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ORIGINAL

The anti-tumor molecular mechanisms of mentioned fruits in the holy Quran; a systematic review

Los mecanismos moleculares antitumorales de las frutas mencionadas en el sagrado Corán; una revisión sistemática

Atefeh Ashtari[1,4], Firoozeh Niazvand[3], Narges Chamkouri[2]

1. Cellular & Molecular Research Center, Medical basic sciences Research Institue, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. Assistant Professor, Department of Anatomical Sciences, Faculty of Medicine, Abadan University of Medical Sciences, Abadan, Iran.
3. Assistant Professor, Department of Biochemistry, Faculty of Medicine, Abadan University of Medical Sciences, Abadan, Iran.
4. Department of Anatomical Sciences, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Corresponding author
Firoozeh Niazvand
Faculty of Medicine, Abadan University of Medical Siences,
Abadan, Iran.
E-mail: niazvandf@gmail.com

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Abstract

Background: Various fruits are discussed in many verses of the Qur'an. Fruits such as pomegranates, grapes, olives, figs, and dates are considered gifts from God because of their myriad benefits. On the other hand, these fruits play an essential role in treating diseases such as cancer. Cancer is the second leading cause of death in developed countries, resulting in the uncontrollable division of cells. Due to high amounts of useful antioxidant compounds, these fruits kill cancer cells by stimulating cell death mechanisms such as apoptosis and necroptosis. This review study investigates the anti-cancer properties of the fruits mentioned in the Quran from a cellular and molecular perspective.
Methods: In this review study, conducted and available researches in databases such as ISI, PubMed, Scopus, Google Scholar, ISC, and SID have been used according to keywords.
Results: We examined the association of these fruits with the mechanism of cell death in cancer cells. As a result of analyzing these fruits' anti-cancer properties, it has been found that they can play an essential role in cancer prevention and treatment via different molecular mechanisms.
Conclusion: We found that the interpretations of the Holy Quran, which is the reference book in Islam, are entirely consistent with the new findings of medical sciences. So, there are many facts in the Quran that need further study and research.

Keywords: Holy Quran fruits, Cancer, Cell death, Molecular Signalling pathway.

Resumen

Antecedentes: En muchos versículos del Corán se habla de varias frutas. Frutas como las granadas, las uvas, las aceitunas, los higos y los dátiles se consideran regalos de Dios por sus innumerables beneficios. Por otra parte, estas frutas desempeñan un papel esencial en el tratamiento de enfermedades como el cáncer. El cáncer es la segunda causa de muerte en los países desarrollados y se debe a la división incontrolada de las células. Debido a las elevadas cantidades de compuestos antioxidantes útiles, estas frutas eliminan las células cancerosas estimulando mecanismos de muerte celular como la apoptosis y la necroptosis. Este estudio de revisión investiga las propiedades anticancerígenas de las frutas mencionadas en el Corán desde una perspectiva celular y molecular.
Métodos: En este estudio de revisión se han utilizado investigaciones realizadas y disponibles en bases de datos como ISI, PubMed, Scopus, Google Scholar, ISC y SID según palabras clave.
Resultados: Examinamos la asociación de estas frutas con el mecanismo de muerte celular en las células cancerosas. Como resultado del análisis de las propiedades anticancerígenas de estas frutas, se ha descubierto que pueden desempeñar un papel esencial en la prevención y el tratamiento del cáncer a través de diferentes mecanismos moleculares.
Conclusión: Hemos comprobado que las interpretaciones del Sagrado Corán, que es el libro de referencia en el Islam, son totalmente coherentes con los nuevos descubrimientos de las ciencias médicas. Por lo tanto, hay muchos hechos en el Corán que necesitan más estudio e investigación.

Palabras clave: Frutos del Sagrado Corán, Cáncer, Muerte celular, Vía de señalización molecular.

Introduction

In the holy Quran, special attention is paid to nutrition. The Holy Quran is available as a religious book for Muslims in different languages. It has 114 suras, some of which were revealed in Mecca and some in Medina. Each surah is divided into verses. The Quran is one of the best reference books that the importance of fruits can be read in its various chapters, such as Al-Muminun, Al-Rahman, Al-Baqarah, etc. Considering that the Holy Quran has recommended the use of different fruits, but some fruits have been given special attention as a blessing from God and a heavenly gift, which is probably due to their higher nutritional value than other fruits, including; Grapes, pomegranates, dates, figs, and olives[1]. Cancer is the uncontrolled growth of abnormal cells anywhere in the body. Cells become cancerous due to the accumulation of defects or mutations in their DNA. Congenital infections, environmental factors, and poor lifestyle choices such as smoking and heavy alcohol use can also damage DNA and lead to cancer. If a cell is severely damaged and cannot repair itself, it undergoes programmed cell death or apoptosis. Cancer disease occurs when damaged cells grow, divide, and spread abnormally instead of self-destructing as they should[2]. Millions of people worldwide are diagnosed with cancer and, it is estimated that by 2025 this number will reach about 20 million people[3]. Therefore, it is essential to know the drug to prevent and treat cancer.

Methodology

In this review study, conducted and available researches in databases such as ISI, PubMed, Scopus, Google Scholar, ISC, and SID have been used according to keywords: Holy Quran fruits, Cancer, Cell death, Molecular Signalling pathway. The present study is an overview of some properties of the fruits mentioned in the Holy Quran and their application to treat various cancers. The direct relationship between nutrition and cancer has been studied and proven in many studies. Diet can affect the tumor's symptoms, the response to patients' treatment, and the prognosis of the disease[4].

In the mentioned fruits in the Quran, there are polyphenolic compounds that have significant anti-cancer activity. Several studies have demonstrated that these fruits and their constituents have different amounts of polyphenolic compounds in the last few decades, including; ellagitannins, ellagic acid, and other flavonoids quercetin kaempferol, myricetin, and luteolin. In recent years, the consumption of these fruits has been considered in cancer patients[5]. Additionally, several in vitro and in vivo studies have shown that the combination of natural polyphenols with chemotherapeutics can increase the anti-cancer efficacy, reduce the side effects of chemotherapy and overcome the chemo- or radio-resistant cancer cells.

Results

Apoptosis

Cell death and cell cycle control are two critical factors in cancer cell growth progression or inhibition. Apoptosis is a type of regulated cell death program that can happen via various pathways in response to different stimuli and characterize by Deoxyribonucleic acid (DNA) fragmentation, nuclear condensation, and membrane blebbing, and cell shrinkage. A group of proteases called caspases are responsible for this action by activating these pro-enzymes via proteolytic cleavage hence disintegrate cells into apoptotic bodies. Two distinct apoptosis pathways are available, typically the extrinsic and intrinsic pathways. The intrinsic pathway (mitochondrial pathway) is usually activated in response to DNA fragmentation, chromatin degradation, protein cross-linking, and formation of apoptotic bodies wherewith extrinsic pathway is induced by death receptor-ligand binding (fas ligand (FasL) and tumor necrosis factor-alpha (TNF-α))[6]. After DNA damage, the p53 gene is activated and promotes the high expression of pro-apoptotic regulator, Bcl-2-associated X protein (Bax), and low anti-apoptotic gene expression B-cell lymphoma 2 (Bcl-2). Finally, the Bcl-2 family proteins' modulation initiates caspases cascade reaction and activates caspase-3 resulting in nuclear apoptosis[7].

Necroptosis

Recent studies suggest that programmed cell death is not limited to caspase-dependent apoptosis but includes necroptosis, a form of necrotic death governed by receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed lineage kinase domain-like (MLKL). Necroptosis is a vital cell killing mechanism that responds to cellular oxidative stress or blocked apoptosis and can be induced by inflammatory cytokines or chemotherapeutic drugs. At the signaling pathway, necroptosis is caspase-independent and signals by RIPK1, RIPK3, and MLKL, although apoptosis requires caspase activation and is mediated by interplays of the Bcl-2 family proteins or activation of death receptors[8].

Fruits properties

Pomegranate

Pomegranate (Punica granatum) is the fruit of a tree belonging to the family Lythraceae. It is also cultivated in parts of Asia and the United States. The different parts of this fruit, including its seeds, root, bark, and leaves, have healing properties. Hydrolyzable tannins (punicalagin, pedunculagin, punicalin, gallagic acid, ellagic acid,

and esters of glucose) and anthocyanins (delphinidin-3-glucoside, cyanidin-3-glucoside, delphinidin-3, 5-diglucoside, cyanidin-3, 5-diglucoside, pelargonidin-3, 5-diglucoside, and pelargonidin-3-glucoside) among the most important identified contents are pomegranate seeds[9]. Some antioxidants have been found in pomegranates, such as butylated hydroxyanisole and Trolox; it is significantly higher than green tea[10]. Medicinal products and supplements of pomegranate fruit have been considered to treat various cancers[11].

Grape

Grape (Vitis vinifera) is one of the world's most commonly consumed fruits. The beneficial effects of grape and relevant grape-derived food products are believed to be related to various bioactive components in grapes[12]. One major group of these components is phenolic antioxidants, including anthocyanins, catechins, resveratrol, phenolic acids, and procyanidins. Flavonoids constitute the majority of phenolic compounds (65–76%) in grapes. In red grapes, anthocyanins are the primary group of flavonoids[11]. Most grape phenolic antioxidants are distributed in grape skins or seeds. For instance, resveratrol, anthocyanins, and catechins are concentrated in the skin, while procyanidins are concentrated in grape seeds[13]. Grape antioxidants could act as free radical scavengers, and chelating agents reduce physiological reactive oxygen species (ROS). ROS is an essential mediator of apoptosis since apoptosis initiation and regulation are associated with modifications in the oxidative environment[14]. Grapes contain potent flavonoids such as myricetin and quercetin that help protect the cells against free radicals' harmful effects[15]. Previous studies have shown that myricetin has anti-cancer effects on different cancer cells through various cell death mechanisms[15].

Olive

The olive, known by Olea europaea, is a species of small tree in the family Oleaceae. In the Quran, the olive tree has a long history of medicinal and nutritional values[16]. Olive oil chemicals can be classified into two groups of saponifiers and non-saponifiers, from 90-99% and 0.4-5% of the oil. The most essential Saponifiers compounds are free fatty acids and their derivatives such as mono- and diacylglycerols, phosphatides, waxes, and esters. Olive oil polyphenols, especially hydroxytyrosol, tyrosol and their derivatives oleuropein, oleoresin and oleocanthal, express anti-cancer activity on different cancer cells. These polyphenolic compounds can act on gene expression that controls proliferation, apoptosis, and differentiation of cancer cells. The concentrations are easily reachable after the usual intake of olive oil[16].

Fig

The fig (common fig), known by the scientific name Ficus carica, is belongs to the family Moraceae. Fig has long been used as a cancer treatment in different cultures and is one of the Quran's fruits. Many scientific studies have used in vitro and in vivo methods to point out this natural medicine's anti-cancer properties. It is divided into three groups based on their geographical distribution, mainly Central and South America, Asia, Australasia, and Africa. Each part of the fig tree is used to treat various diseases such as cuts and wounds, diarrhea, cholera, mumps, jaundice, and cancer6. Ficus carica leaves and fruits contain active polyphenolic compounds and their derivatives. Therefore, they are considered an anti-cancer agent. Quercetin and luteolin are the main phenolic compounds found in fig leaves. Quercetin can stimulate the apoptosis of colon cancer cells (Caco-2 and HT-29) and leukemia cancer cells (HL-60) by stimulating the release of cytochrome c from mitochondria[17].

Date

The date or date palm, scientifically known by the name Phoenix dactylifera, is the oldest and most authentic tree in southwest Asia and North Africa. The most important quality features to grade dates are color, flavor (sugar level), moisture (26-30%), and absence of defects such as insect, damage, cracks, and surface damage. The date fruit is a good source of valuable nutrients. It is rich in carbohydrates, dietary fibers, proteins, minerals, and vitamin B complexes, such as thiamine (B1), riboflavin (B2), niacin (B3), pantothenic (B5), pyridoxine (B6), and folate (B9).

Essential Minerals in date fruits are calcium, iron, magnesium, selenium, copper, phosphorus, potassium, zinc, sulfur, cobalt, fluorine, manganese, and boron[18]. The aglycone metabolites of Ajwa dates such as luteolin, myricetin, apigenin, quercetin, and petunidin have been reported to induce apoptosis in cancers[19]. The dates mentioned in the Holy Quran are known as a popular food among the people. "A fresh date tree falls to the ground, shaking its trunk"[1].

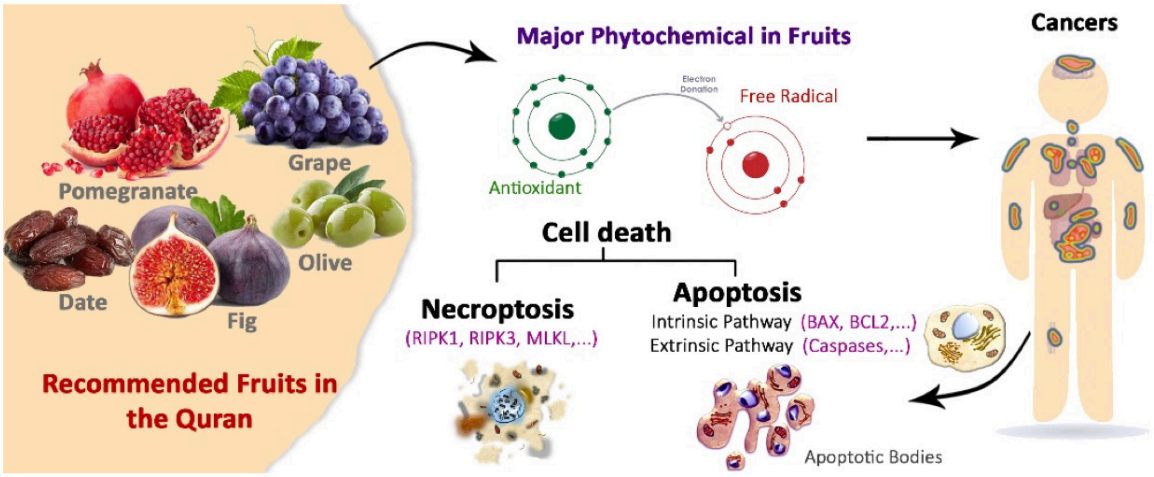
The effect of the mentioned fruits in the Holy Quran on different cancer cells' molecular mechanisms is described here (**Figure 1**).

Fruits anti-cancer activities

Breast cancer

The second most common cancer in women worldwide is breast cancer. Studies show the beneficial effects of pomegranate products on the process of breast cancer. In vivo research of breast cancer cells of the estrogen-dependent type has been[20] demonstrated that methanolic pomegranate extract has a modulating effect on estrogen deficiency in the absence of estrogen inhibits the growth of these cells[21]. Another study shows that the compounds in pomegranate extract can affect the expression of pro-apoptotic and anti-apoptotic genes (Bax/Bcl-2 ratio) and cascading waterfall (cytochrome c, Caspase-3, caspase-7, caspase-9) and eventually, by regulating the expression of these genes, it increases

Figure 1: The effect of the mentioned fruits in the Holy Quran on the molecular mechanisms of different cancer cells.



apoptosis[22]. Since high expression of aromatase (an enzyme that converts androgen to estrogen) is an essential factor in the development of breast cancer, and inhibition of aromatase/estrogen biosynthesis is considered as a therapeutic potential for this cancer, on the other hand, grape juice was the most effective in inhibiting the activity of human aromatase (methanol extract of grape juice and red wine suppresses aromatase in a dose-dependent)[23]. Quercetin induced breast cancer cell apoptosis by modulating signaling pathways (protein kinase B (AKT), nuclear factor-kappa B (NF-κB)) or regulatory molecules associated with apoptosis (p53, Bcl-2 family, FasL)[24]. Luteolin inhibited metastatic breast cancer cell lines by reducing vascular endothelial growth factor (VEGF)[25]. Quercetin has also been found to modulate the phosphoinositide 3-kinases (PI3K)/AKT/ mammalian target of rapamycin (mTOR) signaling pathway. The flavonoid has structural homology to the PI3K inhibitor, LY294002 (LY), and as expected, the phytochemical was found to inhibit the PI3K/AKT pathway to the inhibition elicited by LY in the breast cancer cell line[26]. Pinoresinol showed cytotoxic, anti-proliferative, and pro-oxidant activity in human breast tumor cells, independent of their estrogen receptor status. Also, pinoresinol exerted antioxidant activity and prevented DNA damage associated with oxidative stress in human mammary epithelial cells[27]. The active components in fig leaves, including bergapten and psoralen benzaldehyde, amylose, and selenium, have known anti-cancer effects and increase the expression of genes associated with apoptosis, including (Bax, and p53)[19]. Through up-regulation of pro-apoptotic molecules such as; p53, Bax, Fas, and FasL and down-regulation of Bcl-2 and suppression of AKT/mTOR signaling pathway[28].

Prostate cancer

About 9.7% of cancers in men are due to prostate cancer; it is the second most common cause of death after lung cancer. The effects of pomegranate extract on prostate cancer have been proven by cell culture studies, clinical trials, and animal studies. Pomegranate compounds such as ellagic acid, caffeic acid, luteolin, and punicic have been shown to reduce invasiveness and metastasis in prostate cancer cells (PC3 cells). Pomegranate fruit extract (PFE) regulated the expression of cyclin-dependent kinases (CDK) and the expression of cell cycle regulatory cyclins D1, D2, E, as well as decreased Bcl-2 expression and increased Bax expression, increasing the incidence of apoptotic cell death in these cells [29].Grape seed compounds such as proanthocyanidin induced apoptosis in the PC3 cells through an activation caspase-dependent pathway.

Furthermore, Bax/Bcl-2 ratio in these cells increased after treatment with grape seed extract[30]. Olive leaf hexane extract has cytotoxic effects on the human prostate cancer cell line[31]. In these cancer cells treated with ethyl acetate fractions of Ajwa dates, all the evidence for apoptosis, including (cell shrinkage, loss of cytoskeletal structure, DNA fragmentation), has been seen[32].

Lung cancer

Lung cancer is one of the most common and severe types of cancer. There are studies on the inhibition of pomegranate extract on lung cancer cells (A549 and H1299), which suggest that this effect has been achieved by inhibiting the signaling pathways of mitogen-activated protein kinase (MAPK), PI3K/AKT, and NF-κB[33]. Previous studies about non-small cell lung cancer (NSCLC) proliferation have shown that grape seed extract (GSE) releases cytochrome c to the cytosol and activates caspases 3 and 9. Moreover, it phosphorylates extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase 1/2 (JNK1/2), and these results indicate an increase in apoptosis in these cells[34]. A high amount of oleic acid in olive oil can inhibit lung cancer progression through inhibition of prostaglandin E (PGE2) production and inactivation of the ERK pathway[35]. An

investigation has shown that Fig (F. auriculata) activates apoptosis in the human lung cancer adenocarcinoma cancer cells (A549) through a pathway independent of caspases[6]. Studies have shown that extracts of both types, both Barhi date palm kernels (BDPK) extracts, and purified phytochemicals, cause apoptosis on A549 and HT-29 cells. BDPK extracts exhibited a dependent mitochondrial signaling pathway, reported with caspase-9 and induced receptor-mediated (extrinsic) apoptotic pathway as seen with caspase-8[28].

Colorectal cancer

Colorectal cancer is also known as bowel cancer, colon cancer, or rectal cancer. It is the second leading cause of cancer death in women and the third for men. The risk of developing this cancer is somewhat reduced by eating fresh fruits and vegetables that contain polyphenols. Consumption of pomegranate extract has shown to increase the expression of peroxisome proliferator-activated receptor (PPAR) gamma protein in non-tumor colonies, indicating the ability to inhibit the tumor[35]. The GSE inhibits cell growth and induces cell cycle (G1 phase) arrest and apoptosis in human colorectal cancer cells, and modulates cell cycle regulators with a substantial effect for Cip1/p21 up-regulation[36].

Activating transcription factor (ATF3) is one of the critical transcription factors involved in mechanisms such as apoptosis, cell proliferation, and invasion, and its reduction has been seen in various cancers. Studies have shown that resveratrol in grapes can induce apoptosis by increasing ATF3 expression in colorectal cancer cells[37]. Olive oil contains different polyphenolic compounds, which can induce apoptosis in various cancer cells. The Mediterranean diet is rich in extra virgin olive oil and associated with a lower incidence of colorectal cancer[16]. One of the critical polyphenolic compounds in virgin olive oil is hydroxytyrosol, which can induce apoptosis cell death in human colon adenocarcinoma cells (DLD1) via ROS generation[19]. Research has shown that Leaves and latex extracts of F. carica have strong anti-proliferative properties on colon cancer cells (HT-29 and HCT-11)[38].

Skin cancer (Squamous cell carcinoma)

Skin cancer is one of the most common cancers in the world. Non-melanoma skin diseases refer to a group of diseases that slowly develop in the skin's upper layer. Studies in nude mice have shown that pomegranate extract can play a role in repairing pathways on DNA damage and inflammation caused by ultraviolet B (UVB) in skin cells. Ingredients in pomegranate peel can stop the cell cycle in the G0 / G1 phase, increase caspase activity, and increase the NF-κB factor in human skin fibroblast cells[39]. Examining skin cancer cells in mice showed that proanthocyanidins in grape seeds had protective effects on these skin cells. The grape seed results have been reported to activate two mitogen-activating kinases and the NF-κB signaling pathway[40]. Olive oil contains large quantities of squalene, which, found in large amounts in the Mediterranean diet, reduces skin cancer incidence. Although alpha-tocopherol (vitamin E) and carotenoid contents in the number of olive oil consumed daily are low, continuous consumption of olive oil will have considerable antioxidant effects in humans[41]. Fig latex inhibited cell growth and induced apoptosis through caspase and the Bcl-2 family signaling pathway and by extrinsic death receptor and intrinsic mitochondrial-dependent apoptotic signaling pathway in human hypopharynx squamous carcinoma cells (FaDu). These findings point to the potential of the latex of Ficus carica to provide a novel chemotherapeutic drug due to its growth inhibition effects and the induction of apoptosis in human oral cancer cells[42]. Date fruit extracts specifically inhibited oral squamous carcinoma cell line viability but did not have a toxic effect on human gingival epithelial cells at a concentration between 5-100 mg/mL for 24 hours (The crude extracts from the Khalal stage demonstrated the best inhibitory effect on reducing of oral squamous carcinoma cell growth)[43].

Liver cancer

Liver cancer is one of the deadliest gastrointestinal diseases. Research into pomegranate extract in mice has shown that its ingredients can reduce the expression of cytochrome p450 and affect the liver's cancer cells by acting on antioxidant and apoptotic mechanisms. Examination of rat cancer hepatic cells showed an increase in pro-apoptotic protein expression (Bax) and anti-apoptotic protein inhibition (Bcl-2) during pomegranate extract consumption. Signaling pathways involved in liver diseases such as NF-κB and Wnt / β-catenin were affected by pomegranate extract[44]. Quercetin reduced the phosphorylation of ERK1/2 and AKT phosphorylation and inhibited the NF-κB pathway in HepG2 liver cancer cells. In HepG2 cells, kaempferol induced apoptosis via endoplasmic reticulum (ER) stress and the CHOP pathway[25].

A study has recently reported that oleuropein promotes apoptosis in liver cancer cells by activating caspases (3, 8, and 9) and regulating mitochondrial proteins, in addition to via reduction PI3K/AKT signaling pathway[45].

F. Carica leaf and fruit extracts' ability to cause liver cancer cells (Huh7it cell) apoptosis is through its ability to induce cell cycle arrest and increase the activity of apoptotic regulating genes (p53 and p21). The potential anti-cancer activity of original fresh fig fruit latex (FFL) against hepatocellular carcinoma cells *in vitro* has investigated the results demonstrated that FFL has an anti-proliferation effect by inducing apoptotic cells, inhibiting DNA synthesis of cancer cells and causing G0/G1 phase arrest of cancer cells[17]. The past studies have revealed the potent growth-inhibitory impact of ethanolic extract of Ajwa date pulp (ADP) against human liver carcinoma (HepG2) cells with little to no effect on

healthy Vero cells. The result was associated with ROS generation and mitochondrial membrane potential (MMP) depletion in cancer cells. ADP extract induced DNA damage in HepG2 cells, leading to cell cycle arrest at S and G2/M phases, followed by apoptosis through a p53-independent pathway[46].

Brain tumors

The most common brain tumor is resistant to treatment and therefore has a poor prognosis in glioma. In the human glioma cell line (U87MG), an increase in cyclin E proteins and a decrease in cyclin A had observed. The compounds in pomegranate peel increase the activity of caspases 3 and 9 and thus increase cell death. It was also reported that cell death of autophagy type in cells treated with pomegranate extract increases, which results from the study of LC3-II protein. Obtained as a proprietary autophagy marker[47]. Studies show that GSE affects p53 and interleukin 6 proteins' expression, thereby acting as an anti-inflammatory to the nervous system[48]. The potential anti-cancer activity of original fresh FFL against human glioma cells in vitro investigated. The results demonstrated that FFL has an anti-proliferation effect by inducing apoptotic cells, inhibiting cancer cells' DNA synthesis, and causing G0/G1 phase arrest of cancer cells[49].

The molecular mechanisms of fruits mentioned in the Holy Quran are summarized in **table I**.

Table I: Cell death molecular mechanisms of fruits in different cancers.

Cancers	Fruits	The molecular mechanism(s)	References
Breast cancer	Pomegranate	Regulating the expression of these genes: cytochrome c, Caspase-3, caspase-7, caspase-9)	22
	Grape	Inhibition of aromatase/estrogen biosynthesis modulating AKT, NF-κB, p53, Bcl-2 family, FasL Reducing expression of VEGF Modulated the PI3K/AKT/mTOR Inhibited the PI3K-AKT pathway	23-26
	Olive	Prevented DNA damage associated with oxidative stress in human mammary epithelial cells	27
	Fig	Increased the expression of Bax, p53, and p21	19
	Date	Up-regulation of p53, Bax, Fas, and FasL along with down-regulation of Bcl-2 suppression of AKT/mTOR signaling pathway	28
Prostate cancer	Pomegranate	Regulated the expression of CDK and the expression of cyclins D1, D2, E decreased Bcl-2	29
	Grape	Increased the Bax/Bcl-2 ratio	30
	Olive	Cytotoxic effects on the human prostate cancer cell line	31
	Date	Induced apoptosis and arrest the cell cycle in S phase	32
Lung cancer	Pomegranate	Inhibiting the signaling pathways of MAPK, PI3K/AKT, and NF-κB	29, 33
		Released cytochrome c caspases 3 and 9	
		Regulated the expression of CDK and the Expression of cell cycle regulatory cyclins D1, D2, E, as well as decreased Bcl-2 expression and increased Bax expression	
	Grape	Released cytochrome c to the cytosol and activates caspases 3 and 9. Phosphorylated ERK1/2 and NK1/2	34
	Olive	Inhibition of PGE2 production	35
		Inactivation of the ERK pathway	
	Fig	Activated the pathway independent of caspases	6
	Date	Induced receptor-mediated (extrinsic) apoptotic pathway as seen with caspase-8	28
Colorectal cancer	Pomegranate	I increased the expression of (PPAR) gamma protein.	35
	Grape	Inhibited cell growth and induces cell cycle (G1 phase) increasing ATF3 expression	36, 37
	Olive	Regulated apoptosis/necrosis by activation of caspase cascade and inhibition of TNF-α-induced NF-κB pathway	16
	Fig	Strong anti-proliferative properties	38
Skin cancer	Pomegranate	Stopped the cell cycle in the G0 / G1 phase, increased caspase activity, and increased the NF-κB factor in human skin fibroblast cells	39
	Grape	Activated two mitogen-activating kinases and the NF-κB signaling pathway	40
	Fig	Inhibited cell growth and induced apoptosis through caspase and the Bcl-2 family signaling pathway	42
	Date	The inhibitory effect on reducing oral squamous carcinoma cell growth	43
Liver cancer	Pomegranate	Increased in the expression of Bax and inhibition of Bcl-2	44
	Grape	Reduced the phosphorylation of ERK1/2 and AKT phosphorylation and inhibited the NF-κB pathway Induced apoptosis via ER stress and CHOP pathway in HepG2 cells	25
	Fig	Induced cell cycle arrest and increase the activity of apoptotic regulating genes (p53 and p21) FFL inhibited DNA synthesis of cancer cells and caused G0/G1 phase arrest	17
	Olive	Promoted apoptosis in liver cancer cells by activating caspases (3, 8, and 9) and regulating mitochondrial proteins, in addition to via reduction PI3K/AKT signaling pathway	45
	Date	ROS generation and MMP depletion ADP extract induced cell cycle arrest at S and G2/M phases and followed by apoptosis through a p53-independent pathway	46
Brain tumors	Pomegranate	Increased the activity of caspases 3 and 9	47
	Grape	GSE affected the expression of p53 and interleukin 6 proteins	48
	Fig	FFL induced apoptotic cells, inhibit DNA synthesis of cancer cells and cause G0/G1 phase arrest of cancer cells	49

Conclusion

This study showed that in the Quran, the Muslims' Holy Book, all aspects of human life had been considered. According to the reviewed studies in the Quran, God has paid particular attention to foodstuffs' therapeutic and beneficial properties, mostly fruits such as pomegranate, grape, olive, date, and fig. In recent years, clinical research has shown that all these fruits' components have important therapeutic activities, such as anti-cancer and antioxidant effects. By studying the types of cell death molecular mechanisms and signaling pathways of mentioned fruits in the Quran, their role in cell death, including apoptosis, is prominent. So, the results can be used in deciphering the treatment of cancers. On the other hand, by referring researchers to the Holy Quran and the cases mentioned in it, there is hope for treating diseases such as cancer.

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