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Effectivity of Some Natural Compounds against Ehrlich Tumor and Associated Diseases

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Authors' contributions

This work was carried out in collaboration between both authors. Author ET designed the study, performed the statistical analysis and wrote the protocol. Author TFM wrote the first draft of the manuscript and managed the analyses of the study. Both authors managed the literature searches, read and approved the final manuscript.

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ABSTRACT

Ehrlich model is mammary cancer it is passed via intraperitoneal passages from a mouse to another. Because of the ability of Ehrlich tumor to grow and spread rapidly after transplantation, it has been used in many experimental studies looking for a way to fight diseases and reduce its risk. The Ehrlich solid tumor (EST), derived from the mouse breast adenocarcinoma which is an aggressive and fast growing carcinoma able to develop both in the ascitic (EAC) or in the solid form depending whether inoculated intraperitoneously or subcutaneously, respectively. Plants and their products have a variety of biological activities that include anti-tumor, anti-inflammation, and antioxidant activities. However, natural products have inspired many researchers who have recommended the use of natural resources to prevent some tumors and chronic diseases.

Keywords: Ehrlich tumor model; EST; EAC; natural products.

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1. INTRODUCTION

Breast cancer has been evaluated as one of the most commonly diagnosed types of cancer among women. Ehrlich tumor is an undifferentiated tumor that appeared principally as spontaneous breast cancer in mice [1-5].

Ehrlich tumor is a malignancy and has a high ability for transplantable, no-regression, fast spread and shorter life period, as well as does not have tumor-specific transplantation antigen (TSTA). Ehrlich tumor was primarily described as a spontaneous murine mammary adenocarcinoma and simulated breast cancer [1,6-8].

Ehrlich model is mammary cancer it is passed from a mouse to another depending on the type of tumor used in the experiment, whether the tumor is solid or ascites (Figs. 1 & 2), when tumor cells are injected into the intraperitoneal the ascites model will be formed, while when tumor cells are injected subcutaneously the solid model is formed [4,7,9,10].

Ehrlich cells grow in two phases following the vaccination into the peritoneal cavity of mice. These two phases are a proliferating phase, in which the number of cells growing exponentially, and a plateau phase followed by a resting phase, in which a number of cells stay almost stable [3,5,11-13].

Ehrlich cells increased through fast cell division in the proliferating phase as well as in the load peritoneal cavity (Fig. 1). The ascites fluids accumulations occurred in parallelism with the proliferation of tumor cells. After some time, the host animal died due to the pressure used via the tumor volume and the damage that resulted from the tumor. Through the transition of the Ehrlich cells from the proliferating phase to the plateau phase, the rates of cell viability did not reduction significantly [14,15]. Moreover, Agrawal et al. [16] concluded that Ehrlich tumor cells excrete a vascular permeability factor that stimulates the accumulation of the ascites fluid and then inspected vessels in the peritoneal cavity of a mouse and the microvascular permeability increased significantly in compared with the control group. This increased permeability was discovered through an effective permeability factor in ascites fluid, but not in the normal plasma and serum.

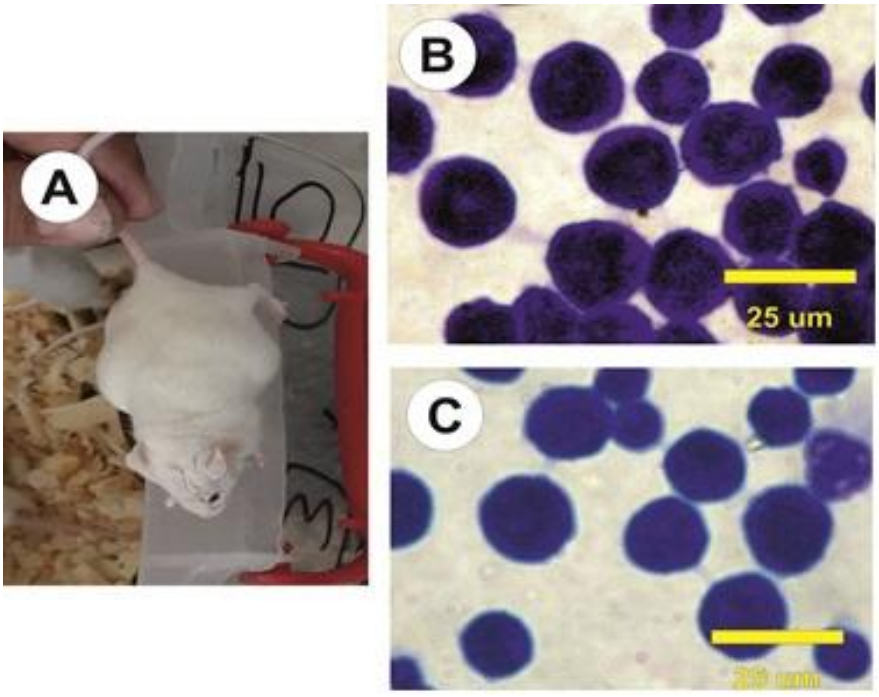

Fig. 1. A: Mouse with Ehrlich ascites carcinoma (EAC). B & C: Ehrlich ascites cells smear showing several tumor cells, nuclear enlargement, mitosis, disarray in cells architectural and marked the degree of cellular anaplasia, by using Giemsa stain Mutar et al. [17]

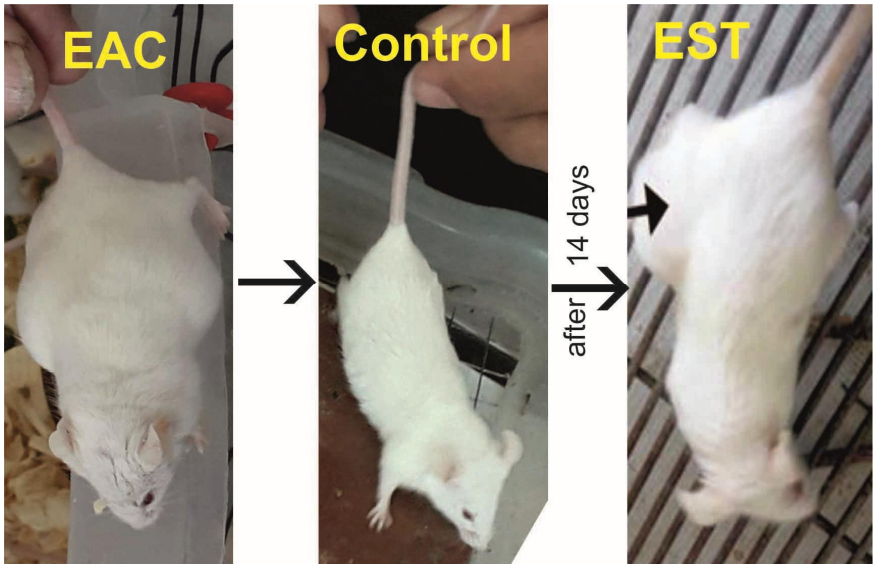

Fig. 2. Mouse with Ehrlich ascites carcinoma (EAC) injected subcutenous to normal mice induced Ehrlich solid tumor (EST) after 14 days El-Atrsh et al. [18]

2. EHRLICH TUMOR AND ASSOCIATED DISEASES

In a cytological study, Ehrlich cells showed induced mitotic cells and cellular changes and a rapid increase ascetic fluid volume in Ehrlich ascites carcinoma (EAC) untreated group according to Funasaka et al. [19]; Nascimento et al. [20]; Osman et al. [21]; Mutar et al. [22]; Tousson et al. [23] reported that the aggregation of ascetic fluid in the peritoneal cavity was either due to a decreased lymphatic recovery system which is linked with the crippling of the lymphatic by carcinoma cells, or because angiogenesis which detected in ascites tumor-bearing peritoneal wall, or either due to microvessels hyperpermeability of the peritoneal cavity.

According to literature research, the development of the Ehrlich tumor in mice was accompanied by changes in renal, liver and hematological parameters. El-Masry et al. [10]; Badr et al. [24]; Donia et al. [25]; Ahmed et al. [26] reported that Ehrlich tumor-induced reductions in the levels of albumin and total proteins in mice as compared to control. Also, Mutar et al. [22]; Salem et al. [27] demonstrated that Ehrlich tumor causes alterations in the biochemical parameters (urea and creatinine) and electrolytes sodium (N+) and potassium (K+) ions in the mice. Moreover, Habib et al. [28]; Khanam et al. [29]; Eldaim et al. [30] informed that Ehrlich tumor has led to kidney injury and significant changes in the renal function in mice through an increase in the levels of urea, creatinine, potassium, and chloride ions and decreased sodium ions.

The elevation of liver enzymes is an index of deterioration hepatic functions due to cancer proliferation as observed in the EAC. Badr et al. [24]; Haldar et al. [31] reported that EAC causes a decrease in the levels of albumin and total proteins in mice. Also, Islam et al. [12]; Donia et al. [25]; Mutar et al. [17] found that EAC induced elevations in alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), and depletions in albumin and total proteins. Also, Islam et al. [12]; Habib et al. [28] reported that the ALP, AST, ALT, glucose, cholesterol, triglyceride and blood urea parameters changed during EAC progression.

Ehrlich ascites carcinomainduced elevations in the alpha-fetoprotein (AFP) marker reflecting its inflammatory effect in mice. Tousson et al. [23]; Aldubayan et al. [32] who reported that the increase of AFP level in serum can be a reflection of hepatic inflammatory activity and may be associated with elevation AST, ALT and ALP enzymes. Also, Ehrlich tumor-induced DNA damage in the liver and kidney tissues and increase in tail length, tail DNA% and tail moment [12,17,30].

Ehrlich tumor-induced alterations in hematological parameters via decrease in red blood cells (RBCs), hemoglobin (HGB), hematocrit (HCT), and gradual increase in

platelets and white blood cells (WBCs), as well induced changes in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels, which was observed in EAC bearing untreated mice group which is described by [16,17,28,29,33]. Furthermore, Kabeer et al. [15]; Badr et al. [24]; Hashem et al. [34] reported that the hematological parameters detected a significant decrease of RBCs in the EAC bearing mice group perhaps due to the suppressive influence of EAC on bone marrow erythropoiesis. However, the granulocytic leukocytosis that was observed might because of the stress due to the increase of fluid ascites cells or the acute inflammatory response.

In the histopathological examination in the liver, EAC induced liver injury and many remarkable degenerative changes by disorganizations of the hepatic cords, in addition to karyomegaly and pyknotic nuclei indicating apoptosis, moderate fibrosis, and marked diffuse necrosis of hepatic tissue, marked inflammatory cells and congested blood sinusoids [17,24,27,35]. Infiltrations of Ehrlich carcinoma cells may happen because the cancer cells proliferate and transport to the internal organs [6], whereas the aggregations of inflammatory cells may happen because of degeneration of the mitochondria or disorganization of the cytoplasm [36].

In the histopathological examination in the kidney, EAC induced a marked degeneration in glomeruli and some parts of the urinary tubules in kidney sections. El-Wahab and Fouda [6]; Mutar et al. [22]; Medhat et al. [37] revealed that EAC induced cellular infiltration and necrosis in the glomeruli and renal tubules cells in cortex and medulla. In addition, Badr et al. [24]; Salem et al. [27] indicated that EAC induced degenerated in the renal tubules and atrophy in the glomerulus as well as proteinaceous casts and leucocytic infiltration in the lumen of the renal tubules.

In the immunohistochemical examination, Mutar et al. [22]; Eldaim et al. [30] detected that Ehrlich tumor causes proliferation and apoptosis in kidney tissues and induced strong positive expressions in Ki67, P53 and proliferating cell nuclear antigen immunoreactivity (PCNA) proteins in the female mice. Also, Tousson et al. [20]; El-Din et al. [38] reported that a strongly positive reaction for PCNA was observed in nuclei of hepatocytes in liver sections of the EAC group when compared with the normal control. Also, Aldubayan et al. [32] reported that Ehrlich tumor-induced a significant increase in PCNA and Ki67 immunoreactivities. This review aims to describe the wide use of the Ehrlich model in several experimental studies and to know some plant sources used in the prevention of Ehrlich tumor and some diseases.

3. EFFECTIVITY OF SOME PLANT EXTRACTS AGAINST EHRLICH TUMOR

Natural products are defined as a group of biologically active biochemical produced by plants and microorganisms. And more than 40% of therapeutic drugs were produced based on natural products and their derivatives in the past decades [39-42]. Several studies have indicated the important role of natural products in preventing cancer and many diseases and also indicated that a diet rich in fruits and vegetables can reduce free radicals and prevent some chronic diseases [32,43-48].

Ehrlich model was used in several studies that indicate the effectiveness of some plant sources against cancer, this is because of the similarity with human tumors in the fast of growth and undifferentiated and their sensitivity to chemotherapy. Segura et al. [49]; Matsuzaki et al. [50]; David et al. [51] reported that Ehrlich carcinoma has been used to study the antitumor effects of numerous natural and synthetic chemical substances.

In modern studies, paid close attention in reports concerning ameliorative effects of medicines and natural products, in particular of nutritional treatments for Ehrlich tumor. According to several studies which reported that the natural products or treatments are known to produce apoptosis of Ehrlich carcinoma cells by inhibiting DNA damaging, disrupting mitotic apparatus and depleting intracellular nucleotide pool [28,33,50].

Several studies indicated that natural products (anti-oxidant and anti-apoptotic) can be reduced the development and proliferation of (EAC) cells, also showed decrease in the volume, viable percentage, total cell count and increase in the percentage of dead cells, as well increasing life span (ILS) percentage and increasing mean survival time (MST) [52]. The ethyl acetate extract from the flower of *Calotropis gigantea L.* decreases the viable tumor cells and prolonge the survival time against Ehrlich cells [28].

Islam et al. [12] informed that Eucalyptus extract (EuE) has antineoplastic activity against Ehrlich tumor through reducing the number of EAC cells and tumor weight and it also has the ability to the enhancement of life span and hematological parameters. Also, Islam et al. [53] methanol extract of Eucalyptus camaldulensis showed a strong antitumor activity via apoptosis and stimulation of host immunity as well as inhibits and reduces the Ehrlich tumor cells and it has the capacity to improvement hematological and biochemical parameters (cholesterol, triglyceride, ALP, AST, ALT, glucose, blood urea and creatinine).

The treated with leaves of *Chenopodium ambrosioides* L. (*C. ambrosioides*) reduced the weight, the total volume of fluid and the number of tumor cells in Ehrlich ascitic carcinoma and inhibition Ehrlich solid tumor growth [20,50,54].

The treated with *Balanites aegyptiaca (B. aegyptiaca*) extract inhibited Ehrlich tumor cell growth, proliferation and reduced the volume fluid, viable and count cells in the ascites fluid [55,56]. Administrating of curcumin inhibitory effect on the tumor and the reduction in the volume of the EAC and in the count of Ehrlich cells [57,58].

Eldaim et al. [30] reported that the grape seed proanthocyanidins extract (GSPE) improved the levels of kidney functions (urea, creatinine, potassium, and chloride), as well as enhancement the kidney tissue via the examinations of DNA fragmentation, immunohistochemical proteins expression (P53 and PCNA) and histopathological in the Ehrlich tumor mice. Also, Ahmed et al. [26] described that the grape seed proanthocyanidin extract (GSPE) has ameliorating effects against Ehrlich tumor-induced changes in levels of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), tumor necrosis factor-alpha (TNF-α) and hematological parameters, and DNA damage in mice.

El-Khawaga et al. [59]; Hegazi et al. [60] reported that the Egyptian propolis inhibits the growth and proliferation of Ehrlich carcinoma in mice; as well as improvements in the total protein, albumin, urea, and creatinine levels.

The Egyptian sweet orange hesperidin ameliorates the levels of the gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, creatinine, urea, and total lipids in Ehrlich-bearing mice [25,61]. Furthermore, Habib et al. [28] reported that the ethyl acetate extract from the flower of *Calotropis gigantea L.* restored the levels of glucose, cholesterol, triglyceride, ALP, AST, ALT, and blood urea parameters against Ehrlich tumor. Perveen et al. [33] reported that ethanol extract of Alpiniacalcarata Rosc (EEAC) rhizome decreased Ehrlich cell growth and improved the hematological parameters (RBCs, WBCs and Hb%) in mice.

El-Masry et al. [10]; Mutar et al. [22]; Tousson et al. [23] reported that vitamin B17 (VitB17) has therapeutic, antineoplastic and protective effects against Ehrlich tumor through improved levels of TNF-α, AFP, dsDNA, catalase, glutathione (GSH), and superoxide dismutase (SOD) in serum; as well as enhancement the histological and immunohistochemical (P53 and PCNA) proteins investigations in mice tissues. Also, Mutar et al. [22] reported that vitamin B17 has an ameliorative role against Ehrlich carcinoma induced kidney toxicity, injury, DNA damage, proliferation, and apoptosis alterations in mice. Moreover, Tousson et al. [23] reported that vitamin B17 has an ameliorative role against Ehrlich tumor-induced liver toxicity and injury in bearing mice.

The *Copaifera multijuga* (*C. multijuga*) oil has antineoplastic activity and inhibiting the inflammation through modulates the total protein, prostaglandin E_2 (PGE2), nitric oxide, and TNF in Ehrlich tumor [62]. The oil from *Croton polyandrus* leaves reduced the hepatotoxicity and Ehrlich tumor activity in mice [63].

An antioxidant effect of curcumin was observed in Ehrlich-bearing mice via decrease malondialdehyde and Nitric Oxide levels; also curcumin can induce apoptosis by regulating the proteins Bcl-2 and caspase-3 activation [58,64]. Issa et al. [56] reported that *B. aegyptiaca* decreased the levels of lipid peroxidation and increased antioxidants (SOD and CAT) levels and P53 expression in Ehrlich tumor. Beydogan and Bolkent [65] reported that treated with silibin ameliorative the levels of superoxide dismutase (SOD) and Malondialdehyde as well as induced positive reaction in immunoreactivity in liver Ehrlich-bearing mice.

Issa et al. [56] informed that *B. aegyptiaca* ameliorated the hepatic and splenic sections against Ehrlich ascitic carcinoma. Donia et al. [25] showed that Egyptian sweet orange

hesperidin induced apoptotic genes (Caspase3 and Bax) and anti-apoptotic gene (Bcl2) in the Ehrlich tumor. El-Khayat et al. [66] reported that the flaxseed and corn oils had an ameliorative effect in the treatment of Ehrlich tumor; in addition to its role in improving liver injury via modulating the liver functions, lipid profile, and hepatic tissues.

El-Din et al. [38] reported that the combination of grape seeds (GSE) with grape skin (GSK) reduced tumor volume and weight in Ehrlich-bearing mice and induced apoptosis and cell proliferation inhibition through modify p53 and Ki67 proteins expression. Jaganathan et al. [7] showed that honey and eugenol having a good role in decreased tumor weight and proliferation and the ability to induce apoptosis in Ehrlich-bearing mice.

Manilkara zapota (*M. zapota*) L. stem bark has antitumor activity against Ehrlich tumor via reduced tumor cells and enhancement of the hematological parameters and antioxidant in mice [23]. Ali et al. [67] reported that the methanolic extract of *Kaempferia galanga* Linn. rhizome inhibits Ehrlich tumor development and restored the levels of antioxidants and hematological parameters. Matsuzaki et al. [50] reported that the roots of *Pfaffia paniculata* (Brazilian ginseng) have tumor-cell inhibited and anti-inflammatory effects against Ehrlich carcinoma. Aldubayan et al. [32] informed that Avenanthramides (Avns) are compounds naturally occur in oats that have antioxidant, anti-inflammatory, and antineoplastic activity in Ehrlich bearing mice. David et al. [51] informed that the procyanidin-rich *Pinus pinaster* extract (Pyc) has anti-tumor, antioxidant and anti-inflammatory effects against Ehrlich carcinoma; as it plays a role in improving levels of tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), carbonyl proteins and lipid peroxidation in bearing-mice. Kabir et al. [68] demonstrated that *Solanum tuberosum* lectin that purified from the potato can be inducing apoptosis and inhibiting the proliferation of Ehrlich tumor in mice.

4. CONCLUSION

Ehrlich model has wide use in many experimental studies that revealed the protective efficacy of some natural sources against the Ehrlich tumor, which causes toxicity and damage in mice.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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