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Compositional Quality of Mangoes By-Product and Its Anticancer Activity in Human Cancer Cell Lines: An *in Vitro* Study

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SIGNIFICANT amounts of mango by-products, such as peels and seeds, could be considered as a source of bioactive properties and promising applications. The current research was designed to estimate the compositional quality of both mango kernels (MK) and peels (MP), the anticancer activity on human breast cancer cell line (MCF7), human colon cancer cell line (HCT116) and normal cell line (VERO). MK was significantly higher in moisture, crude protein, total lipids and total carbohydrate contents than MP, while MP was significantly higher in ash and crude fiber contents. Ca, K, Na and Mg were the major elements in mango kernels and peels. Total phenols (TP), total flavonoids (TF) and radical scavenging activity (RSA) were, also, determined. The TP in MK and MP was 2829.25 and 2565.21 mg GAE 100g, respectively. However, the antioxidant activity in MP and MK was 79.11 and 55.33%, respectively. Stearic acid (24.4 %) was the predominant saturated fatty acid in MK while oleic acid (44.34 %) was the main unsaturated one. Ellagic and pyrogallol were the most abundant phenolic acids in both MK and MP extracts through HPLC analysis. The highest flavonoid compound in MK and MP was the hesperidin component. The mixture of MK and MP powders showed a high cytotoxic activity against HCT116 (IC_{50}=45µg/mL) and MCF7(IC_{50}=58 µg/mL). In addition, the by-products samples showed antioxidant activity on all tested cell lines. As conclusion, this study confirmed that mango by-products could provide a natural source of antioxidant and anticancer molecules and can be used as food additives and therapeutic agents.

Keywords: Mango kernel, Peel, Phenolic compounds, Cytotoxicity, Antioxidant.

Introduction

During the last decades, big interest is given to the use of natural resources particularly plants for the discovery of new therapeutic agents. Furthermore, food industry aimed to supplement foods with polyphenols, carotenoids, or tocopherols obtained from natural sources. On the other hand, processed-fruits waste is known as a source of high-value compounds with a wide variety of bioactive properties and promising applications. As example, seeds and kernels are rich in mono- or polyunsaturated fatty acids, while pomace, peels, and some seeds are rich in antioxidants (Kao and Chen, 2013).

Mango *(Mangifera indica L.*) is known as one of the most important tropical fruits in the world. It is produced in large quantities and highly adopted by customers in fresh or refined form. According to the Food and Agriculture Organization (FAO) of the United Nations, Egypt produced more than 600 thousand Tons of mangoes in 2016 (FAO, 2016). Given that mango is a seasonal fruit, approximately 20% of production is processed in products such as nectar, puree and canned slices etc. that have worldwide popularity (Kim et al*.,* 2010). The mango industry uses only the edible parts of this fruit, and large amounts of mango peels and seeds are discarded as waste

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after consumption or industrial processing of the fruit. Industrial mango processing generates about 40-60% of fruit waste (15-20% of seeds and12-15% of peels) depending on the cultivars and products produced; none of them are currently used for commercial purposes (Nawab et al., 2016). Several thousand tons of mango seeds and peels are then discarded annually from the mango processing industry, creating serious environmental issues and if not efficiently used, leading to economic losses. Mango agro-industrial waste contains large amounts of high-value phytochemicals, making it ideal to be processed and used in food and pharmaceutical products. Mango peels are rich in phenolic compounds, dietary fiber, carotenoids, vitamin C and vitamin E (Ajila et al., 2007) whereas mango seed kernels contain substantial health-promoting compounds such as fatty acids and triacylglycerols (Lieb et al., 2018), gallotanins (Luo et al., 2014), and phenolics such as ellagic acid, gallic acid, and its derivatives, mangiferin and coumarin (Mwaurah et al., 2020). In another study, Sultana et al. (2012) reported that polyphenolics from mango kernels and peels exhibit an excellent antioxidant activity. The antioxidant potentials of plant bio resources, mainly contributed by their bioactive compounds, have been closely linked to their ability to suppress growth of cancer cells, likely through decrease oxidative stress, which may play a role in the development and progression of cellular damages underlying cancerous growth. As such, it has been suggested that antioxidant supplementation may reduce cancer recurrence and mortalities (Fleischauer et al., 2003). In particular, consumption of foods and beverages rich in polyphenols such as flavones, catechins and anthocyanins has been associated with a lower occurrence of cancers (Naasani et al., 2003). In addition, several studies reported that polyphenolic from mango peels and kernels exhibit bioactivity in cancer cell line models, including liver, breast, leukemia, cervix, prostate, lung and colon (Abdullah et al., 2015 and Luo et al., 2014).

On the other hand, a number of researchers have carried out remarkable studies on the use of mango kernel (MK) and mango peel powders (MP) in preparing various bakery products. Bandyopadhyay et al. (2014) worked on MK and MP to substitute wheat flour (WF) in cookies. They recommended that by adding MK instead of WF up to 20 %, cookies can be created to get suitable texture, color, flavor and overall acceptability. Ashoush and Gadallah (2011) assessed the sensory, rheological, physical, and antioxidant properties of biscuits by replacing 20, 30, 40 and 50% of MK instead of WF and obtained acceptable suitable mango flavor biscuits by incorporating MK up to 40%. Menon et al. (2014) revealed that by using MK, bread can be formulated with enriched nutrient contents. In another study carried out by El-Faham et al. (2016), mango peel extracts were an effective inhibitor of lipid peroxidation in biscuit during storage, since several antioxidant compounds are found in mango peels. Indeed, the effect of powder mango residues on multiple cancer cell lines was not reported in the literature, although several studies addressed the effect of extracts of mango residues on several cancer cell lines.

Due to the attention towards the possibility of using mango by-products in many food industries and try to discover novel natural health-promoting resources, the present study was designed to estimate the compositional quality of mango by-products (dried kernel and peel), to study their anticancer activity on two different human cancer cell lines and one normal cell lines namely Human breast tumor cell line (MCF7), human colon cancer cell line (HCT116) and normal cell line (VERO) respectively.

Materials and Methods

Plant material, chemicals and cell lines

Full ripe mango fruits, Keitt variety, were purchased during the 2019 summer season, from a well-known hypermarket (Hyper One) at Giza, Egypt. All solvents, standard materials and chemicals were manufactured by Sigma-Aldrich Chemicals Co., USA and purchased from a dealer of Cornell Lab Company, Egypt. The MCF7, HCT116 and normal cell line detectors which were derived from the kidney of an African green monkey (VERO) were obtained from the American Type Culture Collection (ATCC, Minnesota, USA). The tumor cell line maintained at National Cancer Institute (NCI), Cairo, Egypt.

Methods

Preparation of dried mango peels (MP) and mango kernels (MK) powders

Fruit mangoes were washed, peeled with a sharp knife and the mango seeds and peels were manually collected (as by-products) by separating them from the mango fruit flesh using a blunt knife. The seeds were washed, air dried and then the kernels were manually removed from seeds

and chopped. The chopped kernels and peels were separately thin spreaded in trays and dried at 50±2°C reaching a moisture content of around 6%. Each dried material was grounded into powder with a hammer mill (Moulinex, Type 276, Ref: A242SA /700-4406-R, France), to that was passed through the 40 mesh sieve and was kept at -18±2°C in a deep freezer until used.

Chemical analysis

Determination of proximate chemical compositions of mango by-products

Moisture, protein, total lipids, crude fibers, ash contents were determined according to AOAC (2006). Total carbohydrates based on dry weight were calculated by the differences as:
100 – (ash +protein + total fats + crude fibers) in 100 g sample.

Determination of minerals contents in mango by-products

Mineral contents were determined by using Flame Atomic Absorption Spectrophotometer instrument, AAS (Model 3300, Perkin-Elmer, Beacons field, UK) by wet digestion as the procedure of the AOAC (2006) method.

Determination of total phenolic compounds (TP), total flavonoids (TF) compounds, and radical scavenging activity (RSA) in mango by-products

Mango peels and kernels powders were extracted according to the method of Yilmaz and Toledo (2006) to determine TP, TF and RSA. The total phenolic contents of MK and MP were determined using the Folin-Ciocalteu method as described by Arnous et al. (2001). The total flavonoids were determined using Joyeux et al. (1995) method.

The antioxidant activity of by-product mangoes was estimated by determining the radical scavenging activity (RSA %) of by-product mangoes extracts using the 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) assay as described by Brand-Williams et al. (1995). The radical scavenging activity was calculated using the formula:

$$\% \text{ Inhibition} = [(A_b - A_s) / A_b)] \times 100.$$

Where: A_b is absorbance of blank, A_s is the absorbance of the sample extract.

Determination of fatty acids in mango by-products

Fatty acid methyl esters of the tested materials were prepared and injected into Gas Chromatography System (GC), Agilent 6790N series according to ISO 12966-2 which was described in International Organization for Standardization (ISO 2011**)**.

Identification of phenolic acids and flavonoids in mango by-product

A High Performance Liquid Chromatography (HPLC), Agilent, Germany 1200 system equipped with a variable wave length detector was used to determine phenolic acids and flavonoids. Samples preparation and chromatographic conditions were similar to those described by Sagdic et al. (2011).

Determination of anticancer activity

Human cancer ell lines

In the current study, dried mango kernels (MK), peels (MP) and mixture of them (at ratio 1:1) were in-vitro scanned for their anticancer activity on two different human cancer cell lines; Human breast tumor cell line (MCF7), human colon cancer cell line (HCT116), and one normal cell line (VERO). Different concentrations of dried mango kernels and peels that were prepared herein were used to check all the tested cell lines.

Anticancer assay

The antitumor activities of dried mango kernels, peels and all tested cell lines cells were evaluated by sulphorhodamine-B (SRB) assay (Skehan et al., 1990). Briefly, cells were seeded at a density of 3 × 10^3 cells/well in 96-well microtiter plates. They were left to attach for 24 hr before incubation with the tested materials. Next, cells were treated with different concentrations (62.5, 125, 250 and 500 µg/mL) of the tested materials for MCF7, HCT116, and VERO cells. For each concentration, three wells were used and incubation was continued for 48 hr. DMSO (Dimethyl sulphoxide) was used as a control vehicle (1% v/v). At the end of incubation, cells were fixed with 20% trichloroacetic acid, stained with 0.4 % SRB (sulforhodamine B) dye solution. The optical density (OD) of each well was spectrophotometrically measured at 570 nm using ELISA microplate reader (TECAN sunrise™, Germany). The mean survival fraction at each tested materials concentration was calculated as follows:

OD of the treated cells/ OD of the control cells

The IC_{50} (concentration that produce 50% of cell growth inhibition) value of each treatment was calculated using sigmoidal dose response curve-fitting models (Graph Pad Prizm software, version 5).

Antioxidant markers

Determination of malondialdehyde content (MDA)

Lipid peroxidation products were quantified by measuring MDA level in cell culture lysate of control and treated cells using Lipid Peroxidation (MDA) Assay Kit (Sigma Aldrich Chemical Co., St. Louis, USA) following the manufacturer's instructions. The MDA level was calculated in relative to the corresponding protein content. The absorbance was determined at 532 nm using a spectrophotometer (Spectronic, Milton Roy Co., USA).

Determination of superoxide dismutase (SOD)

Lipid peroxidation products were quantified by measuring SOD level in cell culture lysate of control and treated cells by SOD determination kit (Sigma Aldrich Chemical Co., St. Louis, USA) following the manufacturer's instructions. SOD level was calculated in relative to the corresponding protein content. The absorbance of the supernatant was determined at 450 nm using a spectrophotometer (Spectronic, Milton Roy Co., USA).

Determination of reduced glutathione (GSH) content

Reduced glutathione was determined adopting the Ellman's method (1959). MCF7, HCT and VERO cells were harvested, protein was precipitated with trichloroacetic acid and Ellman's reagent [5, 5-dithiobis-(2-nitrobenzoic acid)] (Sigma Aldrich Chemical Co, St. Louis, USA) was added to supernatant. The absorbance was read at 405 nm and total SH was calculated as µM of GSH/mg protein.

Determination of nitric oxide (NO) content

Nitric oxide was determined in culture media of the control and treated cells according to Miranda et al. (2001). Briefly, 0.5 mL cold absolute ethanol was added to 250µL culture media then left for 48 hr at 4^0C to attain complete protein precipitation followed by centrifugation at 13,000 rpm for 1 hr using cooling centrifuge. 100µL of nitrate standard solution were serially diluted in duplicate in a 96-well microplate. Then, 100µL of vanadium chloride were added to each well rapidly followed by 50µL sulfanilamide and 50µl n-(1-naphthyl) ethylenediamine in 2 N hydrochloric acid. The absorbance was measured spectrophotometrically at 540 nm using an ELISA microplate reader (TECAN SunriseTM, Germany), following incubation period of 30 min. The level of total nitrite/nitrate was expressed as mM supernatant media and determined using standard curve.

Statistical analysis

Data were represented as mean± standard deviation (SD). The data were analyzed using one-way analysis of variance (ANOVA) test. To assess the significance of differences the Tukeypost-hoc test was used. p values less than 0.05 were considered to be statically significant. Graphs were performed using Prism software program (graph pad prism software, version 5, CA, USA) and analysis of data was performed using GraphPadInStat, Version 5

Results and Discussion

Composition of mango by-products (Peels and kernels)

The chemical composition of the mango kernels (MK) and mango peels (MP) is recorded in Table 1. Composition analysis showed that moisture, crude proteins, total lipids and total carbohydrates were significantly higher in MK than in MP. Whereas, ash and crud fiber were significantly higher in MP than in MK. Moisture contents of the kernels and peels were relatively low (8.85 and 6.74%, respectively) which is promises along-shelf for further processing.

Crude fiber contents were 2.78% for the kernel and 10.40% for the peelsthus these mangoes by-products especially peels could be an important source of fiber. Previous studies confirmed the efficiency of mango-peels use in functional healthy foods which may reflect an alternative approach for individuals with special calories requirements (Ajila et al., 2008 and Ajila et al., 2010).

On the other hand, the ash contents were 3.60 and 2.32% in the mango peels and kernels respectively. The high ash content of MP and MK indicates that it can be a good source of dietary minerals. The crude protein contents of MK and MP were 6.70 and 4.43%, respectively. Despite the low protein content, protein quality index and essential amino acid index are high that indicating the high quality of the proteins (Abdalla et al., 2007). The total carbohydrates contents were 81.73 and 79.59%, respectively (Table 1). Regarding the total lipids, the mango kernels contain 6.47% which represents a good source of lipids.

Chemical composition of mango by-products in the current study is in accordance with

Mwaurah et al. (2020) study. This researcher reviewed the nutritional composition of mango kernel constitutes which were 32.34 - 76.81% for carbohydrate, 6 - 15.2% for fat, 6.36 - 10.02% for protein, 0.26 - 4.69% for crude fiber, and 1.46 - 3.71% for ash, on a dry weight basis. Presented results are also confirmed by Bandyopadhyay et al. (2014) study.

Minerals contents results are presented in Table 2. Ca, K, Na and Mg were the major elements in mango kernels and peels. Also, Fe, Zn, Cu and Mn were presented in good quantities. Furthermore, high levels of potassium can lead to a mineral balance that favors hypertension control. A diet rich in potassium lowers blood pressure and consequently the risk of morbidity and mortality due to cardiovascular diseases. In addition, potassium intake can decrease urinary calcium excretion and consequently reduce the risk of developing osteoporosis (National Academy of Sciences, 2011).

The current results showed some small differences compared to literature but are in accordance in pattern with those found by Njiru et al. (2014) who reported that Ca was found to be the highest in all the residue parts of mangoes in the order Ca>K>Na>Mg>Fe>Mn>Zn>Cu. Abdelaziz (2018) showed that K, Mg and Ca were the main elements in mango kernel meal. The differences in the levels of the elements in mango by-products may be attributed to differences in soil composition, climatic conditions and varietal differences in parent trees (Kossah et al., 2009).

TABLE 1. Proximate chemical composition of mango by-products powder.

Parameters	MK (%)	MP (%)
Moisture	8.85 ±0.46*	6.74±0.26
Ash**	2.32 ±0.22	3.60±0.14*
Crude Protein**	6.70 ±0.26*	4.43±0.22
Total lipids**	6.47 ±0.18*	1.98±0.23
Crude fiber**	2.78 ±0.18	10.40±0.22*
Total carbohydrates**	81.73±0.13*	79.59±0.14

**On dry weight basis. Each mean value, an average of three replicates ± SD.
* Significant difference (P≤ 0.05)

TABLE 2. Minerals contents of mango by-products .

Minerals	MK*	MP*
Potassium (K)	790.16	830.75
Magnesium (Mg)	130.39	190.27
Calcium (Ca)	939.67	960.84
Sodium (Na)	163.65	219.59
Iron (Fe)	9.37	14.19
Zinc (Zn)	4.44	3.09
Copper (Cu)	1.63	1.1
Manganese (Mn)	1.28	2.72

*Determined as mg/100g in dry weight basis

Total phenolic compounds, total flavonoids and DPPH in mango by-products

Phenolic compounds are a big group of phytochemicals widely spread in plants; they are well known for their beneficial biological effects and favorable uses in food, cosmetic, and pharmaceutical products (Castro-Vargas et al., 2019). The total phenolic content (TPC) and total flavonoid content (TFC) values presented in the extracts of mango by-products were evaluated**.** Table 3 shows the TPC values expressed as mg of Gallic acid equivalents per 100 g of raw material (mg GAE/100 g). The TPC in MK extract were significantly higher than the amounts in MP and were 2829.25 and 2565.21 mg GAE /100 g, respectively.

These results were higher than that (112 mg GAE /100 g dw) found by Abdalla et al. (2007) but lower (11.228-20.034 mg GAE/100g dry basis) than Sogi et al. (2013). On the other hand, the values of TFC in MK and MP were 906.30 and 843.97mg RE /100g, respectively. These results were consistent with the findings of Dorta et al. (2014).

Concerning the radical scavenging activity of MP and Mk against DPPH, the results showed that the mango peels extract was relatively high in its antioxidant activity (79.11%), it was significantly higher than that obtained in the kernel extract (55.79%). These results are in agreement with Castro-Vargas et al. (2019) who studied the DPPH scavenging activity in two mango varieties and found that, the higher DPPH scavenging activity was exhibited by the peel extracts than that obtained by the kernel extracts. In another study, Tokas et al. (2020) documented that high values in DPPH scavenging activity were observed in raw peels (75.3 mg/g in Amarpali and 72.4 mg/g in Dasheri) and ripe mango peels (63.4 and 60.6 mg/g in Amarpali and Dasheri, respectively).

Fatty acids composition

The fatty acid composition of MK and MP is presented in Table 4. The results revealed that MK contained a considerable amount of total saturated fatty acid 39.82%. Stearic acid (25.41%) was the main saturated fatty acid in MK, while oleic acid (44.34%) was the major unsaturated one. These results are in agreement with Rasoanaivo et al. (2014) and Abdel-Razik et al. (2012). Concerning the fatty acid composition of MP lipids, the results revealed that palmitic acid (28.2%) was the main saturated fatty acid, while α Linolenic acid (21.62%) was the major polyunsaturated fatty acid. These results are comparable to reported studies by Deshpande et al. (2016) who studied the fatty acid composition at various stages of mango fruit development and ripening from three cultivars and found that there was an increase in the unsaturated fatty acid content in skin of mango with ripening and making ripened fruits more nutritious.

Many studies investigated the important properties of MK oil. Jeyarani et al. (2015) reported that, it has been tested to be resistant to autooxidation owing to a high content of saturated fatty acids; therefore, it can be stored for a prolonged period without affecting its physicochemical and functional properties. For these reasons, MK oil improves the shelf life and stability of highly oxidative oils when mixed with them. In addition, MK oil is free from trans-fatty acids that are linked with adverse health effects and illnesses, for example, heart disease and coronary (Solís-Fuentes and Duran-de-Bazua, 2011). In another study, Nadeem et al. (2016) revealed that, MK oil is solid at ambient temperature and pressure (melting point 32 to 36 ◦C), hydrogenation is not necessary for its utilization in the food industry.

TABLE 3. Total phenolic compounds, total flavonoids and DPPH in mango by-products.

Parameters	MK	MP
Total Phenoliccompounds (mg GAE /100g) **	2829.25±20.27*	2565.21±66.98
Total Flavonoids (mg RE /100g) **	906.30±4.61*	843.97±20.9
RSA% using DPPH	55.79± 0.62	79.11±0.09*

**On dry weight basis. Each mean value, an average of three replicates ± SD.

* Significant difference (P≤ 0.05)

TABLE 4. Fatty acid composition of mango by-products.

Lipid fractions (% of total fatty acids)		MK	MP
Myristic	C14:0	0.18	4.48
Palmitic acid	C16:0	10.65	28.20
Stearic acid	C18:0	25.41	6.66
Arachidic acid	C20:0	2.73	0.46
Behenic acid	C22:0	0.85	5.56
Saturated fatty acids		39.82	45.36
Oleic acid	C18:1	44.34	18.09
Gadoleic acid	C20:1	0.21	3.60
Linoleic acid	C18:2	14.04	11.33
α Linolenic acid	C18:3n3	1.59	21.62
Unsaturated fatty acids		60.18	54.64

Identification of phenolic compounds

Data in Table 5 showed that the most abundant phenolic acids in both MK and MP extracts were ellagic, pyrogallol, caffeine, vanillic, ferulic and chlorogenic. In MK, ellagic acid (267.57 mg/100g) was the highest phenolic acid followed by pyrogallol (153.75 mg/100g) and caffeine (116.33 mg/100g), while in MP pyrogallol (144.76 mg/100g) was the main phenolic acid followed by ellagic (80.27 mg/100g) and caffeine (51.11mg/100g). In addition, through HPLC analysis, hesperdine was the highest flavonoid compound in both of mango by-products (15.387 and 15.565 mg/100g for MK and MP, respectively). In general, mango kernels were richer source of phenolic compounds than its peels. From the above mentioned data it could be concluded that, mango kernels and peels are a good source of phenolic compounds.

This result is comparable with Gómez-Caravaca et al. (2016) who found that ellagic acid was the most abundant phenolic compound in keitt mango edible fraction and its by-products (peel, seed, and seed husk). The study, also, mentioned that mango by-products could be used as a source of ellagic acid, especially mango seed that contains around 650 mg/100 g d.w. of ellagic acid in form of free and bound ellagic acid. In another study, Luo et al. (2014) reported that, mango kernels and peels of three Chinese cultivars were found to be rich in gallotannins and the antiproliferative activity of the extracts from mango kernel and peel may be caused, at least partially by penta-O-galloyl-glucoside or its analogs with different galloyl groups.

Cytotoxic activity

The results presented in the previous section show that the mango waste is a source of phenolic compounds with antioxidant properties. These substances are also recognized by their beneficial biological effects, including the anticancer activity (Oroian and Escriche, 2015). As illustrated in Table 6 and Fig. 1, the most efficient cytotoxic activity was for sample MK/MP (mixture of MK and MP) against the cell lines for colon cancer (HCT116) with IC_{50}=45µg/mLfollowed by breast cancer (MCF7) with IC_{50}=58 µg/mL, while there was a more efficient cytotoxic activity for sample MK against breast cancer than colon cancer (IC_{50} = 75 µg/mLfor MCF7 and IC_{50}=122 µg/mLfor HCT_{116}). It could be, also noticed that the sample MP was more efficient cytotoxic activity against colon cancer (IC_{50}=55 µg/mLfor HCT_{116}), than against breast cancer (IC_{50}=83 µg/mLfor MCF7). On the other hand, by evaluating the effects of sample MK, MP and MK/MP on VERO normal cell line, it could be, also, noticed that sample MK and MK/MP have no IC_{50} in normal cell line but sample MP has IC_{50} of 460 µg/mL after 48 hr.

TABLE 5. Chromatographic compounds analysis of phenolic acids and Flavonoids in mango by-products.

Phenolic acids (mg/100g)	MK	MP	Flavonoids (mg/100g)	MK	MP
Pyrogallol	153.75	144.76	Apigenin 6-arabinose 8-glacose	10.185	5.348
Gallic	5.08	4.20	Apiening 6-rhamnose 8- glacose	0.326	0.357
Catechein	14.32	6.94	Rutin	nd	2.548
Catechol	1.41	nd	Naringin	8.407	7.533
4-aminobenzoic	0.87	3.93	Luteolin 7 glucose	4.279	4.995
Chlorogenic	27.07	36.29	Hesperdine	15.387	15.565
P-OH- benzoic	26.54	4.26	Rosmarinic	12.628	2.590
Benzoic	14.91	9.7	Quercetrin	2.030	1.789
Caffeic	16.63	3.4	Apigenin-7-glucose	0.906	0.150
Vanillic	43.53	20.22	Quercetin	0.746	0.806
Caffeine	116.33	51.11	Naringenin	0.612	0.119
Ferulic	40.08	29.46	kampferol 3-2 p-coumaryl - glucose	2.501	0.161
Salycillic	5.15	3.73	Kampferol	0.699	0.550
Coumarin	4.07	6.3	Apigenin	0.037	0.022
Ellagic	267.57	80.27			

nd: not detected

TABLE 6. IC_{50} of compounds MK, MP and MK/MP on different cell lines.

Sample	MCF7	HCT_{116}	VERO
	IC_{50}	IC_{50}	IC_{50}
MK	75 ± 2.5	122 ± 3.2	0
MP	83 ± 2	55 ± 1.41	460 ±5
MK/MP	58 ± 1.7	45 ± 1	0

Data are represented as mean of surviving fraction ± S.D of 3 independent experiments performed in 3 replicates

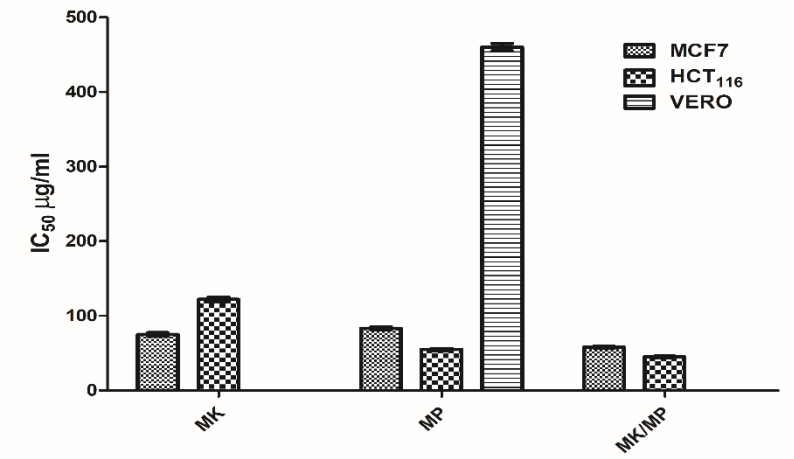

Fig. 1. IC_{50} of compounds MK, MP and MP/MK on different human cancer cell line following 48 hr.

Data are represented as mean of surviving fraction ± S.D of 3 independent experiments performed in 5 replicates.

The current result was confirmed by Abdullah et al. (2015) who observed that ethanolic extracts of mango kernel exhibit antiproliferative effects against breast cancer cell lines (MCF-7 and MDA-MB-231). However, extracts have not been shown to be toxic to normal breast cells (MCF-10A). In another study**,** Castro-Vargas et al. (2019) reported that experiments with antiproliferative effects using mango waste extracts showed that the mango kernel extract has an effect on the efficient cytotoxic activity against A-549, (human lung adenocarcinoma cells), HT-29 (human colorectal adenocarcinoma cells), MDA-MB-231 (human breast adenocarcinoma cells), and PC-3 (human prostate cancer cells). Oroian &Escriche (2015) mentioned that these properties have been related to the phenolic compounds present in mango fruit parts (peel, flesh, and seed). On the other hand, many studies confirmed that the phenolic acids, flavonoids, and galatotanins are noteworthy due to their high anticancer bioactive (Gold-Smith et al., 2016; Rocha et al., 2012;Khurana et al., 2016). In the present study, the observed cytotoxic activity in MK and MP powder may be related to its high phenolic acids and flavonoids contents (Table 5). Noratto et al., (2010) evaluated the antiproliferative ability of phenolic extracts obtained from the flesh of various mango cultivars on several cancer cell lines (breast cancer MDA-MB-231, leukaemia Molt-4, lung cancer A-549, prostate cancer LnCap, and colon cancer SW-480).They found that the phenolics in the extracts were linked with an increase in the mRNA expression of the pro-apoptotic and cell-cycle regulator biomarkers, as well as a decrease in the generation of reactive oxygen species (antioxidant activity).

Antioxidant activity:

The imbalance between oxidant compounds and antioxidant defenses is termed oxidative stress. Oxidizing compounds are endogenously formed or caused by exposure to oxidizing agents via mitochondrial respiration (i.e., ionizing radiation, heavy metals, and hypoxia). There are reactive oxygen species (ROS) such as hydroxyl radicals, peroxyl radicals and superoxide anions among the reactive species, and reactive nitrogen species such as radicals of nitric oxide (NO).

Besides radical compounds, there are non-radical oxidants, such as singlet oxygen, hydrogen peroxide, hypochlorous acid, and peroxylnitrite. These compounds are able to oxidize essential biomolecules, such as DNA, proteins, and lipids. The antioxidant defenses are composed of antioxidant enzymes including SOD (dismutase), CAT (catalase), and GSH (reductase). Non-enzymatic antioxidants are represented by many dietary components such as Vitamin C, Vitamin E, Vitamin A, and phenolic compounds, which comprise the major amount of antioxidants consumed as part of the diet with prospect health benefits (Núñez Selles et al. 2016). Cancer cells are distinguished by an increase in the rate of reactive oxygen species (ROS) production and an altered redox environment compared to normal cells. Most chemotherapy agents increase ROS intracellular levels and can change cancer cell redox homeostasis (Yang et al., 2018).

TABLE 7. The significantly changes of MK, MP and MK/MP in relative of control on MCF7, HCT_{116} and VERO cell lines with respect to some antioxidant parameter.

	MDA significantly decreased by % of control			**NO significantly decreased by % of control**			**GSH significantly increased % of control**			**SOD significantly increased % of control**		
	MCF7	HCT_{116}	VERO	MCF7	HCT_{116}	VERO	MCF7	HCT_{116}	VERO	MCF7	HCT_{116}	VERO
MK	42.0	47.3	46.5	78.0	51.2	52.5	86.4	33.7	40.0	37.8	33.4	18.4
MP	31.4	21.5	17.3	51.0	38.0	17.5	14.4	12.5	15.5	12.3	08.1	09.6
MK/ MP	62.3	61.6	78.1	94.0	72.7	79.3	135	60.5	48.0	49.0	48.5	30.2

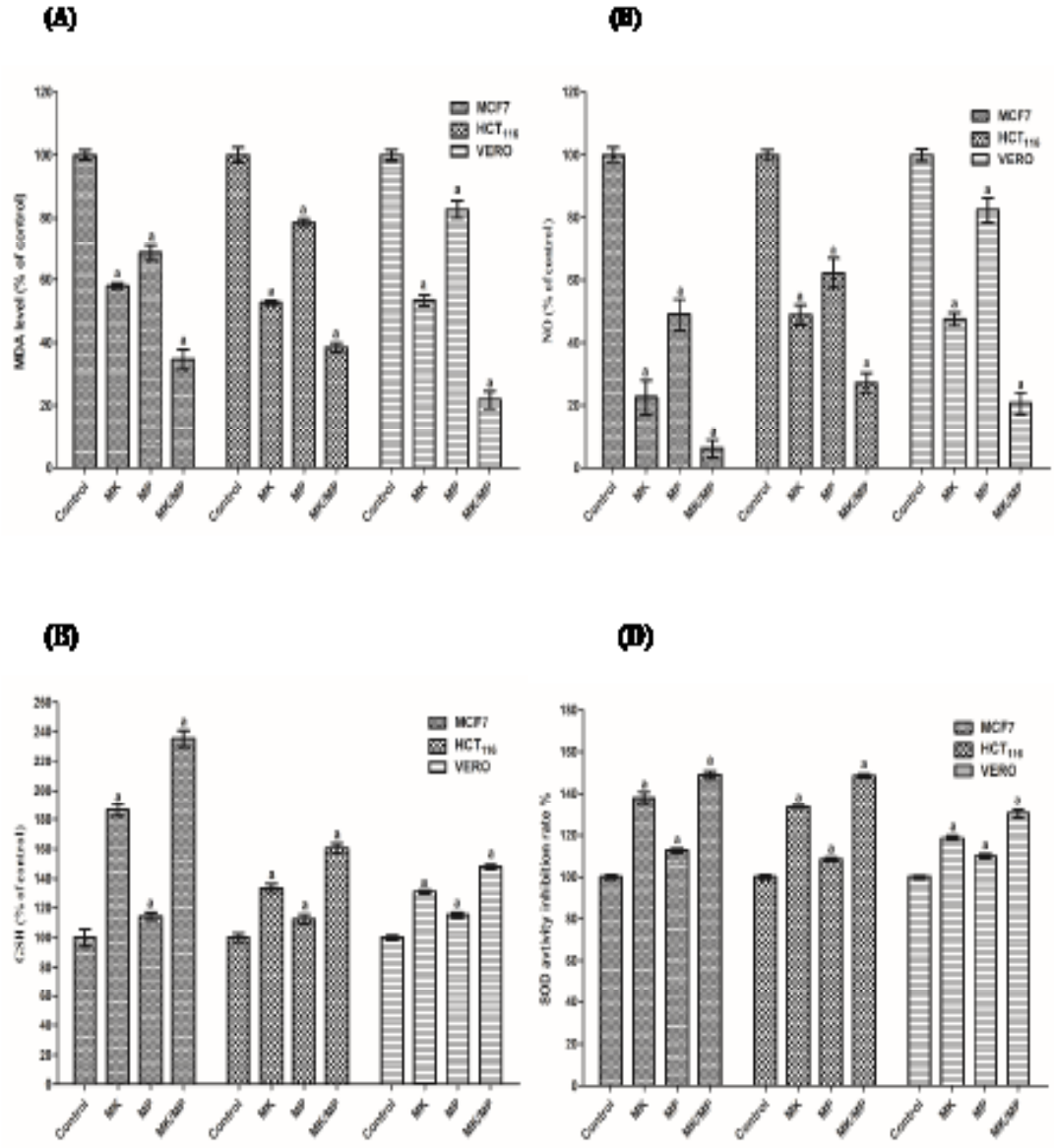

Fig. 2. Effect of sample MK, MP and MK/MP onoxidative stress markers (A): MDA, (B): NO, (C): GSH and (D): SOD in MCF7, HCT_{116} and VERO cells following 48 h. The results are the mean ± SD of 3 separate experiments performed in duplicates. Statistical significance of results was analyzed using one-way ANOVA followed by Tukey's multiple comparison test. [a] Significantly different from control.

Consequently, samples MK, MP and MK/MPwere tested for their antioxidant activity in MCF7, HCT_{116} and VERO cells. They had anti-oxidant effect in all tested cell lines by significantly increased in SOD and GSH while MDA and NO levels were significantly decreasedas showed in Table 7 and Fig. 2 (A, B, C and D). The current results showed that, the most efficient on all tested cell line was sample MK/MP(mixture of MK and MP at ratio 1:1), where a significantly increase in GSH (135.0, 60.5 and 48.0 %) and SOD (49.0, 48.5 and 30.2 %) for MCF7, HCT_{116} and VERO cells, respectively. While MDA and NO levels showed significant decrease (62.3, 61.6 and 78.1%) and (94.0, 72.7 and 79.3 %) for MCF7, HCT $_{116}$ and VERO cells, respectively. The efficient of Sample MK/MP may be due to the proportions of the components of them, for instance, MP contains (Table 4) α Linolenic acid at high concentration (21.62%) compared

to MK (1.59%). Chamberland and Moon (2014) found that administration of α Linolenic acid directly controls the malignant potential (adhesion, proliferation, invasion and colony formation) of human and mouse colon cancer cell lines. Table 4 showed that the concentration of palmitic acid was nearly three times in MP (28.2%) compared to MK (10.65%). Zafaryab et al. (2019) suggested that palmitic acid decreased cell viability in MCF-7 Breast cancer cells and treatment with it increased the expression of apoptosis-related proteins including caspase-3, 9, Bax and p53 protein while the expression of anti-apoptotic protein Bcl-2 was decreased. In addition, the data in Table 6 showed that sample MK was more effective than sample MP on all tested cell lines. These results are in accordance with Abdullah et al. (2015) who mentioned that there were time- and dose-dependent raises in oxidative stress markers and pro-apoptotic factors in the human breast carcinoma (MCF-7) cells by mango kernel extract treatments. The changes induced indicate that the extract, possibly through the activation of oxidative stress, will trigger cancer cell apoptosis. Results in Table 5 illustrated that MK and MP had good quantities of polyphenols especially, ellagic, Pyrogallol and hesperdine. Ellagic acid, a plant polyphenolic compound, has been shown to exert an antitumor effect in several types of cancer for instance; ellagic acid inhibited the growth of MCF-7 breast cancer cells**,** ovarian carcinoma cells and human cervical carcinoma cells (Li et al., 2017).

In another study, Ahn et al. (2019) reported that Pyrogallol which is a major compound contained in mango was known to have antitumor effects in breast cancer, colon cancer, lung cancer, leukemia, and hepatocellular carcinoma. Park (2016), also, suggested that pyrogallol inhibited the growth of human pulmonary fibroblast cells by induced a G1 phase arrest of the cell cycle and also caused cell death via p53 protein increase, the activation of caspase-3, the loss of mitochondrial membrane potential, and Bcl-2 decrease. In addition hesperidin is a major dietary flavanone (which is abundantly found in MP and MK Table 5) has been recognized as a potent anti-carcinogenic and anti-oxidant agent (Roohbakhsh et al., 2015). The anticancer effect of hesperidin in colon cancer was studied by Gilang et al. (2012) who mentioned that, the usage of hesperidin as a combination drug, so that the dosage and also the toxic effects of 5-FU (5-fluorouracil) can be reduced in colon cancer chemotherapy. While Ismai et al. (2012) revealed the requirement of p53 protein in hesperidin mediated apoptosis in colon cancer cells. Moreover, anti-cancer effect of Hesperidin on breast cancer was studied by Natarajan et al. (2011), who revealed that the induced apoptotic cell death in breast cancer indicated by characteristics like increase in LDH (lactate dehydrogenase) level, depletion of GSH (Glutathione) level, DNA fragmentation, accumulation of p53 protein and stimulation of caspase 3 protein.

According to FAO (2016), and Nawab et al. (2016) the expected amounts of mango by-products in Egypt may be approximately around 240- 360 thousand tones. These giant amounts must be utilized in a good manner. As previously mentioned, mango seed kernels and peels could be safely utilized in food stuffs formulas. Therefore, it could be recommended to use such by-products due to their functional properties and to avoid their dangerous impacts on environmental conditions.

Conclusion

Mango by-products, such as peels and seeds, could be considered as an important source of bioactive properties. The *In vitro* assays confirmed that the utilization of the mango-powders by-product could be beneficial as a natural source of antioxidant and anticancer activities and can be used as food additives and therapeutic agents.

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التركيب الكيميائي لمخلفات المانجو ونشاطها المضاد للخلايا السرطانيه البشرية: دراسة في المختبر

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من الممكن أن تمثل الكميات الكبيرة من نواتج المانجو الثانوية ، مثل القشور والبذور، مصدرًا هاماً للعديد من المكونات النشطة بيولوجيًا كما يمكن أن يكون لها كثير من التطبيقات الواعدة. وقد صُممت هذه الدراسة لتقدير الجودة التركيبية لأنوية المانجو (MK) وقشورها (MP) ، تقدير تأثير نشاطها المضاد للسرطان على خلايا سرطان الثدي البشري (MCF7) ، و خلايا سرطان القولون البشري (HCT116) والخلايا الطبيعية (VERO) بالمختبر. و قد وجد ان محتوي MK من الرطوبة والبروتين الخام والدهون الكلية ومحتوى الكربوهيدرات الكلي أعلى معنويًا مقارنة بـ MP ، بينما كان MP أعلى معنويًا في محتواه من الرماد والألياف الخام. وكانت عناصر Ca و K و Na و Mg هي العناصر الرئيسية في أنوية وقشور المانجو. تم أيضًا تقدير الفينولات (TP) و الفلافونويدات (TF) الكلية ونشاط (RSA). وكانت كمية TP في , MP MK هي 2829.25 و 2565.21 مجم GAE/ 100 جم على التوالي. وكان النشاط المضاد للأكسدة فيMP و MK79.11 و55.33 %على التوالي. وكان حمض الإستياريك (24.4 %) هو الحامض الدهني السائد بين الأحماض الدهنية المشبعة في MK بينما كان حمض الأوليك (44.34 %) هو الحامض الدهني غير المشبع السائد. كان Ellagic و Pyrogallol أكثر الأحماض الفينولية وفرة في كل من مستخلصات MK و MP من خلال تحليل HPLC. و كان الهيسبيريدين هو أعلى مركبات الفلافونويد تواجدا في MK و MP. وكان خليط مساحيق MK و MP أكثر فعالية في السمية ضد خلايا سرطان القولون (HCT116) و سرطان الثدي (MCF7).و بصفة عامة فقد تم التأكد ان عينات المنتجات الثانوية للمانجو قد أظهرت نشاطاً مضادًا للأكسدة في جميع الخلايا المختبرة. ويمكن التأكيد على أن استخدام المنتجات الثانوية للمانجو يمكن أن توفر مصدراً طبيعيًا لأنشطة مضادات الأكسدة وكمضادات للسرطان ويمكن استخدامها كإضافات غذائية وعوامل علاجية..