes T2DM	Three-arm randomized controlled crossover design. Mango and Sapota effects on glycemic responses compared to banana in people with type 2 diabetes (T2DM, n=10). Banana control Outcomes: Glucose	Mango Fruit (M) Diets: Control (banana)* Mango* Sapota* *equi-25 g carbohydrate Acute 3 h	↔ glucose (AUC) M vs Control	
69	Edo AE 2011	Diabetes T2DM	Multi-arm randomized controlled crossover design. Various fruits, including mango, were studied in people with type 2 diabetes mellitus (T2DM, n=10). Glucose as control. Outcomes: Plasma glucose resposnes (PGR) was assessed by peak plasma glucose concentration (PPPG), maximum increase in postprandial plasma glucose (MIPG), 2h PG, incremental area under the glucose curve (IAUGC).	Mango Fruit (M) Diets: Control (glucose)* Mango* Other Fruits* *equi-50 g carbohydrate acute 2 h	M vs Control ↓ Glucose (PGR) M vs other fruits ↓ MIPG, IAUGC	

70	Elizondo-Montemayor L 2015	Diabetes Healthy	Three-arm randomized controlled crossover design. Healthy Mexican adults (n=38, 19 male, 19 female) participated in a randomized cross-over clinical trial to test glycemic responses to fresh mango puree (Tommy Atkins) processed by hydrostatic pressure (HP) vs unprocessed (UnP) Outcomes: glycemic index (GI) and postprandial glycemic responses.	Mango Puree (MP) Diets: Control (glucose) UnP-MP HP-MP acute 2 h	MP vs Control ↓ AUC Glucose, GI HP-MP vs UnP-MP ↓ Glucose (AUC), GI	↑ puree viscosity with HP
71	Evans SF 2014	Obesity Obese	One-arm human trial. Twenty obese adults (11 males, 9 females) ages 20-50 years old consumed freeze-dried mango pulp (10 g/d) for 12 weeks. Outcomes: Anthropometrics, biochemical parameters, and body composition were assessed at baseline and after 12 weeks mango supplementation.	Mango Pulp (M) Diets: freeze-dried M 10 g/d 12 week	M vs baseline ↔ BW ↔ Body Composition ↓ glucose	↓ hip circumference (males)
72	Fatema K 2003	Diabetes T2DM	Three-arm randomized controlled crossover design. Ranking of mango and papaya (Bangladeshi type) on glycemic index (GI) and insulinemic index (II) in people with type 2 diabetes (T2DM, n=13) over 3 h. White bread (WB) control. Outcomes: Insulin, glucose, C-peptide Serum C-peptide	Mango Fruit (M) Diets: Control (WB)* 250 g Mango* 602 g Papaya* *equi-25 g carbohydrate Acute 3 h	M vs Control ↑ glucose ↔ insulin, C-peptide	72

73	Guevarra MT 2000	Diabetes T2DM	Multi-arm randomized controlled crossover design. Ranking of fruits, including mango on glycemic responses in people with type 2 diabetes (T2DM, n=10). Wheat bread (WB) control. Outcomes: Glucose and Glycemic index (GI)	Mango Fruit (M) Diets: Control (WB)* Mango* Other tropical fruits* *equi-25 g carbohydrate Acute 3 h	M vs Control ↓ glucose (AUC) GI ~ 59
74	Roongpisuthipong C 1991	Diabetes T2DM	Multi-arm randomized crossover design. Mango compared to 4 other tropical fruits (banana, B; pineapple, P; durian, D; rambutan, R) on glycemic responses in people with type 2 diabetes (T2DM, female, n=10). No control group. Outcomes: Glucose and Insulin	Mango Fruit (M) Diets: Mango* Other tropical fruits* *equi-25 g carbohydrate Acute 3 h	M vs P, D, R ↓ glucose (AUC) M vs B ↔ glucose (AUC) M vs D ↓ insulin (AUC) M vs B, P, R ↔ Insulin (AUC)

92	Gerstgrasser A 2016	CVD Healthy	Two-arm, double-blinded, randomized cross over design. No control group. Healthy adults (n=10) consumed Careless™ (pure unripe mango fruit powder, Kili-Mooku cultivar). Outcomes: Microcirculation and endothelial function were assessed by the Oxygen-to-see system and EndoPAT™, respectively	Mango Fruit powder Careless™ 100, 300 mg no control group Acute 6 h	↑ cutaneous blood flow vs Baseline (w/100 mg dose) ↔ hyperemia	*In vitro* ↑ eNOS dose-dependently (Careless™ tested at 0-3000 µg/mL)

Arrows: ↓(decrease); ↔ (no effect); ↑(increase)

AUC: area under curve; BW: body weight; eNOS: endothelial nitric oxide synthase

Table 5: Emerging Areas of Mango Health Benefits: *In vivo* animal research in brain, skin and intestinal health.

STUDY DETAILS					RESULTS	
Ref #	**First Author Date**	**Disease area and Model**	**Methods, generally**	**Treatments Duration**	**Risk factors/ Biomarkers** ↓, ↔, ↑	**Oxidative & Inflammation Biomarkers** ↓, ↔, ↑
75	Kim H 2016	Intestinal Rat DSS-induced Colitis	Mango (Keitt) and pomegranate (POM) beverages were tested in colitis model on intestinal inflammation and pro-inflammatory cytokines in mucosa and serum. Outcomes: intestinal ulceration, pro- and anti-inflammatory cytokines	Mango Pulp beverage (MB) Diets: Control MB Pomogranate (POM) 10 weeks	↔ ulceration ↔ saquamous metaplasia ↓ colonic cell proliferation	↓ mucosal mRNA TNF-α, IL-1β, IL-6 ↓ serum: IL-1β, IL-6 ↑ IL-10 ↓ PI3K/AKT/ mTOR ↓ miR-126, Let-7a ↔ miR-21, miR-145, and miR-155
76	Kim H 2016	Intestinal Rat DSS-induced Colitis	Mango (Keitt) beverage was tested in colitis model assessing intestinal inflammation and pro-inflammatory cytokines in mucosa. Outcomes: intestinal ulceration, inflammatory cytokines, NF-κB, iNOS, COX-2 and IGF-1R-AKT/mTOR	Mango Pulp beverage (MB) Diets: Control (0 g MB) MB ~90 mg GAE/kg/d 6-8 weeks	↔ ulceration	↓ mucosal mRNA TNF-α, IL-1β, iNOS, COX-2 ↓ protein levels of : TNF-α, IL-1β, IL-6, iNOS ↓ PI3K/AKT/ mTOR ↓ miR-126, Let-7a ↔ miR-21, miR-145, miR-155

108	Kumar S 2009	Brain memory Mice	Ethanol extract of ripe Mango from local store was fed to mice for 7 days. Cognitive performances were examined using step down passive avoidance task and elevated plus maze task.	Mango Fruit Extract (MFE) Diets: Control (0 mg/kg MFE) 250 MFE mg/kg 500 MFE mg/kg 250 VitC mg/kg 7 day	↓ aging and scopolamine induced memory deficits in both tasks. Similar to Vit C	
109	Wattanathorn J 2014	Brain memory Rats MCI	Effects of mango fruit extract on memory impairment, cholinergic dysfunction, and oxidative stress damage in animal model of mild cognitive impairment. Outcomes: spatial memory, cholinergic neurons density, MDA level, and the activities of SOD, CAT, and GSH-Px enzymes in hippocampus.	Mango Fruit Extract (MFE) Diets: Control 12.5 MFE mg/kg 50 MFE mg/kg 200 VitC mg/kg 2 weeks pre- and 1 week post- MCI induction	↑ memory ↑ cholinergic neuron density (50, 200 mg doses)	All dose ↓ Ox Stress hippo campus ↓ MDA ↑ SOD GSH-Px

111	Song JH 2013	Skin Mice UVB-induced skin aging	Evaluation of water extract from dried mango against UVB-induced skin aging in hairless mice. Outcomes: wrinkle formation, epidermal thickness, collagen fiber damage. Control condition includes no UVB and no ME.	Mango Extract (ME) Diets: Control UVB (0 mg/kg ME) UVB (100 mg/kg ME) 12 weeks	↓ Wrinkle length and depth ↓ collagen fiber damage ↓ skin thickness

Arrows: ↓(decrease); ↔ (no effect); ↑(increase)

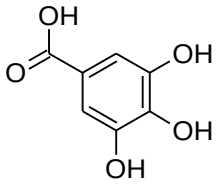
CAT: catalase; COX-2: cyclooxygenase-2; DSS: dextran sodium sulfate; GAE: gallic acid equivalent; GSH-Px; glutathione peroxidase; iNOS: inducible nitric oxide synthase; IL-1β: interleukin-1 beta; IL-6: interleukin-6; IL-10: interleukin-10; MCI: mild cognitive impairment; MDA: malondialdehyde; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-B; Ox: oxidative; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-alpha; UVB: ultraviolet B; Vit C: vitamin C

Figure Legends

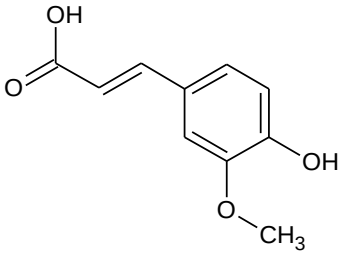
Figure 1: Major phytochemicals in Mango pulp.

Figure 2: Potential health benefits of Mango consumption.

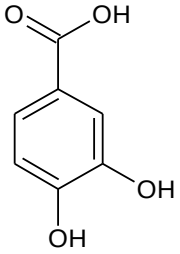
Phenolic acids



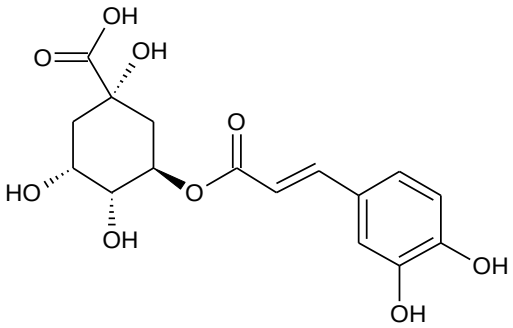
Gallic acid



Ferulic acid

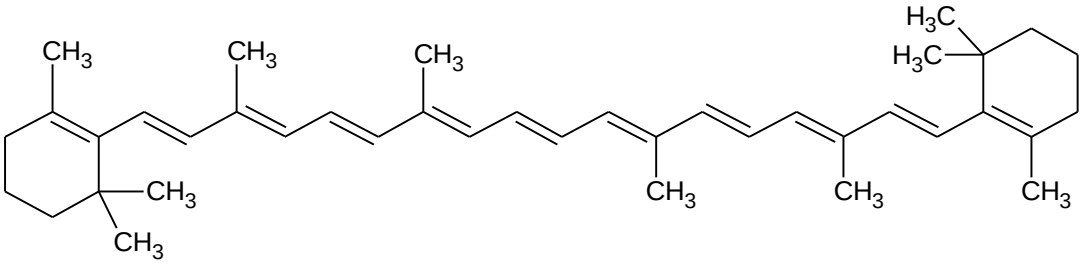


Protocatechuic acid



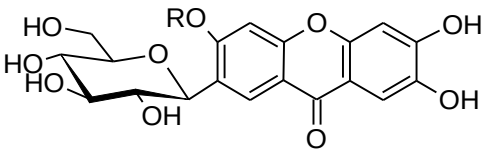
Chlorogenic acid

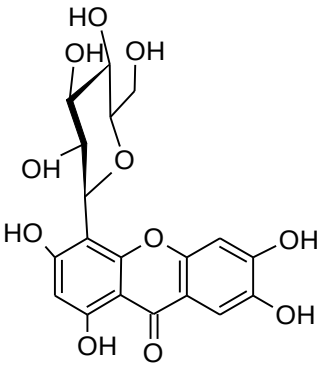
Carotenoids



Beta carotene

Xanthones/Xanthonoids



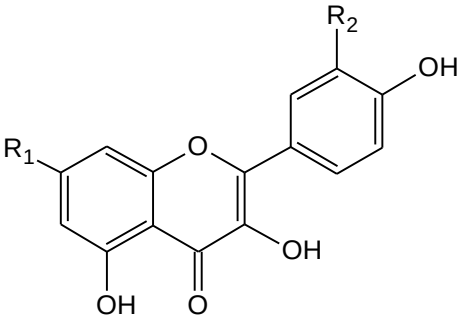


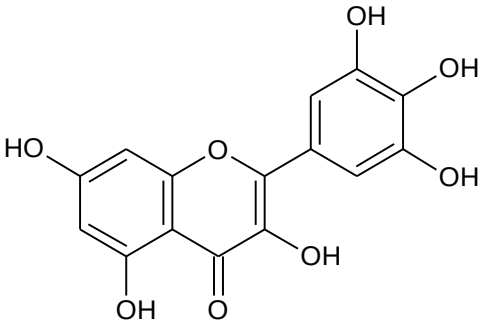
Mangiferin R=H

Homomangiferin R=Methyl group

Isomangiferin

Flavonols





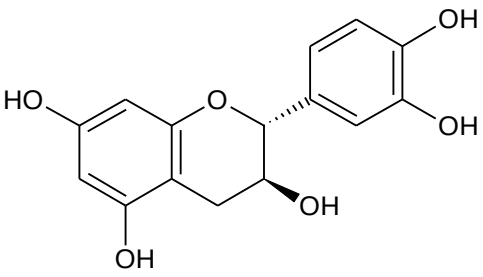
Kaempferol R_1=OH, R_2=H

Quercetin R_1=OH, R_2=OH

Isorhamnetin R_1=OH, R_2=OMe

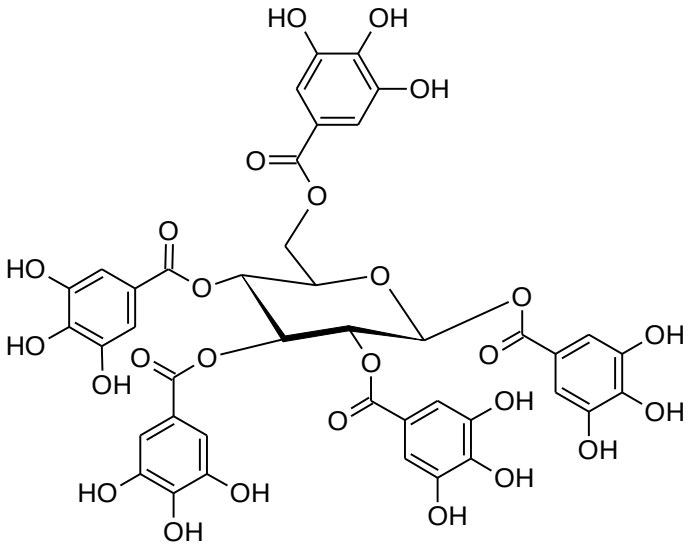
Myricetin

Flavan-3-als



Catechin

Gallotannins



Pentagalloylglucose

Figure 1

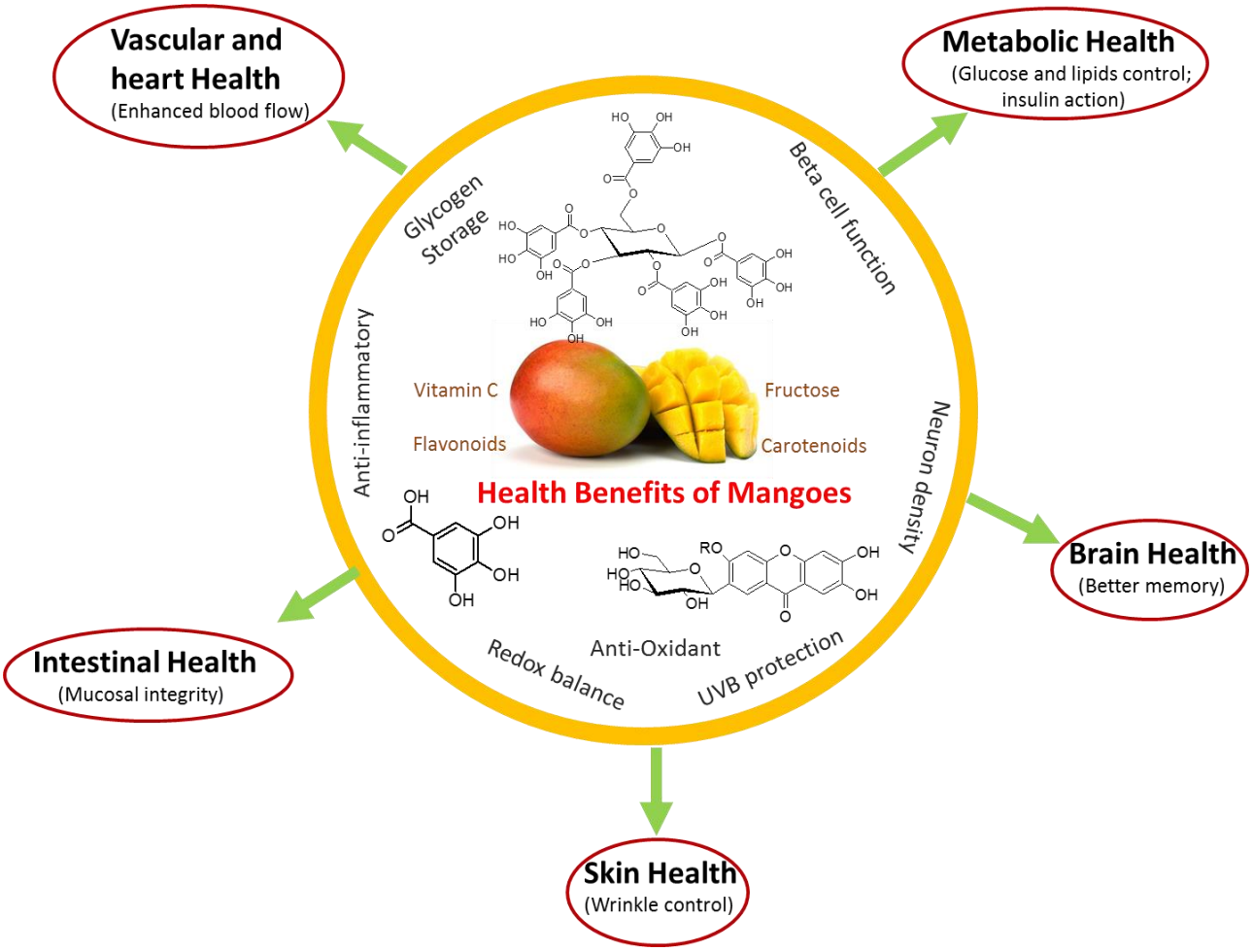

Vascular and heart Health
(Enhanced blood flow)
Metabolic Health
(Glucose and lipids control; insulin action)
Glycogen Storage
Beta cell function
Anti-inflammatory
Neuron density
Vitamin C
Fructose
Flavonoids
Carotenoids
Health Benefits of Mangoes
Anti-Oxidant
Redox balance
UVB protection
Brain Health
(Better memory)
Intestinal Health
(Mucosal integrity)
Skin Health
(Wrinkle control)

Figure 2