Review

Active Ingredients of Some Egyptian Plants Species with Anticancer Activity and Its Mode of Action

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ABSTRACT

Egyptian desert and natural reserves are enriched areas with varieties of medicinal plants. Due to specific environmental conditions these plants have been professionally used by Ancient Egyptians against several identified diseases at that time, including dental, gynecological, gastrointestinal, and urinary disorders. Nowadays, Egyptians depends on advanced knowledge of these plants as an alternative medicine. Thus, after accumulative experience Egyptians were able to describe the preparation methods, usage part of the plant and against which disease.. The oldest medicinal document was Among these phytochemicals, the Egyptian environmental conditions in the desert areas are induce successive accumulation of different active compounds such as phenolic, flavonoids, plant acids, terpenoids, alkaloids, glycosides etc.. The Egyptian flora has been extensively tested for its active ingredient, antioxidant and anticancer properties. The structure, function relationship have been also evaluated. As well as, the mechanisms of actions against human cancer cell lines such as apoptosis, necrosis, and cell cycle arrest and reduced angiogenesis. . This review closely summarizes the biological activities of different Egyptian medicinal plants (EMP) as antioxidant and anticancer properties as well as the mechanism of actions of the active ingredients isolated from these plants along with their possible future applications in medicinal field.

Key words: *Egyptian plants; Active ingredients; anticancer activity; Antioxidants; Apoptosis; Mode of action*

INTRODUCTION

The development of powerful chemotherapeutic medicines has advanced significantly, but cancer is still a deadly and aggressive illness. After heart disease, cancer is the second most common cause of death globally. In 2018, there were 9.6 million cancer-related deaths and 18.1 million new cases

worldwide. It is estimated that there would be 17 million annual deaths from cancer and 26 million new cases by 2030 [1, 2]. An astounding USD 1.16 trillion was predicted to be the disease's annual total economic cost.

One of the most popular forms of anti-cancer medication therapy is chemotherapy. However, a key component of treating malignant disorders is the development of cancer cells' resistance to cytotoxic medicines. [3] Doxorubicin is one medication that can be used to treat various cancers, however it is quite expensive and only works on specific types of tumours. Additionally, the tumour frequently becomes resistant to several medications.

Furthermore, most of the cancer drugs have extreme side effects for the patients. In this concern, there is a continuing demand for developing treatments that are effective in fighting cancerous cells with less harmful than existing therapies. For covering these problems, one approach is to obtain the anticancer drug candidates from secondary metabolite of natural resources, such as plants [4]. At the last few years, a vast development in the area of herbal medicine has been experienced and these herbal medicines are attaining popularity in developing as well as in developed countries. Medicinal plants have been used by humans for centuries in folklore medicine by Egyptian, Chinese and other countries [5].Traditional medicine has a long history in the prevention of human diseases risk [6]. In developing countries, medicinal plants have been used as an alternative strategy for the medical systems depends on the ethnobotanics tradition [7]. Different active ingredients were isolated from these plants (Figure 1) and studied for numbers of diseases including cancer, diabetes, Alzheimer, coronary heart disease and aging. More than 3,000 plants worldwide have been reported to exert cytotoxicity toward cancer cells and have been identified to possess antineoplastic activities [8].

The reactive oxygen species ROS are important for the body turn-over, but the excessive production leads to cellular DNA and protein damage which associated with oxidative stress, therefore. Induce disease disorder. Free radicals are made naturally in the body and show a significant role in various normal cellular processes. High concentrations of free radicals can be harmful to the body and damage all major mechanisms of cells that include DNA, proteins, and cell membranes which may also play a role in the development of cancer and other health conditions. Antioxidants are substances that interact and neutralize free radicals, thus avoiding them to cause damage. The plants are rich in secondary metabolites with interesting biological activities. Therefore, these secondary metabolites have an important source with a variety of structural arrangements and properties [9]. Also, dietary antioxidants may reduce the risks of these diseases and improve general human health.

Second-ary metabolites were used to identify the active ingredients of several plant-based medications; at least 12,000 of these active phytomolecules were chemically identified. Alkaloids, flavonoids, phenols, essential oils, polyphenols, and terpenoids are among the bioactive components that have been found to have therapeutic value and are crucial in the treatment of cancer [10]. Given the temperature differences between the country's eastern and western regions as well as its northern and southern regions, Egyptian plants constitute a rich source of natural compounds and represent significant biodiversity. Historical records indicate that the Egyptians were the first to notice the growth of tumours in different body areas as early as 3,500 BC [11]. Tumours were listed as an illness in the Ramayana's traditional manuscripts in 2000 BC [11].

The primary aim of this review is to document some plants and natural products that are used as foods and medicines in Egypt with a focus on those with antioxidants and anticancer activities. The structure of the active principles and its mode of action at the molecular level were also illustrated against cancer.

The selected plants which grown in Egypt

For simplicity sake we are focusing on eight plants grown in Egypt in this review which was studied by our group for their biological activities, identification of the active ingredients and mode of action as

anticancer agents. The steps of extraction, isolation and purification of extracts as well as chemical identification of the active principles were followed according to scheme given in Figure (1).

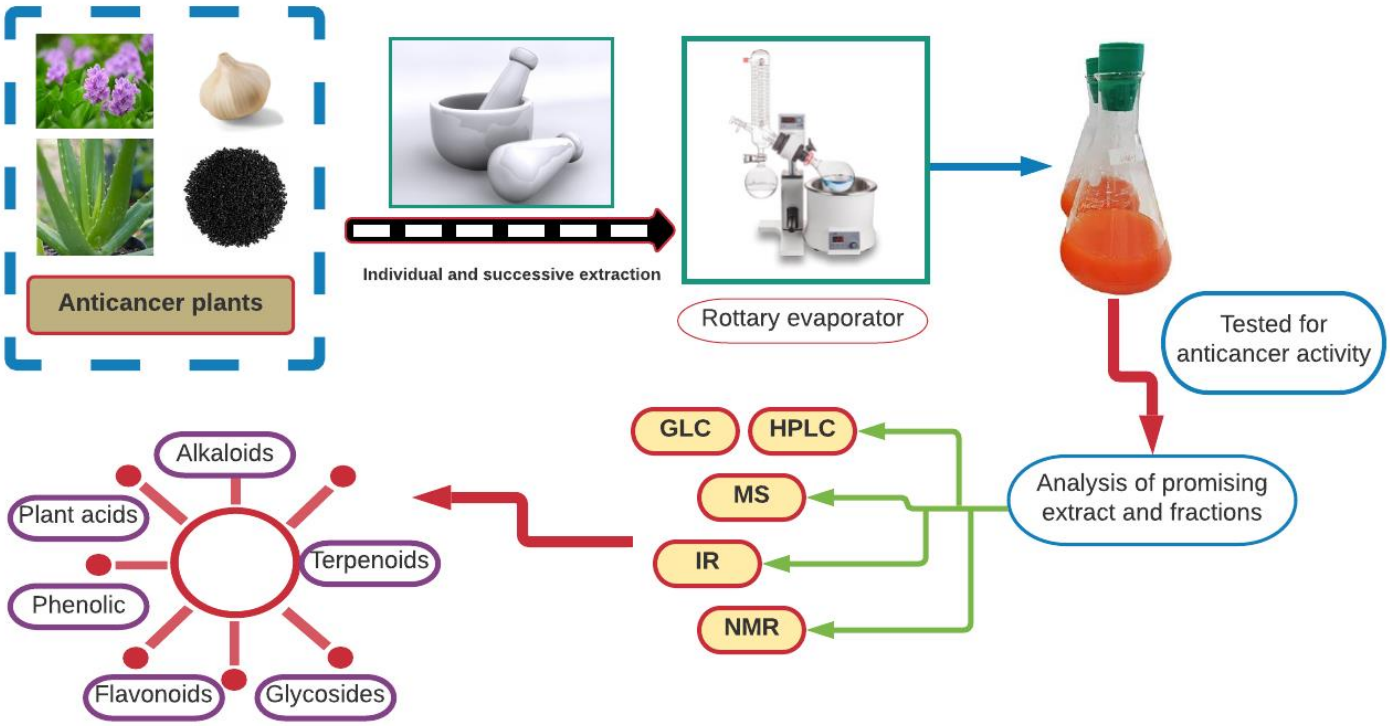


Figure 1: Main practical steps for isolation and identification the anticancer compounds from plants

The eight plants which have been studied and chosen in this review included *Eichhornia crassipes* (water hyacinth), *Nigella sativa* L., (Al-Habba Al-Barakah" or black cumin), Cassia italica (Senegal senna), *Salix safsaf* (Willow), Solanum nigrum (Black nightshade), *Aloe vera* (Allevera), Allium sativum L. (Garlic) and Piper nigrum (Black pepper). The description of Habitat and Ecology of each plant were given and illustrated in Figure (2).

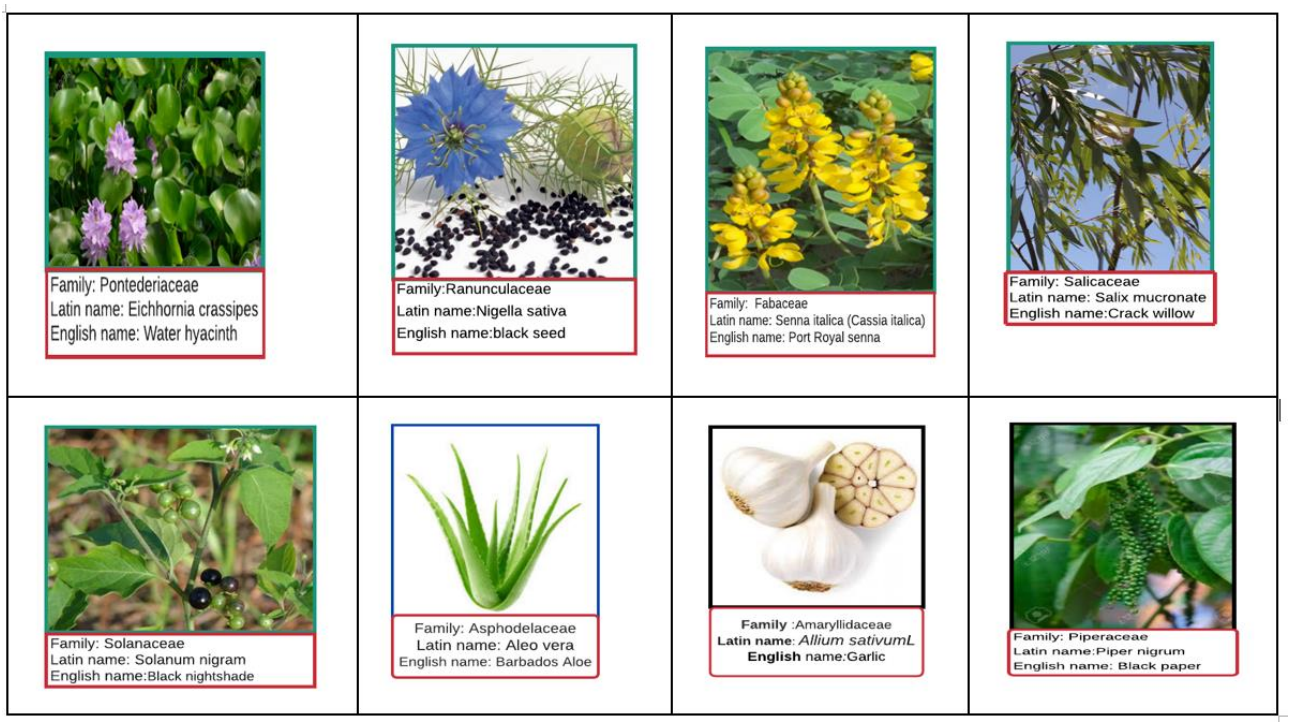


Figure 2: Some Egyptian plant pictures and its taxonomy

The anticancer compounds derived from these plants are shown in Figure (3: a and b). As well as, the suggested mechanism for the role of each active compound on inhibition of cancer cell's growth, as anticancer (cancer cell formation pathway) was illustrated in Figure (4).

Eichhornia crassipes

Description, Habitat and Ecology

Water hyacinth, as it is sometimes called, can float up to one metre (3 feet) over the water's surface [12].On a stem that floats above the water's surface thanks to buoyant bulb-like nodules at its base, the leaves are 10–20 cm (4–8 inches) broad. Their stalks are tall, bulbous, and spongy (Figure 2). Tropical deserts, subtropical regions, mild temperate deserts, and rainforests are among its habitats.

The water hyacinth can withstand the following temperatures: 12 °C is its minimum growth temperature; 25–30 °C is its ideal growth temperature; 33–35 °C is its maximum growth temperature; and 5.0–7.5 is its estimated pH tolerance. Frost kills leaves, and plants cannot withstand water temperatures higher than 34 °C. Where the average salinity is more than 15% of seawater, water hyacinths cannot thrive. By 2010, water hyacinth had spread to at least 62 countries in North America, Asia, and Africa.

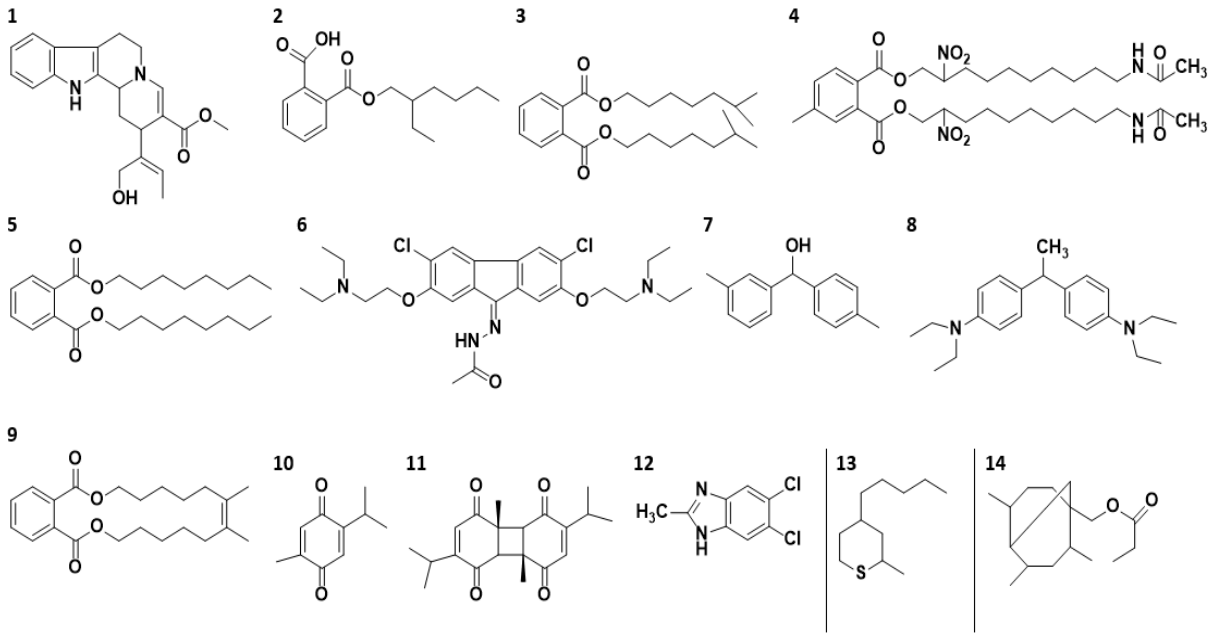
General biological activities

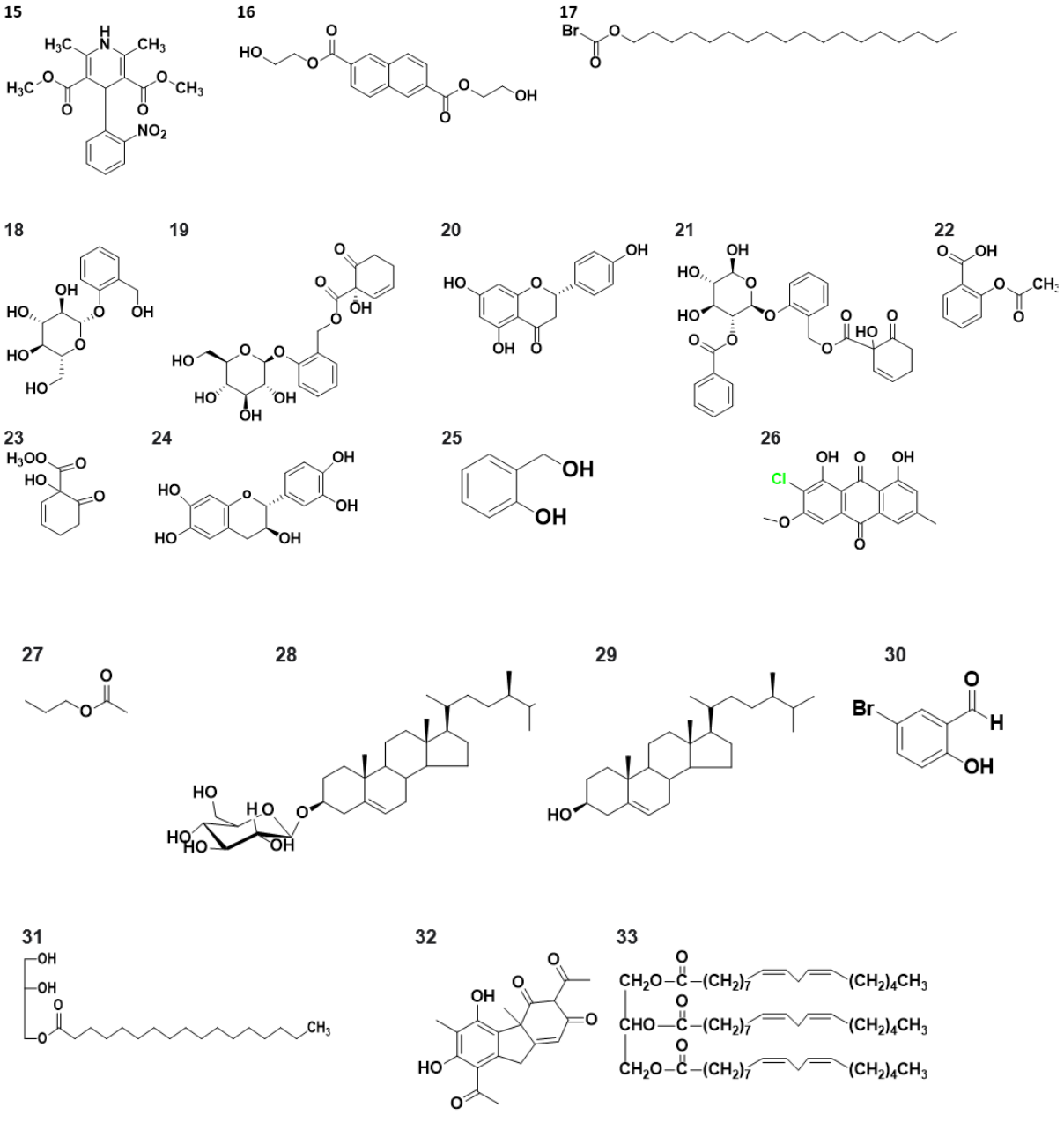
Due to its rapid growth, *E. crassipes* is a great source of several active compounds with biological properties such as antibacterial, antioxidant, anticancer, fertiliser, phytoremediation, and biofuel production [13]. Furthermore, it has been revealed that water hyacinth is a rich source of novel and practical antibiotics that are effective against certain harmful strains of bacteria, fungi, and algae [14,15].

Active ingredients as anticancer and mode of action

A crude methanolic extract of water hyacinth was used to separate and identify nine pure chemicals, which demonstrated a variety of biological actions, including anticancer and radical scavenging [13]. According to Figure (3), the nine chemicals identified by the spectroscopic analysis were the alkaloid derivatives (compounds No. 1, 4, and 6) and the terpenoid derivatives (compounds No. 2, 3, 5, 7, 8, and 9). The crude extract of E. crosses and its derivative fractions were tested for anticancer efficacy against three distinct solid tumour cell lines and one liquid cell line (Ehrich Ascites Carcinoma Cells, EACC) using the SRB assay.

With IC_{50} values of 1.6 and 1.2 µg/mL, respectively, the crude methanolic extract demonstrated satisfactory efficacy against the HeLa and MCF-7 cell lines. However, when compared to the standard anticancer medication doxorubicin, which had IC_{50} values of 0.28, 0.42, and 0.42 µg/mL against Hela, HepG2, and MCF-7, respectively, HepG2 and EACC cell lines shown greater resistance to the crude methanolic extract, with IC_{50} values of 7.6 and 6.04 µg/mL. With an IC_{50} of 0.8µg/mL for the HepG2 liver cancer cell line, compound I had the strongest cytotoxic profile of all the fractions after fractionation.

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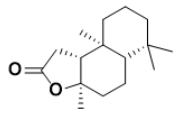
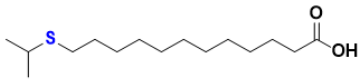
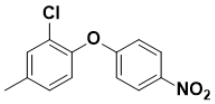
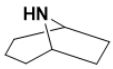
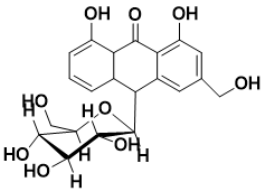
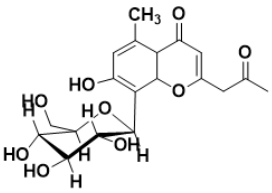
34 

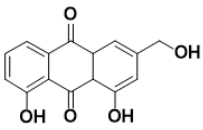
35 

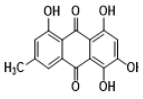
36 

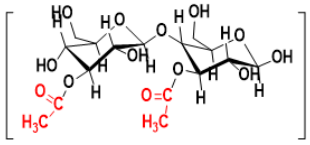
37 

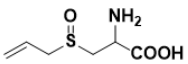
38 

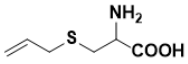
39 

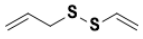
40 

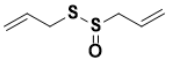
41 

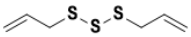
42 

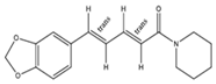
43 

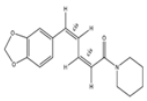
44 

45 

46 

47 

48 

49 

S.N	Chemical name	S.N	Chemical name	S.N	Chemical name
1	18, 19-Secoyohimban-19-oic acid, 16, 17, 20, 21-tetradehydro-16-(hydroxymethyl)-, methyl ester (15 beta, 16 E)	2	1,2-Benzene dicarboxylic acid, mono-(2-ethylhexyl ester)	3	1, 2 Benzene dicarboxylic acid, diisooctyl ester
4	Di amino-di nitro-Methyl dioctyl phthalate	5	1, 2 Benzene dicarboxylic acid, dioctyl ester	6	9-(2,2-Dimethyl propanoilhydrazono)-2,7-bis-[2-{diethylamino)-ethoxy] fluorine
7	3-Methyl phenyl-phenyl methanol	8	4- (diethylamino)-alpha-[4-(diethylamino) phenyl]	9	Isooctyl phthalate
10	Thymoquinone	11	dithymoquinone	12	5,6-dichloro-2-methyl-1H-benzimidazole
13	Trans-2-methyl-4-n-pentylthiane	14	Propionic acid (3,6,7,8-tetrahydro-3,7-methano-2,4,6-trimethyl-2H-oxocin-7-yl) methyl ester	15	Nifedipine
16	Naphthalene dicarboxylase ester	17	Octadecyl bromoacetate	18	Salicin
19	Salicortin	20	Naringenin	21	Tremulacin
22	Aspirin	23	methyl 1-hydroxy-6-oxocyclohex-2-enecarboxylate	24	(+) catechin
25	Catechol	26	Fragilin	27	Propyl acetate

S.N	Chemical name	S.N	Chemical name	S.N	Chemical name
28	β-sitosterol glucopyranoside	**29**	β sitosterol	**30**	5-Bromosalicylaldehyde
31	2,3 Dihydroxypropyl elaidate	**32**	Usnic acid monoacetate	**33**	Trilinolein
34	Naphtho [2,1-b]furan-2(1H)-one,decahydro-3a,6,6,9a-tetramethy	**35**	12-sulfanyldodecanoic acid	**36**	Niclofen
37	8-Azabicyclo	**38**	Aloin	**39**	Aloesin
40	Aloe-emodin	**41**	Emodin	**42**	Acemannan
43	Alliin	**44**	S-allyl Cystein (SAC)	**45**	Diallyldisulphide (DADS)
46	Allicin	**47**	Diallyltrisulphide (DATS)	**48**	Piperine
49	Chavicine				

Figure 3: Chemical structure of active ingredients isolated from the promising Egyptian plants as anticancer activity

The remaining compounds had moderate cytotoxic effects, with IC_{50}s ranging from 7.7 to 14.1 μg/mL, whereas compound No. 4 demonstrated very potent cytotoxicity against the HeLa cervix cancer cell line (IC_{50} = 4.3 μg/mL). Compounds 1, 2, and 8 had the highest cytotoxic profile against the breast cancer cell line MCF-7, with IC_{50} values of 11.1 μg/mL, 13.4 μg/mL, and 13.6 ± 5.3 μg/mL, respectively. Furthermore, the IC_{50} values of the other substances (No. 3 and 7) ranged from 17.5 to 69.1 μg/mL, indicating minor cytotoxic effects. With IC_{50} values ranging from 14.9 to 74.2 μg/mL, the other drugs demonstrated a significantly more modest cytotoxicity profile against the HepG2 cell line.

Compounds 1, 3, 4, and 5 shown strong efficacy in relation to EACC, with corresponding IC_{50} values of 6.42, 7.29, 8.19, and 8.61 μg/mL. The IC_{50} values for compounds 7, 8, and 9 were 12.32, 12.67, and 22.79 μg/mL, respectively, indicating a moderate impact.According to the mode of action of the water hyacinth compounds that were isolated, the chemical molecules of the separated active compounds may improve the release of methyl ions as carbonium ions, which react with the DNA or cell proteins of cancer cells. This freed methyl ion group can attach itself to the DNA's N7-guanine base (or other bases) and cause a mutation that stops the cell cycle or kills the cancer cells [13,16,17].

As demonstrated by the development of a DNA laddering on an agarose gel, this occurrence led to notable intensities of internucleosomal DNA fragmentations. Furthermore, only compound No. 1 was able to enterchelate with DNA; the other eight compounds (2–9) were unable to do so. After 2 and 24 hours of incubation, the absorbance of the DNA+ chemical mixture at 260 nm increased in comparison to DNA alone (loss of hypo-chromecity), indicating DNA damage. Therefore, the harm that certain natural compounds caused to cancer cells was not only dependent on their ability to enterchelate with DNA; it might also result from the cleavage of DNA strands (denaturation), base damage (from alkylation and/or free radical attack), or release of DNA.

In this concern, natural anticancer substances can affect cancer cells through their DNA damage by different probability mechanisms [13].

From the previous collected information and results we can conclude that the isolated compounds from water hyacinth may effect on steps No. 2, 3 and 4 of the cancer formation cycle as shown in Figure (4).

Nigella sativa L

Description, Habitat and Ecology

Native to South-west Asia, *Nigella sativa* L. (Ranunculaceae) is an annual herbaceous plant that has been grown and naturalized throughout North Africa and Europe [18]. Its cultivation dates back over 3,000 years to the Assyrian and ancient Egyptian kingdoms [19]. N. sativa is a herb with finely split, linear leaves that grows to a height of 30 to 60 cm [20] (Figure 2). Typically, the flowers have five to ten petals and are white and pastel blue. The fruit is a big, inflated capsule made up of three to seven

connected follicles, each of which has many tiny, black seeds inside [18]. In Arabic, it is called "Al-Habba Al-Sauda" or "Al-Habba Al-Barakah," while in English, it is called "black cumin" or "black caraway" [21].Biological activity in general

The antitumor effects of N. sativa against hard splenic mass were investigated by Ibn-Sina [22]. Many active ingredients have been separated from N. sativa seeds and its oil. These compounds recorded monstrous pharmaceutical activities which include immune stimulation. N. sativa oil is emphasized as an important natural radio-protective agent against side effects of ionizing radiation like immunosuppressive and oxidative effects [23]. Its anti-inflammation, hypoglycemic, antihypertensive, antiasthmatic, antimicrobial, antiparasitic, antioxidant and anticancer activities have been also reviewed [21, 24].

Active ingredients as anticancer and mode of action

Nigella sativa seeds have been shown to possess an important role as natural remedy for many diseases in traditional medicine. Also it has been considered as an increasingly valuable source of bioactive compounds of substantial medicinal merit. However, many active ingredients have been isolated and identified from N. sativa (Figure 3, compounds No. 10-11). These compounds include thymoquinone, thymohydroquinone and alpha-hederin [21, 25, and 26]. Several terpenes like ß-Pinene, O-Cymene Terpinen-4-ol, Limonen-6- ol, were identified in N sativa using GC-MS analysis [24]. Four potentially active phytochemicals have been separated from methanol extract of *N. Sativa* such as alkaloids, phenol, flavonoids and [27]. Different nanoformulation of thymoquinone (TQ) as natural anticancer against glioma cancer cells [28]. TQ has poor water solubility and insufficient targeting capacity so they have innovated novel core-shell nanoformulations for TQ delivery using mesoporous silica nanoparticles (MSNs) as a carrier. The author prepared the core-shell nanoformulations with a core of MSNs loaded with TQ (MSNTQ), and the shell consisted of whey protein and Arabic gum (MSNTQ-WA), or chitosan and stearic acid (MSNTQ-CS). They evaluated the anticancer activity of those nanoformulations on brain cancer cells (SW1088 and A172) and compared with cortical neuronal cells-2 (HCN2) as normal cells using MTT assay. Their results indicated a high anticancer efficiency for MSNTQ-WA compared to free TQ, and low cytotoxicity in HCN2 normal cells. These results showed a significant variable reduction in cancer cells viability ($p<0.05$) when SW1088 cancer cells were treated with 100 µg/mL of complexes for 48h. The viability reached to 24.7 % for MSNTQ, 25.3 % for TQ, 26.5 % for MSNTQ-WA, and 29.2 % for MSNTQ-CS. After 48 h for A172 cancer cells, the lowest viability values were found when cells were treated with 100 µg/mL, ordered as follows: 23.1 % (TQ), 26.1 % (MSNTQ), 31.4 % (MSNTQ-WA), and 34.8 % (MSNTQ-CS). The data concluded that the use of MSNs loaded with TQ as a delivery system permit improved cancer selectivity and considered a great hope to translating TQ into clinical application. The mode of action of thymoquione and its nanoformulatios as anticancers were studied by [28]). They evaluated the anticancer effect of these compounds on relation with cell life cycle of the cancer cells and their content from cytochrome C. The data revealed that the caspase 3 activity and cytochrome C significantly increased in cancer cell line compared to HCN2 normal cells. They detected that nanoformulations improve intracellular release of cytochrome C in brain cancer compared to normal cell cells. They also found that nanoformulations improved cell cycle arrest at the G2/M phase in same cancer cells. In addition, N. sativa and thymoquione could modulate cell cycle regulatory proteins which involved in G1, S-phase or G2 to M-phase transition [29]. The arrest of G1-phase by Thymoquinone was correlated with an increase of p21-WAFI, which possibly blocks cell cycle regulatory proteins (cdk2, cdk4 and cdk6). P53-dependent as well as p53-independent apoptosis in cancer cell lines can be induced by Thymoquinone [30, 31]. Inhibition of NF-B activation was recorded by Thymoquinone. In addition, Thymoquinone has shown to cause down regulation of the expression of NF-kappa-B-regulated antiapoptotic (IAP1, IAP2, XIAP

Bcl-2 and Bcl-xL), proliferative (cyclin D1, cyclooxygenase-2, and c-Myc), and angiogenic (matrix metalloproteinase-9 and vascular endothelial growth factor) gene products [32, 33]
From the previous collected data and results we can conclude that the isolated compounds from black seeds (N. sativa) may effect on steps No. 4, 6 and 7 of the tumor formation cycle as shown in Figure (4).

Cassia italica

Description, Habitat and Ecology

A member of the genus Senna, *Cassia italica* is a woody legume tree. Solid stems typically grow to a height of less than two meters. The compound leaves of this species have pinnate veining. Each leaf has roughly four to six leaflets. *Senna italica* grows in grasslands from sea level to 1850 meters above sea level in the driest parts of equatorial Africa. Figure 2 [34].
General biological activities
Numerous studies have suggested that certain species of Cassia can be used to cure a range of illnesses, including hair problems, and that its active compounds have antibacterial, anti-inflammatory, and anti-cancer properties [34]. Cassia is a significant source of numerous active and pharmacological substances. It is necessary to investigate the pharmacological potential of the other plant species in the genus ([13, 35, and 36]).

Active ingredients as anticancer and mode of action

Six pure compounds were separated and identified from ethanolic extracts of *Cassia italica* (No. 12-17) which have anticancer and antioxidant activities as shown in Figure (3). The ingtedients in this figure mostly belong to the terpenoids and alkaloids compounds and recorded high anticancer effects. From the figure, the first compound; 5,6-dichloro-2-methyl-1H-benzimidazole has high. Another research reported that all the extracts which exhibited high antitumor potency have high antioxidant activity while the opposite trend is not observed [37,38].The mode of action of the isolated compounds from Cassia italica as anticancer revealed that several isolated compounds have anticancer activity [13]. As well as, these compounds enhances apoptosis induction via control caspases enzymes pathway. From the previous collected data we can conclude that the isolated compounds from Cassia sp may effect on steps No. 4 and 6 of the tumor formation cycle as shown in Figure (4).

Salix safsaf

Description, Habitat and Ecology

The Egyptian willow (*Salix safsaf*) is a small tree growing in Egypt since pre-historic times. The *Salix mucronata* (safsaf willow), widely distributed along the Nile River in Egypt (Figure 2) and commonly called the Cape silver willow (or Safsaf willow), is a tall, graceful [39]. The genus Salix (willow) comprises of about 300 species of deciduous trees and shrubs and it grows along riverbanks and widespread in Africa and Arabia and is used for a wide range of traditional medicines [40]. The genus is subdivided into a number of different species (subspecies) includes: S. m. hirsuta (silver willow), S. m. mucronata (Safsaf willow), S. m. woodii (flute willow), S. m. capensis [41] . Leaves are linear-elliptic when young, sometimes obovate-elliptic when mature, bright green above, whitish beneath; margin finely serrate. The Other species of Salix have similar chemistry and pharmacology. Flowers in catkin-like spikes, sexes separate on different trees. Fruit a capsule, is splitting lengthwise to release tufted windborne seeds. Willow (Ssafsaf willow) trees may grow 6 to 18 m in height.

General biological activities

The medicinal use of willow dates back 6,000 years. Ancient civilizations used willow tree extracts to treat pain, inflammation, and musculoskeletal conditions. Egyptians used willow to treat joint pain and inflammatory conditions associated with wounds. Chinese civilizations used willow to treat fever, pain, colds, hemorrhages, goiter, and rheumatic fever and applied willow as an antiseptic for wounds and abscesses. Leaves extracts were used applied for treating of different diseases hence they showed Anti-

inflammatory and antioxidant activity, Arthritis, Lower back pain, Rheumatic pain, in addition to other uses for treatment of Platelet aggregation and Gout [42] . White willow which is also known as the salicin willow has been used for its health benefits for thousands of years. The phenolic compounds isolated were mainly salicylic glycosides which were the most abundant with reported analgesic, antipyretic, antiinflammatory and antirheumatic properties [43]. Willow bark can be an effective analgesic if the salicylate content is adequate which showed anticancer, antioxidant and anti-inflammatory activity.

In the Hearst medical papyrus seeds are recommended for cooling the vessels, and for cooling a bone after it has been set [44] . In addition, Willow is moderately digestible and highly palatable for livestock and it is a source of minerals for grazing livestock, including calcium, magnesium, potassium and zinc[45]. The young developing leaves of willow (*Salix safsaf*) trees have antileukemic activity. The incubation of the crude water extracts of the leaves killed a majority of the blasts of acute myeloid leukemia (AML), [46,9] . Our group did more studies for the anticancer activity of *Salix safsaf* using different cell lines: (MCF-7), colorectal (HCT-116), cervical (HeLa) and liver (HepG2), [10,47,48] . However, it is better to mention that Toxicity information on the use of willow bark is limited.

Active ingredients as anticancer and mode of action

Many novel compounds (32) have been identified in Salix sp. though no exhaustive metabolite profiles were available in 2006 (Figure 3, compounds No. 18-29). Salicylates, Naringenin glycosides, ligomeric procyanidins, and condensed tannins, presumably derived from the simpler flavonols (willow barks). Phytochemical investigations on the genus Salix have led to reports on phenolic compounds, flavonoids, terpenes and lignans. Willow species synthesize low molecular phenolic glycosides, such as salicin and/or condensed tannin [49]. The phenolic compounds are salicylic glycosides, hence salicin and salicortin are the primary salicylates found in white willow (*salix safsaf*). They are metabolized by intestinal flora to saligenin [50], absorbed into the blood stream, and metabolized by the liver to salicylic acid; excretion is primarily through renal [51,52]. The ester glycosides salicortin, tremulacin, and fragilin can be considered to be prodrugs of salicylic acid. Naringenin glycosides, oligomeric procyanidins, and condensed tannins, presumably derived from the simpler flavonols. Naringenin glycosidic form is naringin which has the addition of the disaccharide neohesperidose attached via a glycosidic linkage at carbon 7. It is better to mention that Salix is a major source of salicylic acid (Aspirin). Salix subserrata showed promising eight compounds acting as antibacterial, antifungal, and antialgal activities as follows: (+) catechin , 1,2-benzenedicarboxylic acid, bis (2-ethylhexyl) ester , saligenin, methyl 1-hydroxy-6-oxocyclohex-2-enecarboxylate, catechol, propyl acetate, β sitosterol, β-sitosterol glucopyranoside. Eight compounds were isolated from leaf and bark Salix subserrata and the studies indicated that compound 1, mixture of compounds 3/4, and 7 showed good antibacterial, fungicidal, and algicidal properties [49] .The ester glycosides salicortin, tremulacin, and fragilin are considered to be prodrugs of salicylic acid, which deliver this compound into the systemic circulation without irritating the GI tract. Also, salicylic acid inhibits cyclooxygenase enzymes, which are involved in prostaglandin synthesis. The anti-inflammatory efficacy of tremulacin, a derivative of salicin, has been found. Six known phenolic compounds inhibited lipid peroxidation (LPO) and cyclooxygenase enzymes (COX-1 and -2). Salicin is hydrolyzed in the intestine to saligenin (o-hydroxybenzyl alcohol), which is absorbed and then oxidized to salicylic acid [50].

The active principles of the willow leaf extracts (Salicin and Saliginin chemicals related to salicylic acid) have anti-leukemia agents as mentioned [46]. The effect of these two compounds in willow leaf extracts on the viability of tumor cells and the mechanism is due to apoptotic pathway and DNA degradation [10].The study also showed that apoptosis is independent of reactive oxygen species (ROS) produced from cancer cells. In addition, significant up-regulation of pro-apoptotic protein and mRNA

markers for Caspase-3, p53 and Bax, provide a cytoprotective and antioxidant capacity against generated oxidative stress. In acute lymphoblastic leukaemia (ALL) and AML (acute myeloid leukaemia) salix active ingredients showed DNA fragmentation patterns within treated cells inferred targeted cell death by apoptosis. The metabolites within the willow extract may act as tumor inhibitors that promote apoptosis, cause DNA damage, and affect cell membranes and/or denature proteins [53].
In conclusion, the findings highlight the importance of natural phenolic and flavonoid compounds from *Salix safsaf*. Also the previous collected data and results let us to conclude that the isolated compounds from Salix sp may effect on steps No. 4,6 and 7 of the cancer formation cycle as shown in Figure (4).

Solanum nigrum

Description, Habitat and Ecology

Solanum nigrum (Black nightshade) is a common herb or short-lived perennial shrub, found in many wooded areas, as well as disturbed habitats. It reaches a height of 30 to 120 cm, leaves 4.0 to 7.5 cm long and 2 to 5 cm wide; ovate to heart-shaped (Figure 2), with wavy or large-toothed edges [54]; both surfaces hairy or hairless; petiole 1 to 3 cm long with a winged upper portion. It is difficult to grow under the condition of high temperature and high humidity. The plant grows slowly, the tender shoot is easy to aging fibre and the commodity is poor [55].

General biological activities

Solanum nigrum is known as a natural medicinal plant from family Solanaceae. The family is well known and has been screened by researchers for their medical actions. The plants were extensively used to treat diseases disorders such as pain, inflammation and fever [56].As well, plants were used as an antitumorigenic, antioxidant, anti-inflammatory, hepatoprotective, diuretic, and antipyretic agent [46,57].

Active ingredients as anticancer and mode of action

Eight pure compounds were separated and identified from ethanolic extracts of *Solanum nigrum* which have anticancer and antioxidant activities as shown in Figure (3, compounds No. 30-37).
The identified compounds in Figure 3 mostly belong to the phenolic compounds and showed high potency to cancer cells. These extracts contain major phenolic compounds as usnic acid (U. barbata) and norstictic acid (T. candida). The Usnic acid showed strongest anticancer activity towards both FemX (human melanoma) and LS174 (human colon carcinoma) cell lines, while Trilinolein has anticancer activity against HepG2 cells [58].Data extracted from another study have beenindicated that the active ingredients isolated from Solanum nigrum markedly inhibited cell viability of MCF-7 breast cancer cells through apoptosis induction and cell cycle arrest mediated by activation of caspase-3 and production of reactive oxygen species. Furthermore, mitochondrial fission was observed in MCF-7 breast cancer cells treated with Solanum plane extract [59]. In addition to elevation of E-cadherin, down regulation of ZEB1, N-cadherin, and vimentin was found in AESN-treated MCF-7 breast cancer cells. These results suggested that AESN could inhibit EMT of MCF-7 breast cancer cells mediated by attenuation of mitochondrial function.
From the previous results we can conclude that the isolated compounds from *Solanum nigrum* may effect on steps No. 3, 4 and 6 of the tumor formation pathway as shown in Figure (4).

Aloe vera

Description, Habitat and Ecology

Aloe vera is household plant belong to Liliaceae plant family, north Africa is the main habitat as the plan can survive the lack of water and poor soil. Aloe vera is a steamless or very short stem plant which is 40 inches tall. The leaves are green to grey in colour, and each leaf is thick and composed of three different layers. Long and complicated statement, cut into two parts and simplify [60].

General biological activities

Several phytochemicals were isolated tested for antibacterial, antioxidants, anticancer and other pharmacological activities. Among them, *Aloe vera*-derived compounds exhibit various pharmaceutical activities [61], antimicrobial [60,62] anti-Inflammatory [63], antioxidant [64]and anticancer impact [65]. This review provides an overview of the anticancer activity of aloe vera derived compounds.

Active ingredients as anticancer and mode of action

Aloe vera contains a number of secondary metabolites such as aloe-emodin, aloin, aloesin, emodin, and acemannan (Figure 3, compounds No. 38-42). *Aloe vera* derived phytochemicals were extensively tested for antiproliferation activity against various cell lines and animal models including, breast, ovarian, colon and pancreas human cancers. Studded. Aloe-emodin exhibited a reduction in cell growth progress against MCF-7 cells and HeLa cells via apoptosis induction and inhibiting the COX pathway. In addition, aloes in plays a vital role in reducing ovarian cancer growth in in vitro and in vivo by inhibiting MAPK signaling pathway [66]. Emodin has anticancer activity against human oral mucosa carcinoma KB cells by reducing Bcl-2 protein levels and apoptosis induction [67].

From the previous collected data we can say that the isolated compounds from *Aleo vera* may affect steps No. 4 and 6 of the tumor formation pathway as shown in Figure (4).

Allium sativum L. (Garlic)

Description, Habitat and Ecology

Egyptian garlic can be consumed raw, thinly sliced and added to salads (Figure 2), or incorporated into many traditional dishes. Garlic has been used in Egypt since ancient times and was highly referred for its intense flavour. Egyptians believed garlic would protect the pharaoh's body from evil spirits due to its strong odour. Egyptian would also chew cloves of garlic before taking a journey during the night to shield them from misfortune and evil. In addition to protection, Ancient Egyptians thought that garlic would provide strength, and the cloves were fed to the builders of the pyramids to increase their endurance.

General biological activities

Garlic (*Allium sativum* L.) is a common spice, several bioactive compounds are derived from garlic, including organic sulfides, saponins, phenolic compounds, and polysaccharides [68,69]. It has a long history of being utilized as a traditional medicine in Egypt [70]. In recent decades, several scientific reports have investigated the remarkable biological functions of garlic, including antioxidant, cardiovascular protective, anticancer, anti-inflammatory, immunomodulatory, anti-diabetic, anti-obesity and antibacterial properties [71,72]. It has been reported that garlic crude extracts have direct anticancer activity. For an example, the raw garlic extract (RGE) showed anticancer activity against eight different human cancer cell lines. Furthermore, no cytotoxic effect of RGE was observed against non-cancerous cells [73,74].

Active ingredients as anticancer and mode of action

Garlic contains a huge number of derived secondary metabolites (Figure 3, compounds No. 43-47), which include organosulfur compounds alliin, alliinase, allicin, S-allyl cysteine (SAC), diallyldisulphide (DADS) and diallyltrisulphide (DATS). The presence of flavonoids such as quercetin and cyaniding is responsible for the antioxidant properties of garlic [75]. In addition, several studies indicated that garlic is enriched in the minerals such as germanium, calcium, copper, iron, potassium, magnesium, selenium, zinc. Moreover, many researhes were highlighting the presence of some vitamins such as vitamin A, B1, and C in garlic [76]. The chemical structures of garlic-derived organosulfur compounds that play a role as anticancer are depicted in Figure 2. Garlic attractive researchers interested in cancer therapy as an alternative pharmacutical treatment. Garlic and their derived compounds displayed potential and

significant activities against different cancer cell lines. Moreover, garlic has shown a high significant inhibition activity into transplanted tumor in animal models.

Inhibition of cell cycle progression

The anticancer mode of actions of garlic-derived compounds have been attributed to interrubtion of the various stages of cancer progression, initiation, promotion and progression. In the initiation stage, garlic-derived phytochemicals block the activation of carcinogens through antioxidation, antimutagenesis and detoxication. In the promotion stage, phytochemicals suppress the cell proliferation by modulating protein folding and DNA repair. In the progression stage, garlic inhibits the growth by changing the cell behaviours, including antiproliferation, apoptosis induction and immune-competence [77].

Different studies have shown that garlic-derived OSC, DADS and DATS were suppressing cancer cells growth by inducing cell cycle arrest in G2/M phase of the cell cycle [78]. In addition, DADS extracts have shown a significant reduction in the kinase activity of the Cdk1/cyclin B1 complex, and therefore a decrease in Cdc25C protein level in human colon cancer cells. However, DATS have much more effective than either DADS or OSC in G2/M phase cell cycle arrest in PC-3 and DU145 human prostate cancer cells [78].

Apoptosis Induction

One of the anticancer mechanisms for new tested drugs is apoptosis induction. Garlic-derived OSC has a potential to trigger apoptosis induction by modulating different key elements linked to apoptosis pathway. Moreover, garlic-derived thiosulfinate and thiosulfinate compounds play a vital role in the activation of the immune response against the uncontrolled growth and therefore prevented cancer cells from developing tumors in animals [79]. The anticancer activity of garlic also implemented in the apoptosis induction by the increase of DNA fragmentation and intracellular free-calcium, upregulation of Caspase-3, p53 and Bax, and downregulation of Bcl-2, Bcl-xL.

In addition, garlic-derived OSC disrupts mitochondrial membrane and releases pro-apoptotic key regulators to cytosol in order to initiate apoptosis pathway [80]. OSC also destabilizes the levels of some apoptotic proteins by decreasing and increasing the levels of proapoptotic P53, Bax and Bak proteins [81]. Garlic-derived compounds are trigger apoptosis induction by modulating the levels of Bcl-2 proteins. Recently, investigation on the study of garlic-derived organosulfur, indicated that OSC also induces apoptosis by increasing the free intracellular calcium [82]. The isolated compounds from garlic plant may effect on steps No. 2, 3, 4, 5 and 6 of the tumor formation pathway as shown in Figure (4).

Black pepper

Description, Habitat and Ecology

Piper nigrum is called the black pepper and known as the “King” of spices. The fruit of *Piper nigrum*, is also called as pepper. It is an ancient and famous spice throughout the world. It is a large climbing liana (up to 20 m in length) of evergreen forests in southwest India (Figure 2), black pepper (*Piper nigrum*), a perennial crop of the tropics belongs to Piperaceae family [83].

General biological activities

Many studies have previously reported that black pepper extracts have diverse biological effects in the gastrointestinal tract, kidney and liver [84]. Black pepper extracts have been shown to exert different biological activities such as antimicrobial, anticancer activities in addition to inhibition of carcinogenesis immunomodulatory agents [85, 86]. The Black pepper yield of pure Pip is from 6- 9g/ 100g dry weight [87]. Pipper (Pip) has been used in traditional Chinese, Indian, and Arabic medicine as a remedy for many diseases (e.g., pain killer indigestion, chills, rheumatism, infection, fever). Pip

improves the bioavailability of drugs [88]. Also it has anti-inflammatory [89], neuroprotective [90] ,antioxidant and antitumor effects [91].

Active ingredients as anticancer and mode of action

There are 55 molecules isolated from black pepper and the major component is piperine. Piperine is an alkaloid of special interest (Figure 3, compounds No. 48 and 49). The hot burning pungent taste of black pepper is caused by four isomers of piperine [83].

Black pepper derived piperine (Pip) was developed a novel anticancer targeted delivery system that assessed the solubility and release of this prodrug into cancer cells and normal cells at different pHs [91]. The authors developed a novel anticancer targeted delivery system for piperine (Pip) which was loaded into HAPs and HAP-Ps at pH 7.2 and 9.3 and coated with gum Arabic to obtain nanoformulations. They tested it against normal WI-38 fibroblast cells and HCT116 colon cancer cells. This nanoformulation has been shown an enhancement in the anticancer activity with full inhibition of monolayer HCT116 colon cancer cells compared to piperine. These functionalized nanoformulations had the lowest cytotoxicity towards normal WI-38 fibroblast cells. The mode of action of piperine was reviewed by [92]. The study demonstrated that piperine possesses cytotoxic action against HER2 overexpressing breast cancer cells. Piperine inhibited proliferation and enhanced apoptosis by activating caspase-3 and cleaving PARP [91). The inhibition of AP-1 and NF-κB activation was detected after piperine treatment. It blocked extracellular signal-regulated kinase (ERK1/2), P38 mitogen-activated protein kinase (p38 MAPK) and Akt signaling pathways. Moreover, it suppressed epidermal growth factor (EGF)-induced MMP-9 expression [93].

From the previous results it can be concluded that the isolated compounds from black paper affect steps No. 4, 5 and 6 of the cancer formation cycle (pathway) as shown in Figure (4).

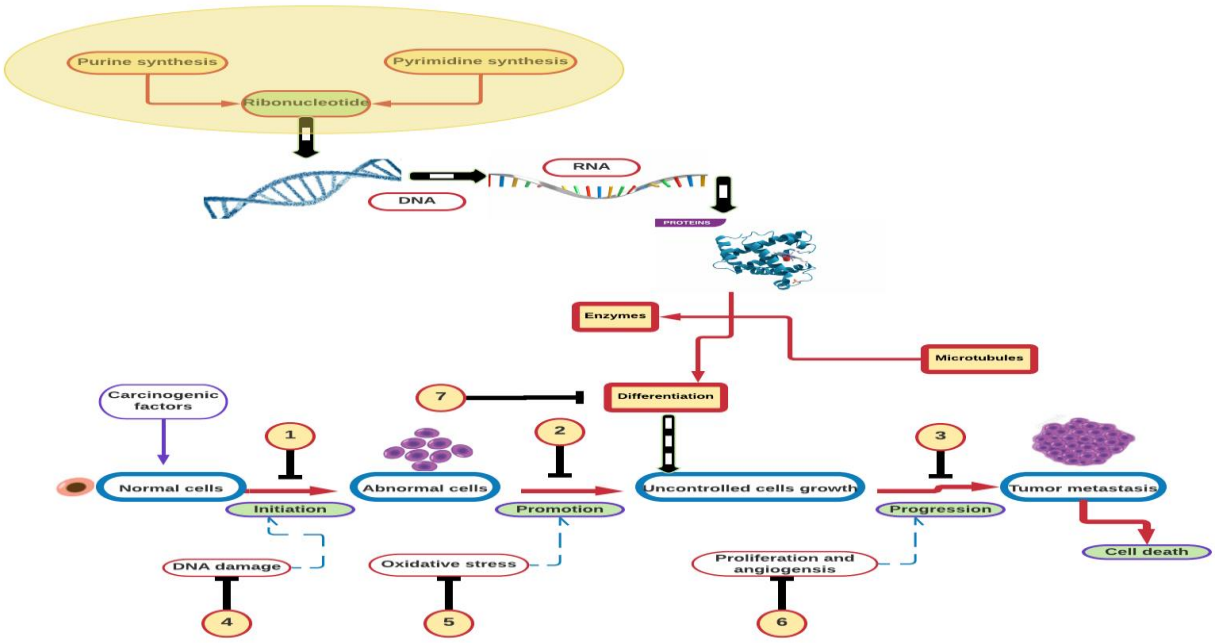


Figure 4: Suggested mechanism of isolated compounds from different Egyptian plants as anticancer activity

Conclusion

Egyptian Medicinal plants are displayed various human health benefits. Natural products derived from medicinal plants have played a safely role in cancer treatments no side effect. In this review we discuss the role of some Egyptian medicinal plants in cancer treatment. These plants possess displayed antioxidant, anti-inflammatory, anticancer properties. In this article the general biological activities of each plant have been illustrated. Highlighting, the isolated active ingredients and the mode of action as anticancer. Medicinal plants containing extensive amounts of active ingredients that can be used as an alternative pharmaceutical applications. In this context, Egyptian flora containing wide range of phytochemicals accumulated in response to specific environmental conditions. Herein, we are highlighting eight different plants that are wildly distributed in different areas displayed anticancer properties against different cancer cell lines. The chemical structure of active ingredients isolated from these plants have been shown in Figure (3. The mode of action of selected plants as anticancer by several pathways including, cell cycle arrest, apoptosis induction at transcription and post-translational levels (Figure 4). As well as, compounds isolated from these plants inhibits the cancer progression in different cancer stages (initiation, promotion and progression). However, most of these isolated compounds required further clinical trials.

Overall, all these knowledge in this review boost the therapeutic efficacy of selected plants and their active constitutes as anticancer agents. There is a significant need to incorporate them into a novel promising medical formulations.

Availability of data and materials:

They are available as Supporting information.

Ethics approval and consent to participate:

Not applicable in this section.

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The authors declare no conflict of interest.

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