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# ANTICANCER ACTIVITY OF POMEGRANATE PEELS AND LEAVES, FIG LEAVES, GUAVA LEAVES AND OLIVE LEAVES CRUDE JUICES

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## Abstract

Plants produce a vast range of vital substances which can be used as a source of drugs for curing of diverse diseases. The main objective of the present study was to estimate the pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices produced by the mechanical press as a source of natural anticancer substances. The results pointed out that pomegranate peels crude juice treatment reduced the viability of breast adenocarcinoma cells (MCF-7) and human colon cancer cells (HCT-116). However, pomegranate peels crude juice exhibited less $IC_{50}$ as compared to doxorubicin (anticancer synthetic drug). Fig leaves crude juice showed only anticancer activity on human colon cancer (HCT-116) while pomegranate leaves, guava leaves and olive leaves crude juices exhibited no significant anticancer activity on the cancer cell lines under study. Accordingly, pomegranate peels crude juice can be applied as a source of naturalistic anticancer substances which can be used as anticancer medicine especially for breast cancer or in combination with chemotherapy to raise the anticancer efficacy, minimize the deleterious influences of chemotherapy and overcome the chemo- or radio-resistivity of cancer cells.

***Key words:*** Crude juices, Anticancer activity, MTT method.

## Introduction

Cancer is vastly recognized for the time being as the ailment of the century due to the numeral of rising cases worldwide. In addition, enormous studies consecrated to this domain and its rising rate of success (Hassanpour and Dehghani, 2017).

Breast cancer is the second very prevalent cancer worldwide and the most commonly malignancy that taking place in women. It has markedly higher happening than any cancer else between ailments in women (Del Pup and Peccatori, 2018). Also,the breast cancer has incursive attributes and an altitude proportion of metastasis, which lead to high ailment and death-rate (Acevedo-Diaz *et al.,* 2019 and Parvin *et al.,* 2019).

Colorectal cancer represents about 10% of whole yearly diagnosed cancers and deaths-related to cancer throughout the world and deem as the second very popular cancer diagnosed in women and third most in men (Bray *et al.,* 2018). It is the world's fourth most fatal cancer with nearly 900,000 deaths yearly (Dekker *et al.,* 2019).

The present therapies of cancer are surgery, radiotherapy and systemic therapy, *i.e.*, general chemotherapy, hormonal therapy, immunotherapy and targeted treatments. These treatments fail in very numerous patients and cancer stays a big challenge to clinical involvements. A necessity subsists to find out extra efficient ways for attacking cancer and novel ways of disease handling might provide some prospects (Block *et al.,* 2015).

Plants produce a vast range of vital substances referred as phytochemicals which can be used as a source of drugs for curing of diverse ailments. These phytochemicals not only safe for human consumption but also friendly environment. Several studies indicate that consuming of fruits and vegetable wealthy in phytochemicals, decreases the peril of cancer (Wang *et al.,* 2018).

Pomegranate *(Punicagranatum* L.) belongs to *Punicaceae* family is one of the ancient edible fruits vastly cultured in Far-East countries and extend to the Middle-East and European continent through to the Mediterranean zone (Konsoula, 2016). Moreover, pomegranate botanical parts have the ability to treat some chronic ailments such as breast, colon, prostate, skin cancers, stomach ulcers because of its anticancer features (Derakhshan *et al.,* 2018).

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Olive *(Oleaeuropaea* L.) is related to the *Oleaceae* family and its origin is Mediterranean region. Olive oil, fruits and leaves have been renowned as important constituents of medicine and of a healthful diet. It was indicated that olive leaves extract have anticancer, antioxidative, anti-inflammatory characteristics also, has the ability to prevent or treat diabetes, atherosclerosis and many other traditional medicinal utilizations (Anter *et al.,* 2011 and Imran *et al.,* 2018).

Fig *(Ficuscarica* L.) is a vital member in *Moraceae* family. The provenance of fig is the Middle East and West Asia and extended to several territories in the world. Products of fig are vastly applied as food sources and medicine to cure diverse ailments (Barolo *et al.,* 2014).

Guava *(Psidiumguajava* L.) is a prospective medicinal plant belongs to family *Myrtaceae* and native to South America, but now immensely cultivated in tropical and subtropical territories of different countries of the world (Kareem *et al.,* 2018). Guava leaves utilized for the co-therapy of diverse ailments with high prevalence worldwide, supporting the traditional medicine in cases such as cancer, diabetes mellitus, parasitic infections and cardiovascular diseases (Diaz-de-Cerio *et al.,* 2017).

Researchers are investigating novel forms of therapy and studying the constituents of diverse botanical origins to fight diseases. Phenols have a great history of offered benefits in preventing and curing of chronicailments such as cancer (Zhou *et al.,* 2016). These components possess anticancer properties vias ever al varied mechanisms of action, such as the inhibition of tumor cell growth, the induction of apoptos is, DNA damage, topoisomerases I and IIinhibition, the stimulation of apoptosis and others (Lichota and Gwozdzinski, 2018).

Several*in vitro* and *in vivo* researches have indicted that the combining of naturalistic polyphenols with chemotherapeutics is able to enhance the anticancer efficiency, lowering the bad impacts of chemotherapy and get over the chemo- or radio-resistivity of cancer cells (Fantini *et al.,* 2015 and Nurgali *et al.,* 2018). Subsequently, the present study was focused on the anticancer activity of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices on breast adenocarcinoma (MCF-7) and human colon cancer (HCT-116) cell lines.

## Materials and Methods

### Plant samples

Fresh leaves of pomegranate *(Punica granatum* L., *cv.* Wonderful), fig *(Ficus carica* L., *cv.* Conadria), guava *(Psidium guajava* L., *cv.* white guava) and olive *(Oleae uropaea* L., *cv.* Coratina) were collected in September, 2017, while ripe fruits of pomegranate were collected in October, 2017 from the Research Farm of Faculty of Agriculture, Cairo University, Giza, Egypt. Samples were hand picked from different trees and the authentication was done by Dr. Abdalatif, A.M. Assistant Professor of Horticulture Department, Faculty of Agriculture, Cairo University.

### Preparation of plant crude juices

A mechanical press was conducted to the leaves of fig, guava, olive and pomegranate and peels of ripe pomegranate fruits by a Carver hydraulic laboratory press (Carver model C S/N 37000- 156; Fred S. Carver Inc, Menomonee Falls, WI, USA, raise force 10 tones/inch$^2$, capacity 1 kg) after thoroughly was hing with tap water to remove all the unwanted materials to ensure that the peels and leaves were clean. Crude juices were lyophilized by utilizing a freeze- dryer (Labconco Corporation, Kansas City, M.O. USA) then preserved at -5 ºC in brown bottles till use.

### Cancer cell lines sources and culture

Cell culture Human transformed cell lines, from colon (HCT-116) and breast (MCF-7) were obtained from American Type Culture Collection (ATCC). Cells were preserved in Dulbecco's Modified Eagle Medium (DMEM) complemented with 10 % fetal bovine serum and 1% penicillin G potassium and streptomycin in humidified atmosphere and 5 % $CO_2$ at 37 °C with complete medium in a 25 cm$^3$ cell culture flask.

### Determination of anticancer activity by 3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) method

The anticancer activity of pomegranate peels and leaves, fig leaves, guava leaves and olive leaves crude juices was accomplished by MTT (3- (4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide) method based on the detection of mitochondrial dehydrogenase activity in living cells as described by Vijayakumar *et al*., (2018).

Cells were cultured in $CO_2$ incubators with 5 % $CO_2$ at 37°C in DMEM medium. After 90 % confluencey, the cells were seeded in 96 wells plates ($45\times10^3$cells/well) the nincubated for 24 h at 37°C. The cells were then treated with each tested crude juice (100 µl) at different concentrations and incubated for 48 h, then 40 µl of MTT solution was added to each well. After incubation for another 4 h, the medium was eliminated and dimethyl sulfoxide (DMSO, 150 µl) was added. The maximum absorption of the produced formazan crystals is 490 nm, so cell viability was recorded at 490 nmutilizing a microplate reader. The cell viability was calculated by the

following equation:

Cell viability (%) = $A_{\text{treated cells}}/A_{\text{untreated cells}} \times 100$.

Control (medium only, 100 % viability) and blank (no cells, 0 % viability) groups were also carried out. Data were displayed as means ± standard error. All the experiments were fulfilled in triplicates.

**Statistical analysis**

All results were statistically analyzed by utilizing one-way ANOVA and Tukey tests. All analyses were accomplished in triplicates and data reported as ± standard error. The confidence limits in the present study were based on ($P< 0.01$). Data analysis was fulfilled using ASSISTAT Version 7.7 beta (2014).

## Results and Discussion

Cancer leads to enormous morbidity and mortality allover the world. Socioeconomic, environment and lifestyle parameters participate in the growing cancer spread. Consequently, there is a requirement for efficient prohibition and curing strategies. Phytochemicals such as plant phenols are mostly deemed to have anticancer, anti-inflammatory, antiviral, antimicrobial and immunomodulatory impacts, which spell out their enhancing of the human health (De Silvaand Alcorn, 2019).

The anticancer performance of naturalistic phenols has largely been resulted to their powerful antioxidant and anti-inflammatory efficacies as well as their capabilities to amend molecular targets and signaling pathways, which were correlated with cell survival, proliferation, differentiation, migration, angiogenesis, hormone activities, detoxification enzymes, immune responses, etc. (Li *et al.,* 2013).

Many*in vitro* and *in vivo*researches have indicted that the integration of naturalistic polyphenols with chemotherapeutics were ableto enhance the anticancer efficiency, lowering the bad impacts of chemotherapy and get over the chemo- or radio-resistivity of cancer cells (Fantini *et al.,* 2015 and Nurgali *et al.,* 2018). Accordingly, the main aim of the present study was to estimate pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices as a source of natural anticancer substances.

**Anticancer activity of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices**

Considering the data in Figs. 1 and 2 and table 1, pomegranate peels crude juice treatment decreased the viability of MCF-7 breast adenocarcinoma cells and human colon cancer cells (HCT-116) and showed less $IC_{50}$ (half maximal inhibitory concentration required to inhibit cell viability by 50%) as compared to doxorubicin (anticancer drug). Fig leaves crude juice showed only anticancer activity on human colon cancer (HCT-116) while pomegranate leaves, guava leaves and olive leaves crude juices exhibited no significant anticancer activity on the cancer cell lines under study.

Several authors studied the anticancer activity of pomegranate peels. For instance, Shirode *et al.,* (2014) reported that pomegranate peel extract prevented the proliferation of breast cancer cells and prompted apoptosis

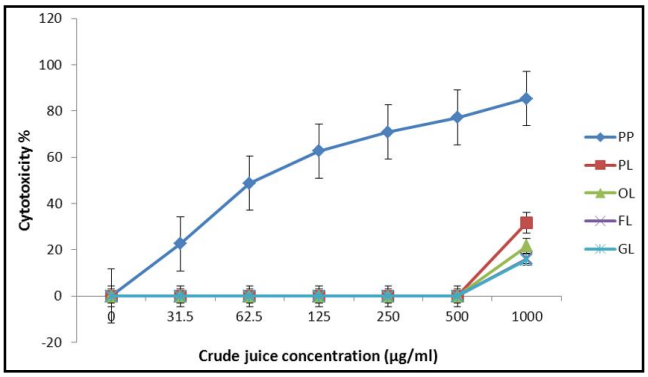


**Fig. 1:** Cytotoxicity effects of different concentrations of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices human breast adenocarcinoma cell line (MCF-7).
MCF-7 refers to Michigan Cancer Foundation-7 (the institute in Detroit where the cell line was established in (1973).
PP, PL, OL, FL and GL refer to pomegranate peels, pomegranate leaves, olive leaves, fig leaves and guava leaves, respectively.
Values are means of three replicates of each parameter ± standard error.

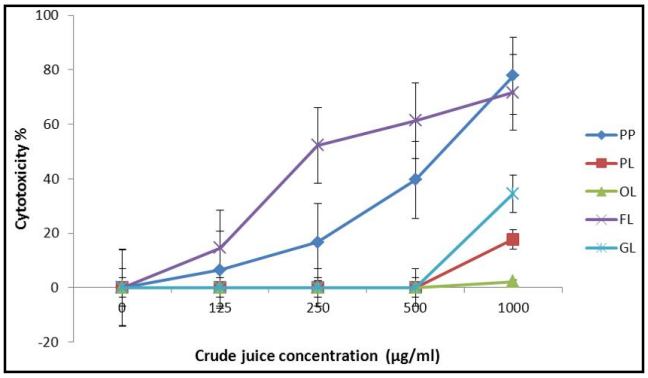


**Fig. 2:** Cytotoxicity effects of different concentrations of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices on human colon cancer cell line (HCT-116).
PP, PL, OL, FL and GL refer to pomegranate peels, pomegranate leaves, olive leaves, fig leaves and guava leaves, respectively.
Values are means ± standard error.

**Table 1:** The $IC_{50}$ values of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves crude juices against HCT-116 and MCF-7 cell lines estimated by MTT assay.

| Samples | $IC_{50}$ (µg/ml ) | |
|---|---|---|
| | HCT-116 | MCF-7 |
| PP | 659.5±10.35e | 100.2±2.03e |
| PL | 2824.9±111.17a | 1577.3±24.54d |
| OL | 21739.1±2417.87b | 2304.1±46.32c |
| FL | 562.3±46.66d | 3030.3±64.93b |
| GL | 1449.3±36.47c | 3164.6±36.18a |
| Doxorubicin(control) | 26.1±1.3f | 23.78±1.71f |

PP, PL, OL, FL and GL refer to pomegranate peels, pomegranate leaves, olive leaves, fig leaves and guava leaves, respectively. Values are means of three replicates of each parameter ± standard error. $IC_{50}$ refers to the half maximal inhibitory concentrationrequired to inhibit cell viability by 50 %.

in MCF-7 breast cancer cells via attacking particular DNA repair pathway which is vital for cancer cellviability and growth. Modaeinama *et al.,* (2015) illustrated that the low doses of methanolic extract of pomegranate peels possessed powerful anti-proliferative impacts in diverse human cancer cells and it seems that MCF-7 breast adenocarcinoma cells are the most cells.

The anticancer activity of some botanicalorigins could be due to their antioxidant features. Furthermore, several plant antioxidants applied as anticancer medicines and could stimulate cancer cells apoptosis (Michels *et al.,* 2006). The findings of Farag *et al.,* (2014) revealed that pomegranate peels crude juice exhibited potent antioxidant efficacy than leaves crude juice, being about 6.59 times as much as the resulted by leaves crude juice.

Various researches denoted that phenolic constituents from pomegranate peel have assorted beneficial attributes to human being health including anticancer activity (Singh *et al.,* 2018). For instance, pomegranate ellagitannins-derivedsubstances, *i.e.*, ellagic acid, gallagic acid and urolithins A and B are possessing anti-proliferation and anti-aromatase potentials in breast cancer cells (Adams *et al.,* 2010).

Numerous researches on MCF-7 breast cancer cells also indicated that gallic acid prevented cell proliferation ($IC_{50}$ = 80.5 µM) and stimulated apoptosis through both the extrinsic and intrinsic pathways (Wang *et al.,* 2014).

Ellagic acid exhibited anti-proliferation and pro-apoptotic influences on colon cancer cell lines in a concentration dependent way (Yousef *et al.,* 2016). Another study based on complementary DNA (cDNA) microarray to understand the molecular mechanisms implicit the ellagic acid-stimulated growth prevention on MCF-7 cells suggests that ellagic acid blocks the growth of breast cancer cells via cell cycle stopping and prevention of proliferation. Ellagic acid also exhibited growth inhibitory effects on MCF-7 breast cancer cells, which was escorted by G0/G1 cell cycle stopping (Chen *et al.,* 2015).

The findings of Naserddine and Mcheick (2018) revealed that the methanolic extract of pomegranate peels extracted by maceration method exhibited potent anti-proliferative efficacy on the HCT-116 cell lines with an $IC_{50}$ of 31.94 ± 4.98 µg/ml.

Mawa *et al.,* (2013) found that quercetin was the remarkable phenolic component in fig. This compound has the capability to induce the apoptosis of Caco-2 and HT-29 colon cancer cells by inducing the releasing of mitochondrial cytochrome C. Also, it displayed aninter active action with cisplatin (chemotherapeutic drug) *in vitro* and *in vivo* by the deactivation of protein kinase C. Another study found that quercetin decreased the tumor volume in HCT-116 colon cancer by inhibiting 5' adenosine monophosphate-activated protein kinase (AMPK) which induced apoptosis (Kim *et al.,* 2012).

HPLC analysis of some medicinal plants conducted by Farag *et al.,* (2014) demonstrated that gallic acid was the main phenolic component in pomegranate peels crude juice while, quercetin was from the phenolic compound that found in pomegranate peels crude juice and not in pomegranate leaves crude juice. Abdel-Aziz *et al*., (2020) found that caftaric acid, quercetin, gallic acid, ellagic acid and kampherol were the main phenolic compounds in fig leaves.

Lee *et al*., (2014) reported that kaempferolstimulated apoptosis by stimulating the death receptor and mitochondrial pathwaysin colon cancercells.

From the aforementioned results, one can point out that pomegranate peels crude juice can be used as a source of natural breast anticancer substance and in combination with chemotherapeutics to enhance the anticancer potency, decrease the badimpacts of chemotherapy and get over the chemo- or radio-resistivity of cancer cells.

## Conclusion

The present work was focused on estimating the anticanceractivity of the resultant crude juices which obtained from the mechanical pressing of pomegranate leaves and peels, fig leaves, guava leaves and olive leaves as a naturalistic anticancer substances. Generally, pomegranate peels crude juice decreased the viability of breast adenocarcinoma cells) MCF-7 (and human colon

cancer cells (HCT-116). Fig leaves crude juice showed only anticancer activity on human colon cancer (HCT-116). Accordingly, pomegranate peels crude juice can be applied as a source of naturalistic anticancer substances which can be used as anticancer medicine especially for breast cancer or in combination with chemotherapy to raise the anticancer efficacy, minimize the deleterious influences of chemotherapy and get over the chemo- or radio-resistivity of cancer cells. The botanical crude juices may open a new line for curing certain types of human cancer.

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### Conflict of interest

The authors declareno conflict of interest.

### Author Contributions

Authors (Radwan S. Farag and Layla S. Tawfeek) contributed to conception or design, contributed to acquisition, analysis and/or interpretation of data, drafted the manuscript and conclusively revised the manuscript for important intellectual content. The mentioned authors gave final approval and agree to be responsible for all sides of the work.

### Ethical statement

This research does not include any studies with human participants, animal studies, clinical trial, or biosecurity that require ethical approval.

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