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The potential of tannins from medicinal plants as anti-cancer agents

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Abstract
Herbal extracts or natural substances derived from plants have long been used as an alternative to pharmaceuticals in the prevention or treatment of various ailments, including cancer. Numerous investigations with plant chemicals sought to identify molecules that selectively cytotoxically affected aberrant cells. Among these are phenolic chemicals, which are significant secondary metabolites found in plants. This study surveys the research over the last five years regarding the potential anticancer effects of tannins derived from medicinal plants. To identify the most important components or plants with anticancer potential, the cytostatic/antitumor activities of the individual chemicals recovered from plants and/or of the polyphenolic extracts of the plants are taken into consideration. The most significant findings about the prevention of cancer using these substances and their derivatives and therapy, the significance of their molecular structure, there in vivo and *in vitro* mechanisms of action, and some elements of their bioavailability are covered. In this study, we discussed the anticancer properties of some plants with high tannin content.

Keywords: Cytotoxicity, anti-cancer, tannin, tumour, aberrant cell, polyphenolic, bioavailability

Introduction
Numerous natural substances have been shown to have significant cytotoxicity and chemo preventive effect through pharmacological and chemical examination of medical plants. These components include primary metabolites like fat, protein, and carbs as well as secondary metabolites like steroids, alkaloids, phenolic components, flavonoids, and tannin, glycoside and organic acid. Primary metabolites are substances that are directly necessary for the growth, development, and survival of plants, whereas secondary metabolites are necessary for plant growth and development but not for plant survival. Plant defence systems are one typical use for secondary metabolites [1, 2]. They are also used in activities that prevent feeding. Also, Secondary metabolites exhibit strong pharmacological action in the forms of antioxidant and antimicrobial properties, among other properties. The focus of current research, however, is on these ingredients' potential as anticancer agents. Additionally, plant secondary metabolites have been identified as a promising approach to cancer chemoprevention, which is defined as "the application of pharmaceutical agents or non-cytotoxic nutrients to enhance physiological mechanisms that protect the organism against mutant clones of malignant cells". This review aims to report on the anticancer activity from tannin [3].

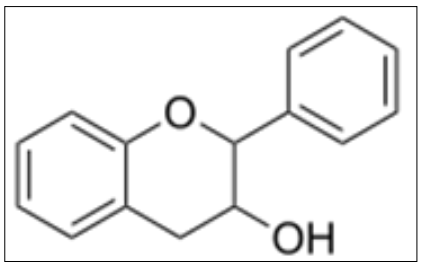

Fig 1: Basic Structure of Tannin

Tannin is found in a wide variety of plant species. These are heavy molecule phenolic chemicals. Tannins are present in the root, bark, stem and outer layer of plant tissue.

They are soluble in both water and alcohol and one of the distinctive properties of tannins is their ability to give object a leather-like hue [4]. Plant-derived tannins are bitter, non-nitrogenous polyphenolic chemicals with molecular weights of up to 20,000 for pro-anthocyanidins and 500-3000 for gallic acid esters. These are colloidal substances that can be hydrolysable tannins [5, 6]. Gallic acid or other similar polyol compounds esterified with glucose make up these molecules, which hydrolyse readily to create acids. Pro-anthocyanidins are regarded as useful naturally occurring substances having anticancer properties with this group [7]. They exist as oligomers or polymers (+) catechin and (-) epicatechin, and some in vivo investigation have shown that they can prevent skin malignancies, breast and prostate cancer, and suppress lung metastases.

Generally speaking, tannins have relatively low bioavailability and are eliminated by the stools after entering the stomach. Furthermore, due to their relatively large molecular size, high molecular weight tannins are rarely absorbed in their original form. If polyphenolic chemicals are effectively disseminated into the circulatory system and accumulate in the target tissues, they may function as modulators of cellular signalling pathways [8, 9]. Due to their high concentration in the gut, plant polyphenols, anticancer effects may only be effective in the digestive systems. Recent research on the interaction between dietary polyphenols and gut bacteria has sparked novel theories on the physiological roles of nonabsorbable polyphenols, like hydrolysable and n0n-hydrolysable tannins. These could include suppressive effects on inflammatory bowel disorders and inhibitory effects on colorectal cancer [10].

The growth of aberrant cells is still the primary cause of cancer, which is an incurable disease with minimal response to standard treatments like radiotherapy, chemotherapy, photodynamic therapy, and active immunotherapy. These operations also cause immunosuppressive activity and have serious side effects. Over the past ten years, there has been a steady increase in the use of herbal extract and natural components from herbs to treat a variety of disease, including cancer. The goal is to identify substances that selectively kill aberrant cells. Among them are phenolic chemicals, which are significant plant secondary metabolites [11]. This study looks at research from the last five years about the antitumor and anticancer properties of tannins that are derived from medicinal plants. The most significant findings about the prevention and treatment of cancer and *in vitro* mechanisms of action and certain bioavailability characteristics.

Since there is no obvious distinction between the groups of phenolic chemicals, tannins are thought to be naturally occurring oligomers and polymers formed from catechins, gallic acid, and ellagic acid.

Particular tannins isolated from medicinal plants with cytotoxic properties

An herbal remedy called corilagin, a gallotannin, has minimally harmful effects on healthy cells and is especially hepatoprotective. When paired with extremely harmful chemotherapy drugs, corilagin may be the perfect supplemental treatment. A number of ethnopharmacological plants, including Phyllanthus niruri L., Phyllanthus emblica L., and Phyllanthus urinaria L., have it as a major active ingredient. In 1951, Schmidt and Lademann isolated corilagin for the first time from Divi-divi (Caesalpina coriaria) plants [12].

1. Corilagin

Corilagin has been shown to exhibit a number of pharmacological properties in recent decades, with the most significant being its anticancer activity.

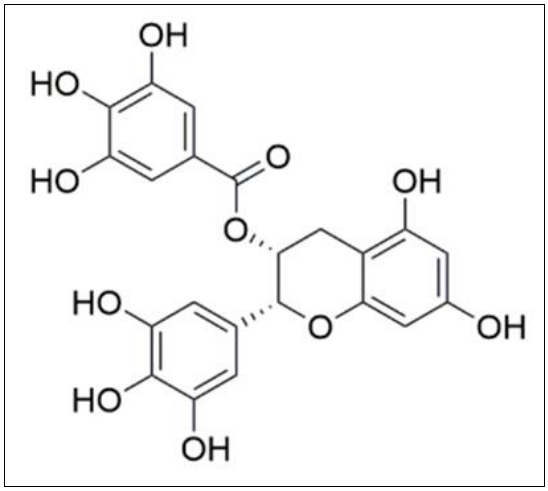

Fig 2: Structure of Corilagin

The anticancer ingredients in the ethyl acetate fraction of P. niruri L., a popular ayurvedic medicinal plant that is referred to as a folk empiric remedy, were isolated using chromatography. Ethyl brevifolin carboxylate and corilagin were the two main chemicals that were found and isolated following NMR and mass spectrometric investigations of the ethyl acetate fraction. The cytotoxicity of the two compounds was evaluated on hepatocellular carcinoma cell line (SMMC7721) and normal cell lines [13]. Results of the experiments indicated that corilagin had a stronger anticancer potential, reduced toxicity in normal cells, and broad-spectrum antitumor action. In the Chang liver normal cell line, corilagin caused a dose-dependent decrease in tumour cell survival and exhibited lesser cytotoxicity (IC50 = 93.3511.99! g/mL) and 14.821.00 in the SMMC7721 cell line. Moreover, corilagin derived from P. niruri L was utilised to inhibit the Notch signalling system *in vitro* and in vivo in order to prevent the formation of cholangiocarcinoma (CCA) [14]. The Golgi system's evolutionary conserved Notch signalling pathway is crucial for determining cell destiny as well as for proliferation, differentiation, and survival. *In vitro*, corilagin suppressed the expression of the Notch1 and Notch signalling pathway proteins, increased CCA cell death, and impeded CCA cell proliferation, migration, and invasion. Corilagin reduced the expression of mTOR and Notch1 and prevented the development of CCA in naked mice. These findings suggest that corilagin may inhibit Notch1 expression to regulate the development of CCA cells [15, 16].

In a different recent study, the anticancer effect of corilagin in hepatocellular carcinoma (HCC) was investigated using flow cytometry tests. The results showed that treatment with 37.5μM corilagin resulted in a 24.1% rate of apoptosis. The results of the western blot and mitochondrial membrane potential assays also indicated that, following corilagin treatment, the rate of cytochrome c release was higher and the mitochondrial transmembrane potential was lower [17]. These observations led to the activation of caspase-9 and caspase-3 as well as the cleavage of poly (ADP-Ribose) Polymerase (PARP) in the cytoplasm. This data points to the activation of the mitochondrial apoptotic pathway at the molecular level. Furthermore, activation of caspase-8 and overexpression of

Fas and FasL were noted following corilagin therapy, indicating the activation of the death receptor pathway [18].

It has been shown that corilagin derived from *P. niruri* L. inhibits the development of ovarian cancer cells by blocking the TGF-β/AKT/ERK signalling pathways. It has been demonstrated that corilagin increases the ovarian cancer cells' susceptibility to chemotherapy. Ovarian cancer cell lines, SKOv3ip, Hey and HO-8910PM-Snail, were treated with different concentrations of corilagin in a combination with paclitaxel and carboplatin, and corilagin certainly boosted the cytostatic impact of paclitaxel and carboplatin. Certain apoptotic and death-related proteins, including caspase 3, caspase 7, and PDCD4, had their expression levels increased by both paclitaxel and carboplatin; these levels increased even more when corilagin was added. Through the downregulation of CD44 and STAT3, corilagin reduced glycolysis, as demonstrated by an extracellular acidification rate investigation performed on the Seahorse XF96. To sum up, corilagin made paclitaxel more sensitive to epithelial ovarian cancer cells [19, 20].

2. Sanguiin H6

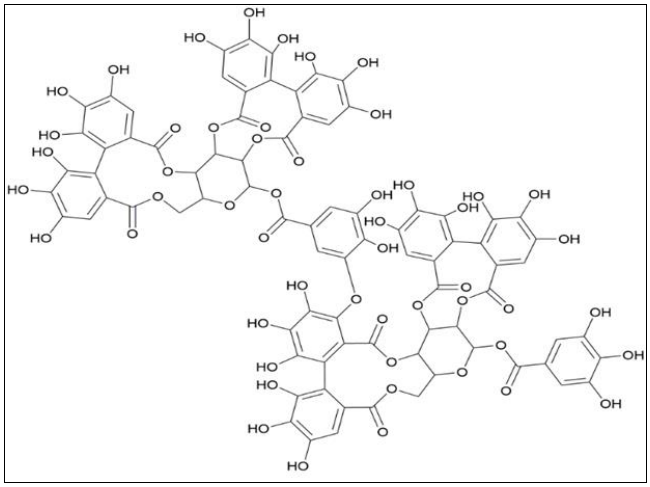

Fig 3: Structure of Sanguiin H6

Sanguiin H6 (Fig.3) is a ellagitannin that is present in berries and Sanguisorbae Radix, which is the dried root of Sanguisorba officinalis L. and is widely used in herbal medicine known as "ZiYu" in Korea [21].

It is known that sanguiin H6 is a dimer of casuarictin connected via a bond between the gallic acid residue and one of the hexahydroxydiphenic acid units. It is a polyphenol chemical with potent antioxidant properties that can stop the growth of endothelial cells by lowering the generation of nitric oxide, which in turn stops the activity of inducible nitric oxide synthase (iNOS) and the expression of mRNA [22, 23]. Sanguiin H6, which was identified and extracted from S. Radix, was studied for its activities and molecular processes. It was shown to be an inhibitor of TGF-β1 activation of the Epithelial-Mesenchymal Transition (EMT) in A549 cells. Sanguiin H6 significantly prevented the production of MMP-9 by TGF-β1 and the activation of Smad2 and Smad3, suppressed E-cadherin expression in TGF-β1-stimulated A549 cells, and decreased TGF-β1 stimulation of cell migration and invasion [24].

Sanguiin H-6 dramatically decreased tumour cell survival in a concentration-dependent way when tested for its anticancer activity and mode of action against two human breast carcinoma cell lines, MCF7 and MDA-MB-231. The rate of apoptosis rose by 33.7% and 40.7%, respectively, at concentrations of 100µM for MCF-7 and 50µM for MDA-MB-231. Apoptosis was brought on by the cleavage of caspase-8, caspase-3, and poly (ADP-ribose) polymerase, which was stimulated by Sanguiin H-6. Sanguiin H-6 also caused an increase in the Bax to Bcl-2 ratio in MCF-7 and MDA-MB-231 cells. According to reports, one important factor influencing apoptosis is an increase in the ratio of pro- and anti-apoptotic proteins, Bax to Bcl-2 [25, 26].

3. Davidiin

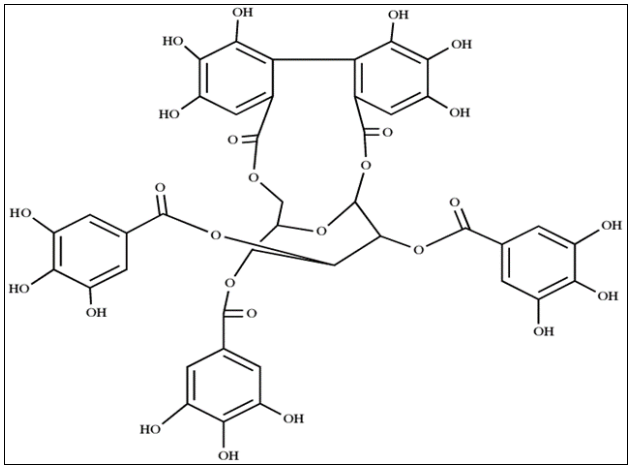

Fig 4: Structure of Davidian

An aqueous acetone extract of dried Davidia involucrata leaves an ornamental plant from southern China that is rich in tannins contained a new ellagitannin called davicratinic acid A as well as four other previously identified ellagitannins: davidiin, granatin A, pedunculagin, and 3-O-galloylgranatin A. Spectroscopic data were used to determine the structure of davicratinic acid A, a monomeric ellagitannin with a distinct skew-boat glucopyranose core, as well as the other known ellagitannins [27]. When these tannins from D. involucrata were applied to human oral squamous cell carcinomas, the cytotoxicity assay showed that davidiin (which has the same skew-boat glucopyranose core, Figure 5) had the strongest antitumor effect of all the tannins tested (TS-tumour specificity index 2.2 compared to 2.9 for resveratrol, which is referenced as a naturally occurring potent antitumor) [28].

It was determined the structure of novel oligomeric hydrolyzable tannins from aqueous acetone extracts of the leaves of the traditional Egyptian medicinal plant Tamarix nilotica. The extracts included four known trimers in addition to two novel ones, nilotinin T2 (trimer) and nilotinin Q1 (tetramer). When applied to human promyelocytic leukaemia cells (CC50 < 10µM), the ellagitannin trimers demonstrated significant tumor-selective cytotoxic effects with great specificity [29, 30].

Gallo tannin was utilised to clarify the apoptotic pathway in DU145, PC-3, and M2182 prostate cancer cells. Gallotannin is found in a number of medicinal plants, including Caesalpiniaspinosa, Paeonia officinalis, Rhus semialata, Quercus infectoria, and Rhus semiaria. The results showed that gallotanin caused apoptotic morphological features, increased the number of terminal deoxynucleotidyl transferase dUTP nick end labelling positive cells, and caused sub-G1 accumulation in the three prostate cancer cell lines. It also exerted dose-dependent cytotoxicity in DU145, PC-3, and M2182 prostate cancer cells [31, 32]. Additionally, procaspases 9 and 3 were expressed less often by gallotannin, which also

reduced the expression of survival genes such Myeloid Cell Leukaemia 1 (Mcl-1), B-cell Lymphoma 2, and B-cell Lymphoma 2 Extra-Large.

4. Geraniin

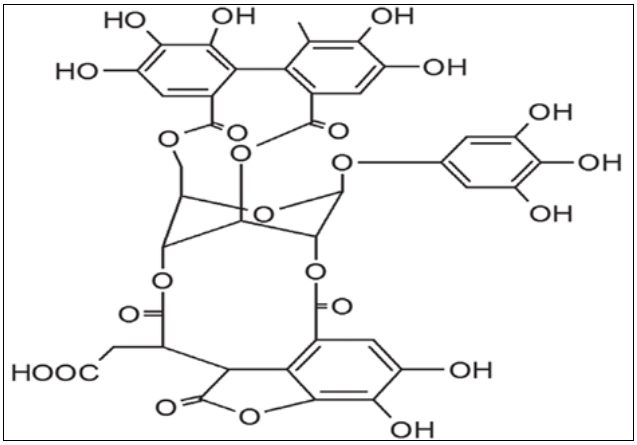

Fig 4: Structure of Geraniin

A polyphenolic component called geraniin was extracted from *Geranium sibiricum* and *Phyllanthus amarus*, two traditional Chinese herbal medicines that have been experimentally used to treat bladder calculi, renal calculi, and gallstones. According to some pharmacological and biological research, geraniin possesses a variety of biological properties, including antiviral, antibacterial, anticancer, antihyperglycemic, and antihypertensive properties.

Research utilising commercial geraniin revealed that this substance hinders EMT generated by TGF-β1 and reduces the migration, invasion, and anoikic resistance of A549 cells. Geraniin's possible roles and molecular processes might include inhibiting EMT by causing vimentin expression and E-to-N-cadherin transition in TGF-β1-activated A549 cells. Furthermore, evidence showed that geraniin attenuated the rise in migration, invasion, and anoikis resistance and significantly reduced Smad2 activation in A549 cells [33-35]. The findings demonstrated that at doses of 15 and 20μM, geraniin suppressed TGF-β1-induced EMT development in A549 lung cancer cells, but had no effect on cell proliferation.

5. PGG (Pentagalloylucose)

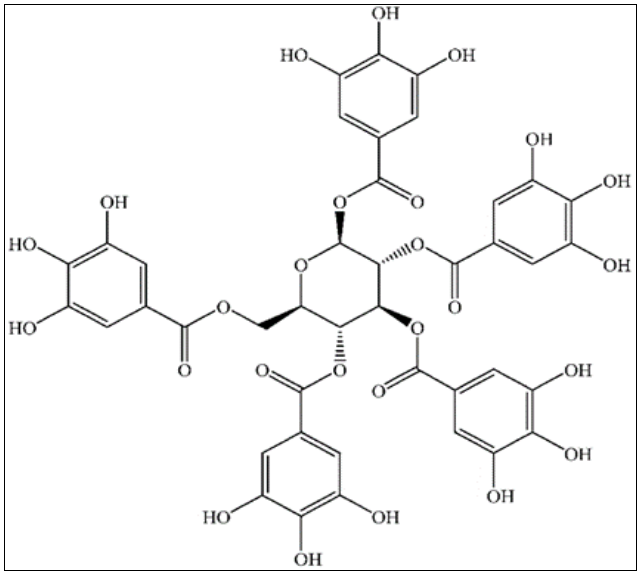

Fig 5: Structure of PGG (Pentagalloylucose)

PGG is primarily found in plants as the fundamental component of the higher galloyl glucoses, which are what make up tannic acid, a commercial preparation. While the amount of free PGG varies between plant species, it is present in sufficient amounts to enable solvent extraction, liquid-liquid partition, and chromatography separation for direct isolation from a variety of Oriental herbs and other plants, including Rhus chinensis Mill, Paeonia suffruticosa, Paeonia lactiflora, Schinus terebinthifolius, Acer truncatum Bunge, and Terminalia chebula [36, 37]. The distribution of PGG in 70 different plant species has been compiled in a recent study, which includes both the scientific and common names. Plant-derived PGG isolation yields varying results. Tannic acid methanolysis for the preparation of PGG

Many plants have copious amounts of higher galloyl esters in their galls, which are sold commercially as tannic acids. The content of tannic acids varies greatly throughout sources; some preparations include mostly PGG and higher esters, while others contain primarily tetragalloyl glucose and lesser esters [38, 39]. Additionally, the primary polyol might be quinic acid or glucose, depending on the circumstances. Hagerman and colleagues synthesised PGG by means of tannic acid methanolysis. Verifying that the beginning material has the right fundamental structure is crucial to producing the intended end result with regard to tannic acids.

6. Acertannin

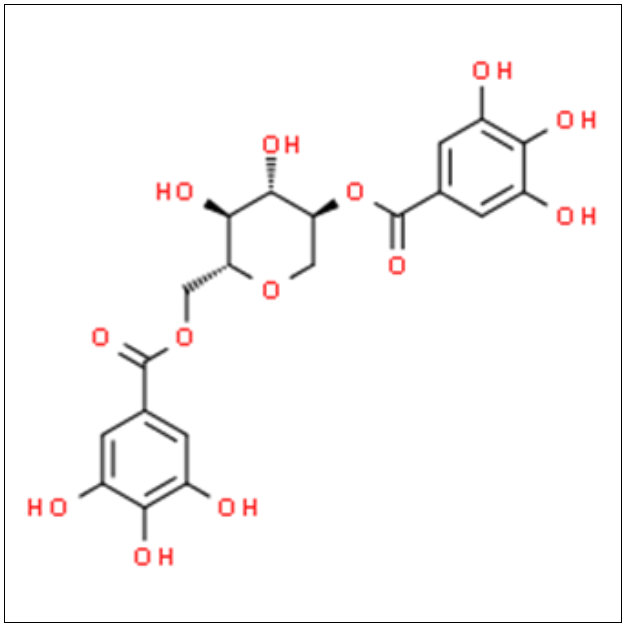

Fig 7: Structure of Acertannin

2,6-digalloyl-1,5-anhydro-D-glucitol is acer tannin. This crystalline substance, which was initially extracted from Acer ginnala leaves, belongs to the type A Gallo tannins structurally, while having a modest binding activity. Significant binding activity was demonstrated by the tri- and tetragalloyl derivatives with depsidically connected galloyl groups [40]. Some researcher was found that anticancer properties in Acertannin.

7. Cisplatin

Liver cancer is the third most common cause of cancer-related deaths in men [39]. TA was found to work in concert with Cisplastin, a powerful antitumor agent, to stop the progression of liver cancer *in vitro* by inducing mitochondrial-mediated apoptosis. Additionally, Mhlanga *et al*. recently reported on

the effect of TA on HepG2 cells, discovering that TA induced apoptotic pathways, increased reactive oxygen and nitrogen species, and decreased antioxidants expression. As a result, DNA fragmentation via caspase-dependent and -independent pathways occurred, leading to instantaneous cell death, as illustrated [41, 42]. It's also important to note that TA has been described as a hepato-protective and anti-fibrotic agent where it was discovered to lower ALT

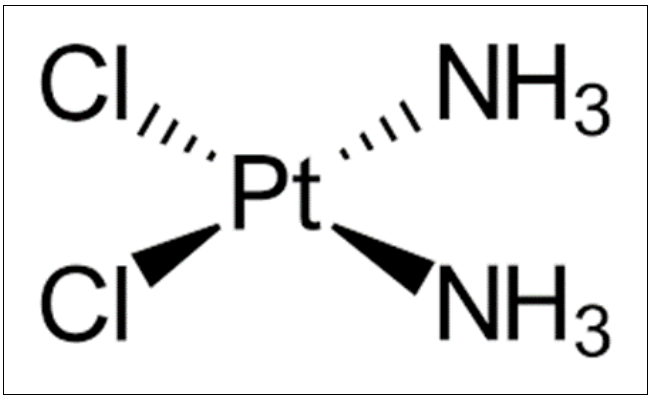

Fig 8: Structure of Cisplatin

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8. Maplexins AI

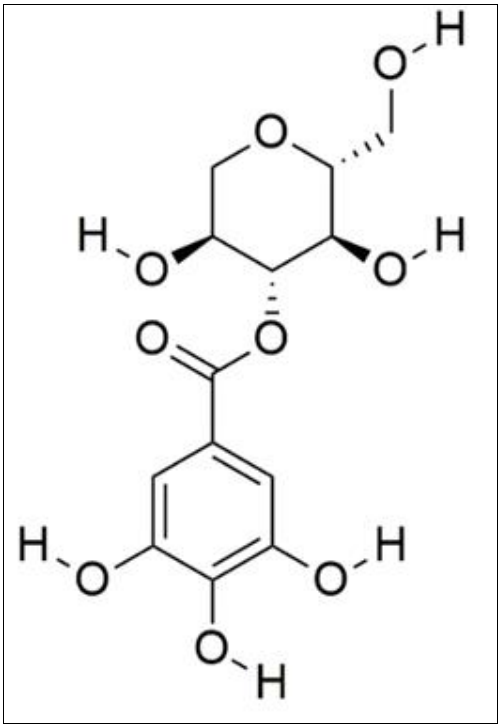

Fig 9: Structure of Maplexins AI

Maplexins AI are new gallotannins previously isolated from the red maple species. Maplexins showed cytotoxic effects against human cancer cells to a greater effect than normal cells. Antiproliferative effects of maplexins were mediated through cell cycle arrest and apoptosis [43, 44]. SAR studies revealed that two galloyl groups on 1,5-anhydro-glucitol is important for anticancer effects.

9. Proanthocyanidins

Yamagishi *et al*. (2003) carried out the first investigation on this topic to demonstrate the impact of proanthocyanidins from cacao liquor, a significant component of chocolate and cocoa, in a rat multi-organ carcinogenesis model[45]. Proanthocyanidin therapy considerably decreased the number and incidence of lung carcinomas without having any negative effects on any other major organ. Next, researching grape seed proanthocyanidins (GSPs) effects on non-small cell lung cancer (NSCLC) *in vitro*, Akhtar *et al*. (2009) in vivo with a model of tumour xenograft mice. GSPs prevented NSCLC cells (A549 and H1299) from proliferating, but not normal bronchial cells called epithelium. Further *in vitro* data demonstrated that GSPs-induced inhibition of NSCLC cell growth might be achieved by protein-3 that binds to insulin-like growth Yamagishi *et al*. (2003) carried out the first investigation on this topic to demonstrate the impact of proanthocyanidins from cacao liquor, a significant component of chocolate and cocoa, in a rat multi-organ carcinogenesis model [46, 47]. Proanthocyanidin therapy considerably decreased the number and incidence of lung carcinomas without having any negative effects on any other major organ. Next, researching grape seed proanthocyanidins (GSPs) effects on non-small cell lung cancer (NSCLC) *in vitro*, Akhtar *et al*. (2009) in vivo with a model of tumour xenograft mice. GSPs prevented NSCLC cells (A549 and H1299) from proliferating, but not normal bronchial cells called epithelium. Further *in vitro* data demonstrated that GSPs-induced inhibition of NSCLC cell growth might be achieved protein-3 that binds to insulin-like growth [48].

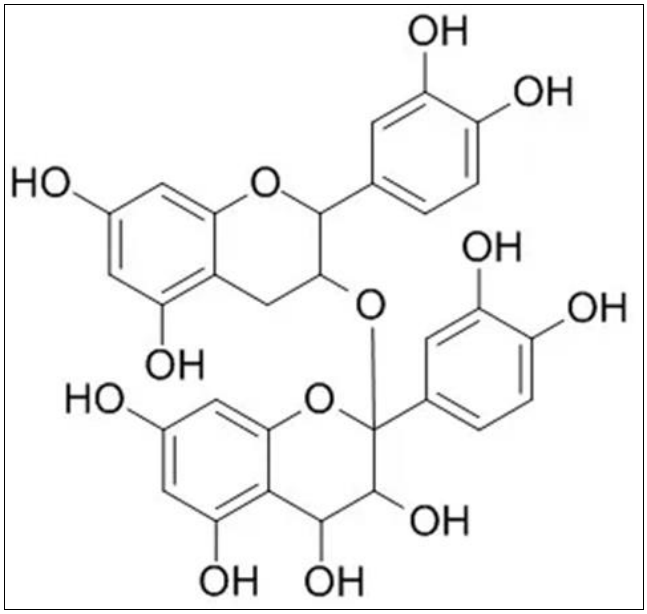

Fig 10: Structure of Proanthocyanidins

10. Procyanidins

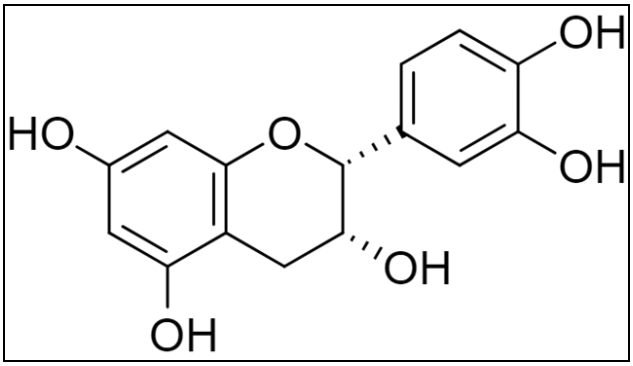

Fig 11: Structure of procyanidins

Cinnamomi procyanidin oligomers isolated from sorghum

grains. It has been demonstrated that grape seed and cortex decrease lung cancer. When C57BL/5J mice with Lewis lung adenocarcinoma are given extract from Sorghum bicolour (Linn.) high in procyanidins Moench inhibited the development of metastases, tumour growth, and VEGF production (Wu (2011), among others). Furthermore, research conducted *in vitro* has demonstrated how procyanidins from Cinnamomi cortex extract limit the development of A549 cells by controlling NRF2 pathways. It has been found that procyanidins inhibit NRF2 expression and NRF-2-mediated action. (Ohnuma *et al*., 2011), specifically block turned-on NRF2 (overexpressed NRF2) (Ohnuma *et al*., 2015), and encourage NRF2 degradation dependent on proteasomes by phosphorylating insulin-like [49-51]. The IGF-1R, or growth factor-1 receptor (Ohnuma *et al*., 2017). Additionally, EMT has a significant impact on the development of cancer metastasis, Procyanidin C1 from Cinnamomi Cortex was investigated by Kin *et al*. (2013) for its ability to prevent TGF-β1-induced EMT in the A549 cell line. Procyanidin C1 was found to suppress TGF-β1-induced morphological alterations, expression of mesenchymal markers, and cellular migration in A549 cells. It's interesting to note that in neoplastic lung cells and tumour xenografts, grape seed procyanidin (GSPC) treatment down-regulated the expression of miRNA linked to cancer (oncomir), such as miRNA-19a, miRNA-19b, and miRNA-17-92 cluster host gene (MIR17HG) [52]. This, in turn, up-regulated the expression of tumour suppressor genes, like insulin-like growth factor II receptor (IGF-2R) and phosphate and tensin homolog (PTEN), their corresponding protein products, and decreased phosphorylation of Akt, ultimately leading expansion of cancerous cells (JT Mao, *et al*., 2016b). In a different study, researchers demonstrated that GSPC inhibits lung cancer cells' ability to proliferate by boosting the synthesis of key eicosanoid metabolic pathways. Such as 15-lipoxygenase-2/15-hydroxyeicosatetraenoic acid (15-LOX-2/15-HETE) and prostacyclin synthase/prostacyclin (PTGIS/PGI2). The pro-apoptotic potential of GSPC was partially inhibited by specific siRNA directed against PTGIS or 15-LOX-2 (J. T. Mao *et al*., 2016a).

11. Oenothein B

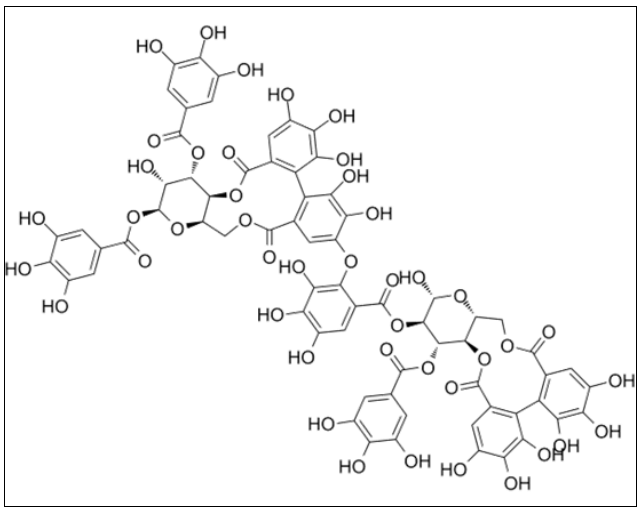

Fig 12: Structure of oenothein B

Dimeric ellagitannin Oenothein B, which is frequently found in the genus Oenothera, successfully stopped the growth of A549 cells by causing cell cycle arrest in the G1 stage (Pei *et al*., 2019) [53]. Conversely, oenothein B raised intracellular ROS levels as well as them expression of many proteins linked to apoptosis and apoptotic processes, but suppressed Akt, NF-kB, and PI3K (phosphatidylinositol 3-kinase) phosphorylation levels.

12. Casuarinin

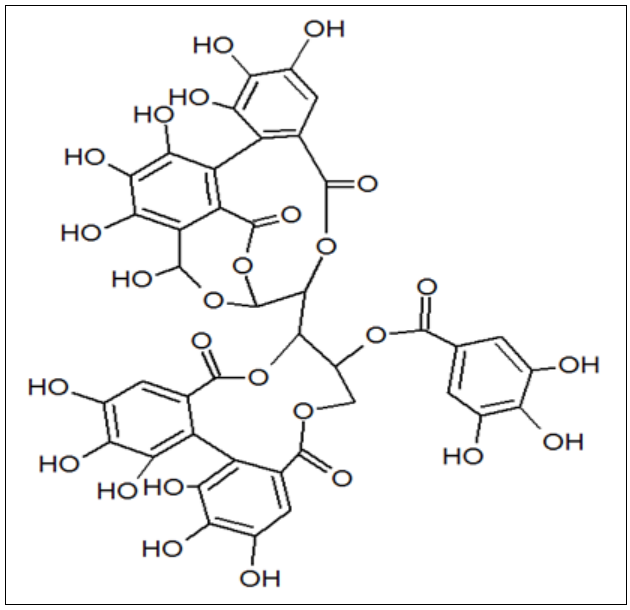

Fig 13: Structure of Casuarinin

Casuarinin extracted from Terminalia Arjuna bark According to reports, Linn may cause cell cycle arrest in A549 cells at the G0/G1 phase. Causing p53-dependent p21/WAF1 induction. Moreover, casuarinin enhanced the expression of soluble/membrane bound FasL and Fas/APO-1 receptor in A549 cells, suggesting a potential function for the Fas/FasL apoptotic pathway in casuarinin-induced apoptosis (P. L. Kuo *et al*., 2005a).

Tannin Extract from Medicinal plants with Anticancer Effect

The cytotoxicity of plant extracts high in tannins was investigated. The edible berries of cornaceae plants are well-known, and their leaves are also used as tea. Aqueous leaf extracts from Cornus mas, C. alba, C. flaviramea, C. kousa, and C. officinalis were analysed for their antiproliferative activity in MCF-7 cells [54]. The content of the plant extracts included flavonoids, total hydroxycinnamic derivatives, total polyphenols, and tannins [55, 56]. The correlation between the polyphenol content (dose: 50-750µg/mL) and its cytotoxicity on MCF-7 cell line was determined using WST-1. The outcomes showed that the examined water extracts had strong antiproliferative effects on MCF-7 cells (after 72 hours, cell survival dropped to 11.2%, 10.3%, and 11.1% with extracts of *C. alba*, *C. officinalis*, and *C. mas*, respectively). Considering the nature of polyphenols, the greater antiproliferative impact was linked to the higher tannin content, and the mild cytotoxic effect on cancer cells was tied with the increased flavonoid and hydroxycinnamic derivative content [57].

The stem bark extract of the African ethnomedicinal plant Crateva dansonii DC induces cytotoxicity in the ER-positive breast cancer cell line MCF-7 and includes a variety of compounds, including citric acid ester derivatives, arylpropanoid, phenylpropanoid, flavonoids, sesquiterpene derivatives, gallotannin, and lignans. Additionally, C. adansonii extract has demonstrated protective properties

against breast cancer in female Wistar rats caused by 7, 12 dimethylbenz(a)anthracene (DMBA) by reducing the carcinogenesis of the mammary glands (78.07% reduction of tumour volume at the extract dose of 75mg/kg) [58]. At the low dose (75 mg/kg), the extract was also shown to have significant antioxidant activity and an antiestrogenic impact; these effects were likely caused by the flavonoid content of the extract. It was determined that C. adansonii had an LD50 of more than 5000 mg/kg.

Caesalpiniaspinosa (P2Et), a plant used traditionally and widely in Peruvian folk medicine to treat fever, colds, and stomach problems, was shown to have a high percentage of gallotannins. The ethanolic extract has higher concentrations of hydrolysable tannins, such as derivatives of galloylquinic acid, and lower concentrations of pentagalloyl glucose and compounds containing gallic acid (gallates) [59]. After being exposed to a gallotannin-rich fraction derived from C spinosa, 4T1 breast tumour cells were treated to assess their anticancer activities and IR activation. While IR and the progression of the tumour after vaccination were evaluated in vivo, apoptosis and the expression of Immunogenic Cell Death (ICD) markers were evaluated *in vitro*. The P2Et fraction caused apoptosis in cells, exhibiting DNA breakage and phosphatidylserine externalisation. ICD markers such calreticulin and release of ATP. The vaccination of 4T1 cells pretreated with P2Et (t-P2Et) improved primary tumour control by producing long-lasting ex vivo multifunctional CD4+ and CD8+ T lymphocytes (interleukin [IL]-2+, Tumour Necrosis Factor [TNF]-α+, interferon [IFN]-γ+) that secrete IL-2, TNF-α, IL-4, IL-5, and IFN-γ following specific stimulation of 4T1 cells [60, 61]. These findings suggest that this fraction may be used as an adjuvant in the management of breast cancer. These conclusions were further supported by research on the anticancer activity of the same ethanolic plant extract from C. spinosa that had a high amount of gallotannins in human and murine cell lines with various cancer resistance profiles. It has been demonstrated that the ethanolic extracts decrease lung and spleen metastases in mice that have had breast cancer cells implanted, indicating a noteworthy anti-Cancer Stem Cell (CSC) effect [62].

The main cell type in charge of metastasis and recurrence is CSC. The combined effects of doxorubicin and a plant extract were tested *in vitro* using a variety of cell lines and in vivo using mice that received transplants of TS/A cells, a highly resistant cell line that is enriched in CD44+CD24low/-CSC [63]. Antioxidant activity and drug efflux reversal were shown to be complementary actions. Short-term administration of C. spinosa extracts improved mice survival (by40%) in a TS/A breast cancer model linked to enhanced calreticulin expression in vivo and shown a synergistic impact with doxorubicin in resistant cell lines. These findings imply that An extract from C. spinosa may be used to traditional chemotherapy as an adjuvant to treat tumours that have a high concentration of CSC [64].

Bioavailability of Tannins

Tannins is basically hydrophobic, which causes limited bioavailability in both human and animal studies. Several phenolic compounds are hydrolysed in the gut under physiological circumstances, where they are metabolised and somewhat absorbed by the gut bacteria. This has been demonstrated in earlier research [65]. Corilagin and its metabolites, Gallic and Ellagic acids, were found in plasma and liver tissue, according to a study on corilagin in diet. Following oral corilagin (1500 mg/kg) administration, plasma samples analysed at various time intervals revealed a maximum concentration of about 55µg/mL in blood, with a half-life of approximately 6 hours, according to another example of in vivo investigations conducted on rats and mice [66]. Another instance involved rats that received a single oral dosage of corilagin (50 mg/kg). Following two hours of oral dosage, the maximal bioavailability of corilagin in plasma was found to be 1.8µg/mL, according to blood tests conducted at several time intervals over a 24-hour period. In comparison to corilagin, ellabic acid and gallic acid showed varying half-lives and bio availabilities in plasma. From this point on, the combined effects of corilagin, gallic acid, and ellagic acid produce the anticancer effect.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

Conclusion

In contrast tannins exhibit substantial cytotoxicity on tumour cells and have identical modes of action, therefore there are no appreciable differences in the results concerning them. Tannin, which have complex oligomeric structures, appear to have more efficacy as bioactive substances, or anticancer medicines. If one wants to understand the mechanisms of action of compounds that are comparable to other polyphenols, there is a greater inclination to deal with isolated compounds from plant extracts and less with synthesis-compounds. Eventually, one may resort to commercial compounds. *In vitro* experiments were conducted in greater numbers than in vivo investigations and clinical trials. In order to confirm that polyphenols (such as Tannin) can be used as a preventive measure and/or supplemental treatment for cancer, as well as whether individual polyphenols or plant extracts are more effective and promising in fighting this disease, more human trials are needed in addition to more sophisticated cellular models and improved research on the metabolism of polyphenols by the intestinal micro biota.

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