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Anti-cancer activity of Grape seed

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ABSTRACT

Introduction*: Grape seed belongs to the plant family of plantain family Plantaginaceae, The plant is native to most of Europe and northern and central Asia, but has widely naturalized elsewhere in the world. The aim of this study was to overview pharmacological properties of grape seed.*

Methods*: This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases. The initial search strategy identified about 102 references. In this study, 44 studies were accepted for further screening and met all our inclusion criteria [in English, full text, therapeutic effects of Grape seed and dated mainly from the year 1992 to 2016.The search terms were "Grape seed", "therapeutic properties", "pharmacological effects".*

Result*: It is commonly used for its Chemotherapeutic effect, Antioxidant effect, Antitumoral effect, Biological effect, Antiviral and Immunoenhancing effect, Mechanical effect Antimicrobial effect, Hematopoietic effect, Anti-cancer effect, Antioxidant effect, wound healing, Neutrophil Respiratory Burst*

Conclusion*: Although the results from this review are quite promising for the use of Grape seed as a multi-purpose medicinal agent, several limitations currently exist in the current literature. While Grape seed has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use. It is also important to recognize that Plantago may be effective not only in isolation, but may actually have a potentiating effect when given in combination with other herbs or drugs.*

Keywords*: Grape seed, Phytochemicals, Therapeutic effects, Pharmacognosy, Alternative and complementary medicine.*

INTRODUCTION

The history of herbal remedies in the treatment of many diseases dated back to ancient times [1-24].Grapes are a type of fruit that grow in clusters of 15 to 300, and can be crimson, black, dark blue, yellow, green, orange, and pink [25]. "White" grapes are actually green in color, and are evolutionarily derived from the purple grape[26]. Mutations in two regulatory genes of white grapes turn off production of anthocyanins, which are responsible for the color of purple grapes [27]. Anthocyanins and other pigment chemicals of the larger family of polyphenols in purple grapes are responsible for the varying shades of purple in red wines [28]. Grapes are typically an ellipsoid shape resembling a prolate spheroid.

Grape therapy, also known as ampelotherapy is a form of naturopathic medicine or alternative medicine that involves heavy consumption of grapes, including seeds, and parts of the vine, including leaves[29]. Although there is some limited evidence of positive benefits from the consumption of grapes for health purposes, extreme claims, such as its ability to cure cancer, have been widely derided as "quackery [30, 31].

Chemical compound

Anthocyanins tend to be the main polyphenolics in purple grapes whereas flavan-3-ols (i.e. catechins) are the more abundant phenolic in white varieties [32]. The flavonols syringetin, syringetin 3-O-galactoside, laricitrin and laricitrin 3-O-galactoside are also found in purple grape but absent in white grape[33].

The chemical composition of grape seeds include vitamin **E** (α-tocopherol), petiole [34], linoleic acid, flavonoids (resveratrol, quercetin and catechin, and Polyphenols (*flavonoids*, *phenolic acids*, *phenolic alcohols*, *stilbenes* and *lignans*)[35], procyanidins B4 and B6, and trimer gallate 2[36, 37].

RESULT

Lung cancer

The bioactivity of oral administration of leuco select phytosome in a lung cancer chemoprevention trial was evaluated. findings support the continued investigation of GSE as an anti-neoplastic and chemo preventive agent against lung cancer[38].

It was hypothesized that grape seed procyanidin extract exerts antineoplastic effects through modulations of on comes and their downstream targets. Findings reveal novel antineoplastic mechanisms by GSE and support the clinical translation of leucoselect phytosome as an anti-neoplastic and chemo preventive agent for lung cancer [39].

Grape seed extract efficacy against a series of non-small-cell lung cancer cell lines against a wide range of lung cancer cells was examined. Because GSE is a widely-consumed dietary agent with no known untoward effects, results support future studies to establish GSE efficacy and usefulness against NSCLC control [40].

In animal study, GSPs-induced G1 cell cycle arrest was mediated through the increased expression of Cdki proteins (Cip1/p21 and Kip1/p27). The results suggest that GSPs may represent a potential therapeutic agent for the non-small cell lung cancer [41].

The chemotherapeutic effect of grape seed proanthocyanidins (GSPs) on human non-small cell lung cancer (NSCLC) cells in vitro and in vivo was assessed. Dietary GSPs have the ability to inhibit the growth of human NSCLC tumor xenografts grown in vivo in athymic nude mice [42].

In an in vitro study, the results indicate sequential inhibition of NO/NOS, GC, and MAPK pathways by GSPs in mediating the inhibitory signals for cell migration, an essential step in invasion and metastasis [43].

Colon cancer

The suppression of Wnt/β-catenin signaling and elevated mitochondrial-mediated apoptosis in colon CSCs support potential clinical testing/application of grape bioactive for colon cancer prevention and/or therapy [44].

grape seed extract (GSE) investigated for its potential to impair pro-tumorigenic signaling of adipocytes on CRC/colon cancer stem cells (CSCs).result suggest the ability of GSE to induce 'brown remodeling' of white adipocytes, which causes functional modification of adipocytes thus impairing their pro-tumorigenic signals on colon CSCs/CRC cells[45].

Effects of purified PC fractions differing in mean degree of polymerization combined with 5-Fluorouracil (5-FU) chemotherapy was investigated. PCs of mDP 2-6 not only enhanced the impact of 5-FU in killing Caco-2 cells, but also surpassed standard 5-FU chemotherapy as an anti-cancer agent. The bioactivity of PC is therefore attributed primarily to lower molecular weight PCs[46].

The effects of increasing grape seed extract doses on the severity of chemotherapy in a rat model and its coincident impact on chemotherapeutic effectiveness in colon cancer cells was investigated. Grape seed extract may represent a new therapeutic option to decrease the symptoms of intestinal mucositis while concurrently impacting on the viability of colon cancer cells [47].

Preventive role of GSPs as dietary agents was examined. findings suggest that GSE could be an effective CAM agent against CRC possibly due to its strong growth inhibitory and apoptosis-inducing effects[48].

Anti-cancer properties at sub-optimal doses of RSV-GSE combination was evaluated. Result suggested that Caspase-3 inhibition and reactive oxygen species suppression attenuated apoptosis induced by the combination. RSV-GSE combination suppressed proliferation and induced apoptosis even in the presence of mitogenic growth factor IGF-1[49].

Biological efficacy of GSE-induced p21 upregulation were investigated. Result demonstrated that GSE was found to increase the stability of p21 message with resultant increase in p21 protein level. Knock-down of p21 abrogated GSE-induced G (1) arrest. Results for the first time identify a central role of p21 induction and associated mechanism in GSE-induced cell cycle arrest in HT29 cells [50].

Bladder cancer

The effects of grape seed procyanidin extract (GSPE) on cell proliferation and apoptosis in human bladder cancer BIU87 cells was evaluated. The findings showed that GSPE inhibits cell proliferation by inducing cell cycle arrest and apoptosis in BIU87 cells, and the effect may be related with its down-regulation of cyclinD1, CDK4 and surviving [51].

Grape seed extract (GSE) efficacy against bladder cancer and associated mechanism in two different bladder cancer cell lines T24 and HTB9 was evaluated. Result showed that GSE-mediated oxidative stress causes a strong programmed cell death in human bladder cancer cells [52]. It was shown that grape seed extract (GSE) prevents azoxymethane (AOM)-induced colon colitis via epigenetic microRNA (miRNA) regulation [53].

The results of a study indicate that inhibition of azoxymethane-induced colon cancer by dietary GSE is mediated through the induction of apoptosis that is associated with alterations in microRNA (miRNA) and cytokine expression profiles as well as β-catenin signaling[54].

Breast cancer

GSPs can inhibit VM information by the suppression of Twist1 protein that could be related to the reversal of epithelial-to-mesenchymal (EMT) process. It is firstly concluded that GSPs may be a potential anti-VM botanical agent for human TNBCs [55].

The biological effect of grape seed extract (GSE) on the highly metastatic MDA-MB231 breast cancer cell line was investigated. The results make GSE a powerful candidate for developing preventive agents against cancer metastasis [56]. The effect of grape seed extract (GSE) on breast cancer cell MCF-7 about the proliferation and the gene expression of surviving was observed. Result showed that GSE can inhibit the proliferation of breast cancer cell MCF-7 through arresting the cell cycle in S periods [57].

The activity of grape seed proanthocyanidin extract (GSPE) in suppression of cellular carcinogenesis induced by repeated exposures to low doses of environmental carcinogens was studied. Model system with biological and molecular target endpoints verified the value of GSPE for the prevention of human breast cell carcinogenesis induced by repeated exposures to low doses of multiple environmental carcinogens [58].

Prostate cancer

B2G2 chemical synthesis at gram-quantity with equivalent biological efficacy wa reported against human PCa cell lines and same molecular targeting profiles at key transcription factors level. The synthetic B2G2 will stimulate more research on prostate and possibly other malignancies in preclinical models and clinical translation [59].

The inhibitory effect of grape seed extract (GSE) on the growth of prostate cancer PC-3 cells was investigated. Result showed that GSE inhibits the growth of prostate cancer PC-3 cells and can be used as a new drug for the treatment of prostate cancer [60].

Histone acetylation, which is regulated by histone acetyltransferases (HATs) and deacetylases, is an epigenetic mechanism that influences eukaryotic transcription. The results indicate that GSE potently inhibits HAT, leading to decreased AR-mediated transcription and cancer cell growth, and implicate GSE as a novel candidate for therapeutic activity against prostate cancer [61].

Studies showed that GSE inhibited DNA-binding activity of the transcription factor nuclear factor kappa B (NFkappaB), which in turn decreased NFkappaB-dependent uPA transcription. Invasion assays revealed the inhibitory effect of GSE on PC3 cell migration. In-vitro experiments demonstrate the therapeutic property of GSE as an antimetastatic agent by targeting uPA [62].

Efficacy of GSE in androgen-independent DU145 and androgen-dependent-22Rv1 human prostate cancer (PCa) cells was evaluated. Findings show the anti-PCa efficacy of gallic acid and provide a rationale for additional studies with this naturally-occurring agent for its efficacy against PCa [57].

The morphological changes of prostate cancer PC-3 cells induced by grape seed extract (GSE) was observed. GSE can cause morphological changes and induce necrosis and apoptosis of PC-3 cells[63].GSE could directly inhibit the kinase activity of purified VEGF receptor 2 .As a result, GSE could inhibit VEGF-induced endothelial cell proliferation and migration as well as sprout formation from aorta ring [64].

It was found that GSE inhibited VEGF messenger RNA (mRNA) and protein expression in U251 human glioma cells and MDA-MB-231 human breast cancer cells. Results indicate that GSE inhibits VEGF expression by reducing HIF-1alpha protein synthesis through blocking Akt activation [65].

Pancreatic cancer

The effect of grape seed proanthocyanidins extract (GSPE) on the growth of pancreatic cancer cells was explored. Result showed that GSPE inhibits AsPC-1 cells' growth and migration partly through down-regulation of miR-27a expression [66].

The effects of a grape seed procyanidin extract (GSPE) on proliferation and apoptosis in the pancreatic adenocarcinoma cell line MIA PaCa-2 was evaluated. The results showed that GSPE inhibits cell proliferation and increases apoptosis in MIA PaCa-2 cells. GSPE also reduced the formation of reactive oxygen species. The component of the extract that possesses the highest antiproliferative and proapoptotic activity was gallic acid [67]. The effect of grape seed proanthocyanidins (GSPs) on pancreatic cancer cell migration was evaluated. This was associated with upregulation of E-cadherin and desmoglein-2 and down-regulation of fibronectin, N-cadherin and vimentin [68].

Head and neck squamous

Grape seed extract (GSE) efficacy and associated mechanism in both cell culture and nude mice xenografts was investigated. The findings show that GSE targets both DNA damage and repair and provide mechanistic insights for its efficacy selectively against HNSCC both in cell culture and mouse xenograft, supporting its translational potential against HNSCC [69].The efficacy of grape seed extract (GSE) to target the redox and bioenergetic alterations in HNSCC cells was investigated. The findings showed that GSE targets ETC complex III and induces oxidative and metabolic stress, thereby, causing autophagy and apoptotic death in HNSCC cells [70].

Cervical cancer

The effect of GSPs on cervical cancer using in vitro and in vivo models was examined. Result indicated that GSPs led to the dose-dependent induction of apoptosis in cancer cells. Besides, Result demonstrated that GSPs could inhibit the growth of

cervical cancer by inducing apoptosis through the mitochondrial pathway, which provides evidence indicating that GSPs may be a potential chemo preventive and/or chemotherapeutic agent for cervical cancer [71].

Colorectal cancer

The potential protein targets of GSE in human colorectal cancer (CRC) cells was assessed. Result revealed that GSE indeed caused ER stress and strongly inhibited PI3k-Akt-mTOR pathway for its biological effects in CRC cells [72].

In azoxymethane-induced colon tumorigenesis study in A/J mice assessing grape seed extract (GSE) efficacy, during necropsy, multiple lung nodules were found suggestive of colon tumor metastasis to lung that were significantly inhibited in GSE fed group. GSE efficacy in inhibiting CRC metastasis to lung in this model further supports its translational potential in controlling CRC growth, progression, and metastasis in patients [73].

Grape seed extract (GSE) ability to target CRC cells was investigated. Result showed that Oxidative stress, loss of mitochondrial membrane potential, modulation of pro- and anti-apoptotic proteins, and involvement of both caspase-dependent/independent apoptotic pathways contributed to GSE-induced CRC cell death. GSE intervention may serve as a multi-targeted CRC therapeutic capable of inducing selective cancer cell death [74].

Skin cancer

The chemo preventive mechanism of dietary grape seed proanthocyanidins (GSPs) against ultraviolet (UV) radiation-induced skin tumor development in mice was determined. The results suggest that dietary GSPs inhibit photo carcinogenesis in mice through the inhibition of UVB-induced inflammation and mediators of inflammation in mouse skin [57].

The hydroethanolic extract obtained from red grape seeds was tested to show having a protective effect on keratinocytes exposed to UVB radiation. The results recommend the use of the BM extract as photo chemo protective agent as such or in combination with sunscreens and/or other natural products with similar or complementary properties [75].

It was investigating whether GSPs reactivate silenced tumor suppressor genes following epigenetic modifications in skin cancer cells. This study showed the epigenetic mechanisms of GSPs and may have significant implications for epigenetic therapy in the treatment/prevention of skin cancers in humans [76].

In vitro effects of a red grape-seed hydroethanolic extract Burgund Mare (BM) and tumor cell lines was investigated. Such treatment resulted in a reversed effect, cell death, malondialdehyde, and PC contents increasing with BM dose enhancement. BM extract treatment prior to subsequent administration of Dox afforded a differential protection against Dox-negative toxic side effects in normal cells without weakening (even enhancing) Dox's antitumor activity [77].

Oral cancer

The efficacy of grape seed procyanidin (GSP) on antiproliferative effects related to p53 functional status of oral squamous cell carcinoma (OSCC) for its chemo adjuvant potential was investigated. Findings clearly suggest that GSP may play a role as a novel chemo preventive or therapeutic agent for OSCC [78].

cranberry and grape seed extracts to quantitate and compare their anti-proliferative effects on the most common type of oral cancer, oral squamous cell carcinoma was evaluated. Result showed that cranberry and grape seed extracts not only inhibit oral cancer proliferation but also that the mechanism of this inhibition may function by triggering key apoptotic regulators in these cell lines[79].

The cytotoxic effects and the mechanism of cell death induced by grape seed extract (GSE) in oral squamous cell carcinoma (KB cells) was investigated. The results showed apoptotic potential of GSE, confirmed by significant inhibition of cell growth and viability in a dose- and time- dependent manner without inducing damage to non-cancerous cell line HUVEC [80].

Grape seed extracts (GSEs) were investigated in yeast cells harboring defects in their antioxidant system. The GSEs play a dual antioxidant/pro-oxidant role in vivo according with the cellular antioxidant system deficiencies and exhibit cytotoxic properties in PC3 and HepG2 2.2.15 cell lines, but no antiviral action against HBV [81].

Antiproliferative effect of GSE has been reported in many cancers but rarely in oral cancer. Differential concentrations of GSE may have a differentially antiproliferative function against oral cancer cells via differential apoptosis, oxidative stress and DNA damage [82].

Intestinal tumorigenesis

GSE efficacy against intestinal tumorigenesis in APC (min/+) mice was investigated. The findings show the chemo preventive potential of GSE against intestinal polyp formation and growth in APC(min/+) mice, which was accompanied with reduced cell proliferation and increased apoptosis together with down-regulation in COX-2, iNOS, beta-catenin, cyclin D1, and c-Myc expression, but increased Cip1/p21[57].

Leukemia cancer

the functional role of c-Jun NH (2)-terminal kinase (JNK) and other apoptotic pathways in grape seed extract (GSE)-induced apoptosis in human leukemia cells was evaluated. The result showed that GSE induces apoptosis in Jurkat cells through a process that involves sustained JNK activation and Cip1/p21 up-regulation, culminating in caspase activation.

CONCLUSION

Although the results from this review are quite promising for the use of Grape seed as a multi-purpose medicinal agent, several limitations currently exist in the current literature. While Grape seed has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use. It is also important to recognize that Plantago may be effective not only in isolation, but may have a potentiating effect when given in combination with other herbs or drugs.

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