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Cancer and its treatment: The scope of Topoisomerase-II inhibitors

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Abstract:

Cancer is defined as Abnormal and regulated proliferation (growth) of cells, arising from cells. Cancer cell have lost their ability to differentiate. There is increase in number of cells, with the positional to invade to other parts of body. Cancer cells have high tendency to dislocate from their own origin and make a pathway into their own blood supply and disperse to other organs. Topoisomerase is an enzyme that regulates the overwinding or underwinding of DNA. Topoisomerase binds to either single-stranded or double-stranded DNA and cut the phosphate backbone of the DNA. They exist in 2 forms topo 1 and 2, which are essential for the cell growth. As a consequence, these enzymes are potential targets for cytotoxic drugs. Herein we descried the role of topoisomerase and its inhibitor in cancer control and treatment.

Keywords: Cancer, Topoisomerase, DNA, Cytotoxic, Anticancer.

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1: Introduction

Cancer is an uneven distribution and irregulated progression of cells. Cancer cell has lost their ability to differentiate. There is an increase in a number of cells, with the positional to invade other parts of the body.Malignant growth cells can make their own blood supply, split away from organ of beginning and spread to different parts of the body.[1]The history of disease starts when Hippocrates depicts a few sorts of malignant growth, alluding to them with a greek word carcinomas (crab). Celsus named cancinos into carcinoma “oma” meaning swelling. The historical backdrop of malignancy depicts the improvement of the field of oncology.The most punctual known portrayals of malignant growth show up in seven papyri, in late nineteenth century, the primary direct information on Egyptian therapeutic practice was given by two of them "Edwin smith" and "George Ebers" composed around 1600 B.C; the most seasoned known depiction and careful treatment was found by them.[2]

The main source of malignant growth was distinguished by British specialist "Pervicallpott" who found in 1775 that malignant growth of scrotum was a typical malady among stack clears, with the spread utilization of magnifying lens in eighteenth century, it was found that the 'disease poison' spreads from the essential tumor through the lymph hubs to different destinations. This view was given somewhere in the range of 1871 and 1874 by English specialist" Campbell de morgan". During the same period, the idea that the body is made up of a large number of cells brought the theory of humuoral imbalance to an end.[3]

Order of malignancy based on the source of cell:

• Carcinoma: diseases got from epithelial cells. This gathering a considerable lot of the most widely recognized tumors especially in old people, diseases in the bosom, prostate, pancreas, and colon.

• Sarcoma: Cancers emerging from connective tissues (bone, ligament, fat).

• Lymphoma or leukemia: These emerge from cells that make blood. Leukemia is regular in kids.

• Germ cell tumor: malignant growth emerging from pluripotent cells, generally normal in testis and ovary.

• Blastoma: malignancy got from juvenile forerunner cells or embryonic tissues.[2]

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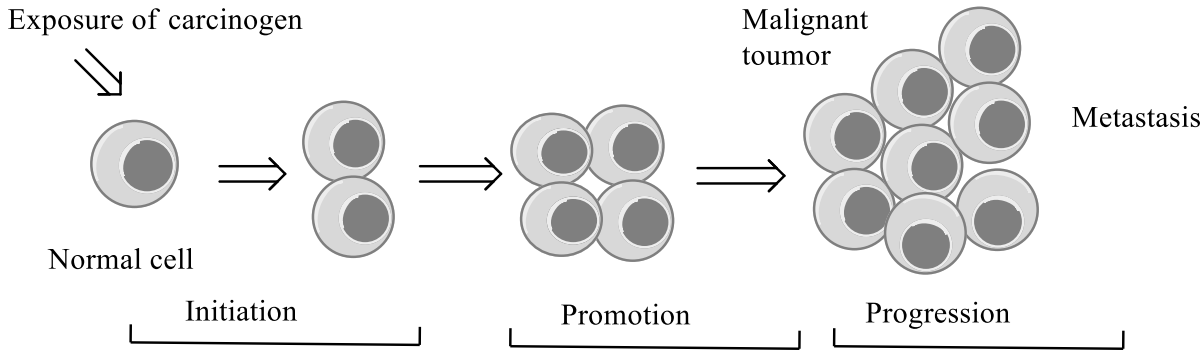


Figure 1: Metastasis.[6]

Figure 1 shows spreading of cancer in the body by metastasis, a normal cell, is converted into the malignant tumor by undergoing different phases of cell division, the normal cell, is converted into malignant by exposure to carcinogenic radiation, chemicals, viruses.[3]

1.1 Risk factors causing cancer:

The various Known and possible risk factors by site in the oral cavity and pharynx: tobaccoand alcohol usage, diet low in fruits, poor oral hygiene, and iron deficiency anaemia. In thedigestive system results in colorectal inflammatory bowel disease, diet high in fat, obesity,and smoking, NSAIDs in the pancreas results in diabetes, smoking, coffee or tea consumption.[7]

In the Stomach due to dietary nitrites, pernicious anemia,infection with helicobacter pyloriin the liver due to infection with hepatitis hepatitis B or C, cirrhosis of liver. The esophaguscancer may be due to tobacco, inadequate diet, and deficiency of nutrients in respiratory system in lungs due totobacco, smoking, air pollution in larynx due to asbestos, alcohol, and smoking. Theskin melanoma is may be due to U.V radiation,organ transplants, HIV infections.[8]

Non melanoma may cause byphotosensitizers in tanning aids, cosmetics while breast cancer may be due to family history, first child born after 30; thyroid goiter, high doses of ionising radiations. The other major risk factors include genetic predisposition, virus, sun exposure etc.[4]

1.2 Diagnosis of cancer:

Cancer diagnosis is done as follows by some symptoms:

Symptomatic: Cough, rectal bleeding, palpation of a breast lump, weight loss, blood in urine, difficulty swallowing.

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Asymptomatic: Blood test for PSA (Prostate-specific antigen), other markers later via radiographic or surgical biopsy,CT, MRI, PET, ultrasound, and then to pathology.

Standing considerations is an important step in diagnosing cancer, which is a prominent way of screening the remedy of choice.[7]

1.3 Anticancer drugs:

These are cytotoxic drugs used to control and kill the cancer cells. Based on the target and basic structures are classified as below[9]:

1. Alkylating agents:

(a) Nitrogen mustards: Mechlorethamine, Cyclophosphamide, Melphalan

(b) Ethylenemine: thio-TEPA

(c) Alkyl sulfonate: Busulfan

(d) Nitrosoureas: Lomustine, Carmustine

(e) Triazine: Decarbazine

(f) Methylhydrazine: Procarbazine

2. Platinum coordination complexes: Cisplatin, Oxaliplatin

3. Antimetabolites:

(a) Folate antagonist: Methotrexate

(b) Ppurine antagonist: 6-Mercaptopurine, Azathioprine

(c) Pyrimidine antagonists: Fuorouracil, Ccytarabine

4. Monoclonal antibodies: Herceptin

5. Mitosis inhibitors: Taxol

6. Steroid hormones: Tamoxifen

7. Topoisomerase inhibitors:

(a)Type1 inhibitors:Topotecan, Irinotecan

(b)Type 2 inhibitors: Etoposide, Peltasol

2. Topoisomerase:

Topoisomerase is an impetus that controls the over turning or under curving of DNA. This widely appealing break empowers DNA to disentangled or released up and around the end the DNA spine is resealed again. Bacterial and human topoisomerase proceed by methods for same framework for replication and translation.[12]

Topo EC-codes are as per the following: EC5.99.1.2 (ATP autonomous breakage of single stranded DNA, trailed by entry and rejoining. It achieves transformation of one topological

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isomer of DNA into other; type II: EC5.99.1.3 (Can bring negative too helical transforms into a twofold stranded DNA.[11]

The twofold helical design that DNA strands normally dwells, makes them hard to isolate but then they should be isolated by helicase chemical, if different compounds are to interpret The addition of DNA into chromosomes and different types of recombination can likewise require the activity of topoisomerase.[19]

2.1 Classes of topoisomerase:

The two classes of chemical agents use a monitored tyrosine. These proteins contrast in structure and instrument.

2.2.1 Type I Topoisomerase**:** It cuts one strand of DNA double helix, relaxation occurs and then the cut strand isreannealed. It is primarily responsible for relaxing positively supercoiled (overwound) ornegatively supercoiled (under wound) DNA.The mechanism is involved rotating the broken strand around the intact strand to relax the strain on the DNA.

Type I topoisomerase has 2 subtypes as follows:

Type IA topoisomerase: It almost has similar mechanism and structure as type II. It coordinates with the 5' end of DNA for eg: topoI and topo III, bacterial topoisomerase I, reverse gyrase.[23]

Type IB topoisomerase (eukaryotic topo): It forms covalent intermediate with 3' end of DNA.

Type IC topoisomerase (TOPO V): Different in structure from type A and B, but has a similar mechanism with B type.

2.2.2Type II topoisomerase: It cuts the two strands of one DNA twofold helix, passes anotherbroken DNA helix through it, and afterward reannealstwo cut strands.[17]

It has 2 subtypes i.e. type IA and types II B, both have similar structure and mechanism.

Example of type II A: Eukaryotic topo II, E.coli.

Type II A: Eukaryotic and eukaryal viral topoisomerase II GYRASE, topoisomerase IV

Type II B: Archaeal TOPOISOMERASE VI

2.2 Reactions of topoisomerases:

A response regular to all topoisomerases is the capacity to unwind adversely supercoiled DNA; that is to change over it into a less-supercoiled structure, or increment its connecting number (Lk).[20]

Type I topoisomerase reaction

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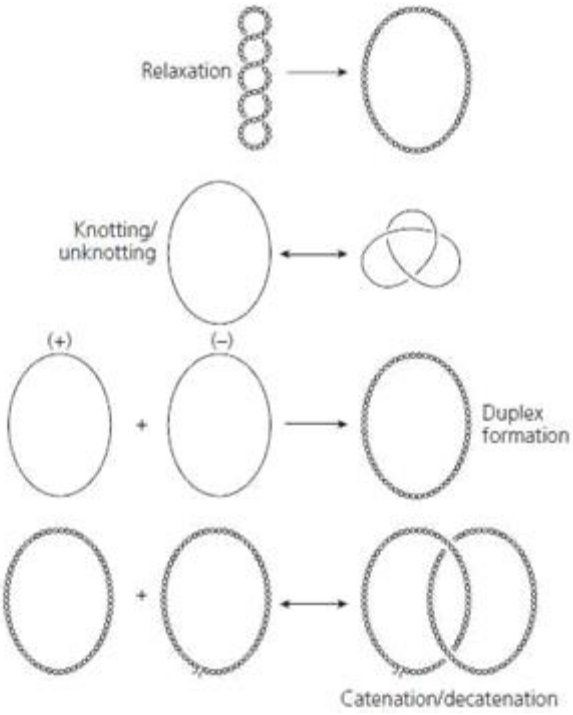


Figure3 mechanism of action of topo I[14]

In figure 3 shows the mechanism of action of topo i enzyme during the process of DNA replication. This figure depicts how topo i enzyme is important for duplex formation when +ive and –ive strands combines.

Type II topoisomerase reaction:

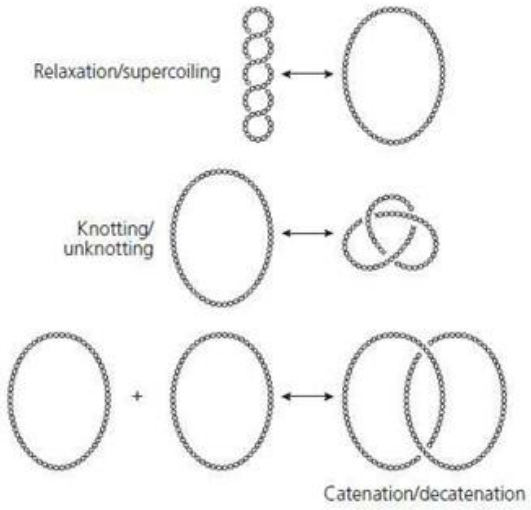


Figure 4: mechanism of action of topo 2[13]

In the above figure represents mechanism of action of topo 2 enzyme It undergoes catenation and decatenation.

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2.3 Topoisomerases as drug targets: We realize that topoisomerases are basic for cell development. As a result, these proteins are the main focus for chemotherapeutic medications.

With regards to topoisomerase Mechanism it is intriguing to think about how these medications may work.[13]The quinolones are thought to act by interfering with the DNA breakage–gathering venture of the gyrase response. Without a doubt, under specific conditions, quinolones can prompt catching of the gyrase–DNA transitional in which the A subunits of the compound are covalently bound to the 5-phosphates of DNA at the break site. The eukaryotic topoisomerases are likewise medicate targets . The medication balances out the complex between the compound and DNA in a way similar to the activity of quinolones on DNA gyrase. Precious stone structure data on human topoisomerase I proposes a model wherein the medication collaborates with the bound[14]

3. Topoisomerase inhibitors:

Topoisomerase inhibitors competes with the activity of compounds (topoisomerase I and II), these agents manages changes in DNA structure by catalyzing the phosphodiester spine of DNA strands during the typical cell cycle. It has become novel attention for chemotherapeutic targets. eg: nalidixicacid and ciprofloxacin. Quinolones tie to these compounds and keep them from decatenation reproducing DNA.[21]

3.1 Natural and synthetic topoisomerase inhibitors:

Etoposide, teniposide, doxorubicin,daunorubicin, mitoxantrone, amsacrine, Ellipticines, aurintricarboxylic acid, HU-331, a quinolone synthesized from cannabidiol. Different plantderived common phenol (genistein, quercetin, resveratrol) have solid topoisomeraseinhibitory properties which influence the two sorts of catalysts. They work like phytoalexins mixes delivered by plants to battle vermin and nuisances.

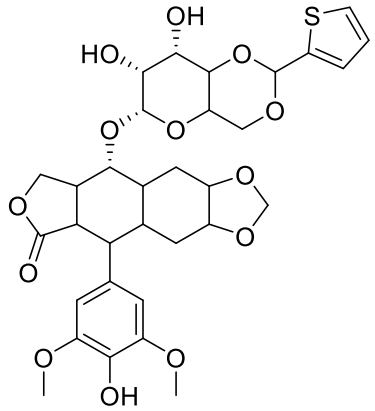
Intensifies that target topo II has been characterized into following 2 classification:

1. Topoisomerase toxic substances: these objective the topoisomerase-DNA complex
2. Topoisomerase inhibitors: these upset synergist turnover. Topo II harms : these objective the topoisomerase-DNA complex topoisomerase inhibitors: these upset reactant turnover.[23]

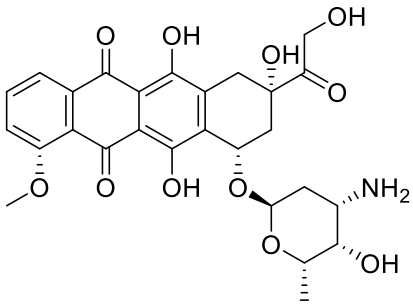
3.2 Topo II Poisons: These compounds target the topoisomerase DNA complexes.they are further classified as: type II topoisomerase inhibitors : these poisons prevent the re-ligation of DNA These drugs are anti-cancer therapies. eg: amsacrine, etoposide[17]

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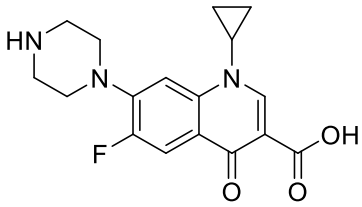


Teniposide



Doxorubicin

Bacterial type II topoisomerase inhibitors: These poisons encourage theforwardcleavage reaction. .These areantibacterials. eg: fluoroquinolones as ciprofloxacin.



Ciprofloxacin

Another classification of poisons is as follows:

(a) Intercalating poisons:These are artificially assorted, and incorporate doxorubicin and different others including m-AMSA, and an assortment of different intensifies that are not as of now in clinical utilize Other than their capacity to intercalate in DNA, there is no other substance similitude that could clarify the capacity of these mixes trap topo II. Different models are: o-AMSA and ethidium bromide.

(b) Non-intercalating poisons: these are for the most part dynamic against prokaryotic kind II topoisomerases. Since non-intercalating Topo 2 toxins don't cooperate emphatically with DNA, it has been proposed that protein medicate communications assume key jobs in their capacity to trap Topo 2 covalent edifices[18]

3.3 Catalytic inhibitors of topo II:

A few classes of mixes have been depicted that target topoisomerase II without balancing out Top2 covalent buildings. The bisdioxopiperazines incorporate ICRF-159, ICRF-187, and MST-16. These medications have two exercises: they are intense chelating specialists and

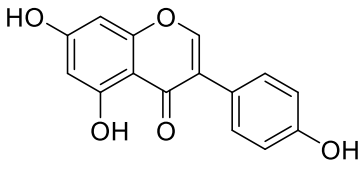
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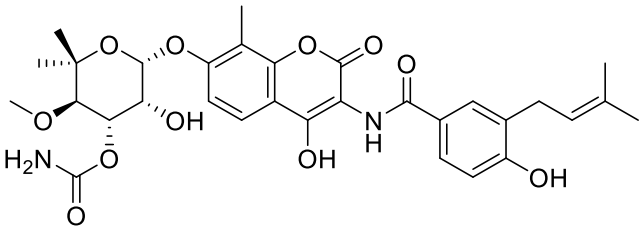
they square Top2 in the synergist cycle after strand entry however before the hydrolysis of the subsequent ATP. Now in the response cycle, Top2 encompasses the strand that the protein had divided; this is the point in the response cycle where the compound is hindered by non-hydrolyzable ATP analogs.[19]

3.4Topo II inhibitors:

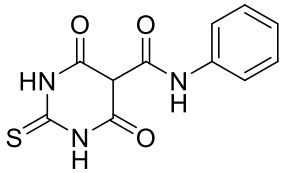
Most noticeable are the bisdioxopiperazines, which hinder the compound ATPase movement non-intensely and trap Top2 as a shut brace ICRF-187, a bisdioxopiperazine, is utilized as a cardioprotectant in certain patients treated with anthracyclines. Other Top2 synergist inhibitors incorporate novobiocin merbarone. Merbarone has pulled in intrigue since it is the main operator that has been found to hinder Top2 cleavage of DNA however not influence protein: DNA restricting QAP1 is a recently portrayed purine simple that was sanely intended to focus on the Top2 ATPase movement. This compound might be especially valuable in surveying the impacts of reactant hindrance of topo II11.[29]



Genistein



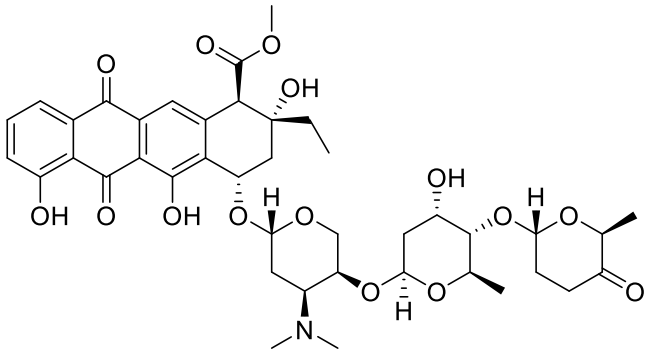
Novobiocin



Merbarone

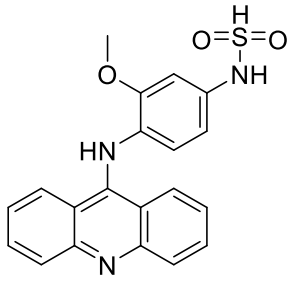
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Aclarubicin

Amsacrine ($C_{21}H_{19}N_3O_3S$) as topo II inhibitor:



Amsacrine is an anticancer operator that shows action against hard-headed intense leukemias just as Hodgkin's and non-Hodgkin's lymphomas. Amsacrine is generally noteworthy in that it was the principal sedate showed to work as a topoisomerase II poison. Despite the fact that it was structured as a DNA restricting operator, the capacity to intercalate does Amsacrine is an anticancer specialist that shows movement against unmanageable intense leukemias just as Hodgkin's and non-Hodgkin's lymphomas. amsacrine is verifiably noteworthy in that it was the main medication showed to work as a topoisomerase II poison. In spite of the fact that it was structured as a DNA restricting operator, the capacity to intercalate doesn't seem, by all accounts, to be the sole determinant of medication movement. Moving the methoxy to the 2'-position, it seems to build the level of rotational opportunity of the headgroup and may hinder associations of the 1'- substituent or different segments of the headgroup inside the ternary gathering.[24]

Uses: Amsacrine has a place with the gathering of disease battling meds called antineoplastics. Amsacrine is utilized to treat intense grown-up leukemia (malignancy of the white platelets) in individuals who have been dealt with already with other disease meds. Amsacrine murders malignancy cells by meddling with their development and reproduction.[24]

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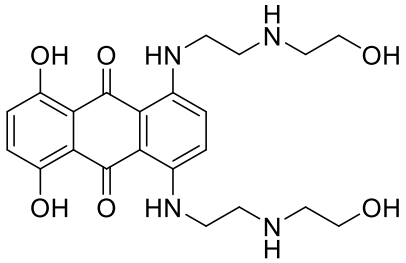
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Portion: The suggested portion and dosing calendar of amsacrine fluctuates as indicated by body size. It is infused into a vein through a site on skin. The portion is frequently infused once per day for 5 days and rehashed each 3 to about a month. At the point when the white platelet tally is leveled out without medicine after treatment with amsacrine, the individual is said to be abating[24]

Contraindications: amsacrine with any of the following medicines is usually not given

Side effects: It causes anaemia , confusional state, dizziness, blood bilirubin increased, headache, convulsion[24]

Anthracenedione-methionine conjugates as topo II inhibitors: Mitoxantrone:



Mitoxantrone, a manufactured anthracenedione, was created during the 1980s as a doxorubicin in order to ameliorate other associated adverse effects as compared to doxorubicin.[22]

Component of activity: Mitoxantrone is viable in lessening infection movement through a wide range of systems of activity. it stifles the expansion of T cells, B cells, and macrophages. It impedes antigen introduction and diminishes the emission of proinflammatory cytokines.

Utilizations: Mitoxantrone is utilized in the treatment of particular kinds of malignant growth, for the most part metastatic bosom disease, intense myeloid leukemia, and non-Hodgkin's lymphoma. It was likewise appeared to improve the endurance pace of kids experiencing first backslide of intense lymphoblastic leukemia. The mix of mitoxantrone and prednisone is affirmed as a second-line treatment for metastatic hormone-recalcitrant prostate malignancy. Mitoxantrone is additionally used to treat different sclerosis (MS), most notably,secondary-dynamic MS. As no solution for numerous sclerosis exists yet, mitoxantrone won't fix the malady, but instead is viable in easing back the movement of optional dynamic MS and expanding the time between backslides in both backsliding dispatching MS[18]

Side effects: Mitoxantrone, may cause a few unfavorable responses of differing seriousness, for example, sickness, retching, male pattern baldness, heart harm, and immunosuppression,

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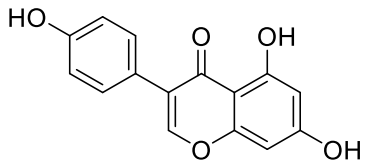
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which may likewise have a deferred beginning. Cardiomyopathy is an especially concerning impact as it is irreversible.

3.5Secondary metabolites as Topo II inhibitors:

3.5.1 Flavanoids as topo inhibitors:[17]

Genistien ($C_{10}H_{15}O_5$):



Genistein and other isoflavones found to inhibit the uncontrolled small growth of cancer 1, most likely by inhibiting the operation ofsubstances in the body that keep control rules small room division and small room still living (growth causes producing effect). Different studies have discovered that moderate amount of genistein have inhibitory effects on malignant growth of the prostate, cervix, brain, chest and body part under stomach. [31]

Genistein has been used to by selection target pre B-cells via system of operation-word forms with ananti-CD19 antibody.[28]

The Shape is rectangular or six sided rods.At the temperature of 297-298deg c it shows slight decomposition. It is soluble in organic solvents.it is found soluble in dilute alkalis with yellow color.it is insoluble in water[26]

Uses: Genistein is speculated to make ready good effects on cardiovascular and bone being healthy and to make less trouble in menopausal symptoms; studies going into with care such end points have been limited in number, on condition that not in agreement decisions in law, or valued soy product using up instead of exposure to genistein alone genistein is got, came together at one point in one on its therapeutic part in menopause.[29]

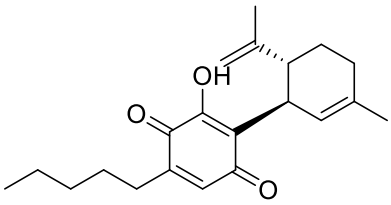
Mechanism: Genistein is aisoflavone derived from soy. It is phytoestrogen having antineoplastic activity.[31]Genistein ties to andinhibits protein-tyrosine kinase, thereby disrupting signal transduction and inciting cell separation. This operator likewise hinders topoisomerase-II, prompting DNA fracture and apoptosis, and actuates G2/M cell cycle capture. Genisteinexhibits cancer prevention agent, antiangiogenic, and immunosuppressive exercises.

HU-331 is a quinine anticarcinogenic tranquilize incorporated from cannabidiol, a cannabinoid in the Cannabis sativa plant. It indicated an incredible adequacy against

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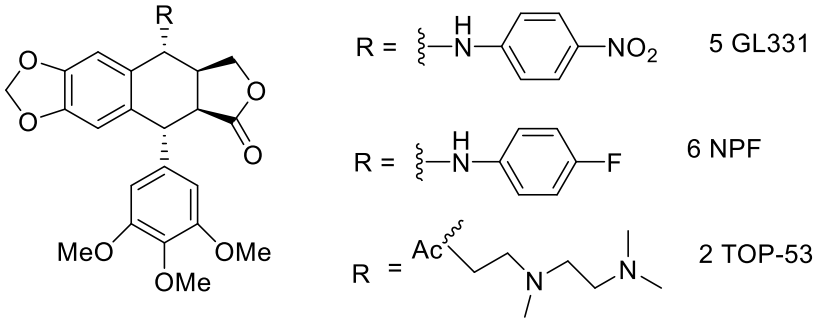
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oncogenic human cells. The cannabinoid quinone HU-331 is a quite certain inhibitor of topoisomerase II, contrasted and most known anticancer quinones[25,26]



Mechanism: Inhibitors of topoisomerases can act at two distinct levels. First repressing topoisomerase, which balance out the topoisomerase-DNA complex and subsequently present DNA breaks in the wires that lead to apoptosis, at that point restraining the reactant movement of topoisomerase, which obstructs the action of these compounds without bringing breaks into the DNA chains. HU-331 is by all accounts a synergist inhibitor of topoisomerase II, presumably by enzymatic ligation to the protein. This atom doesn't make harm DNA, yet shields cells from harm, characteristic, or initiated by different inhibitors of topoisomerase II that go about as inhibitors of topoisomerase. In any event, when 60% of the objective cells are slaughtered by treatment with HU-331, other cells' nucleic content stays safe, with less breakage of DNA chains that control significant cell work[25]

Podophyllotoxin: it is an antimitotic natural in origin. Its inhibitory action on cell regulation enables the improvement of the novel anticancer agents, etoposide, teniposide and the water-dissolvable prodrug, etoposide phosphate.[27]



Top-53:

TOP-53 is a promising anticancer operator that is highly active against cell lung malignancy in creature tumor models. TOP-53 is extensively more proficient than etoposide at improving topoisomerase II-interceded DNA cleavage and displays high movement against topoisomerase II alpha and II beta in vitro and in refined cells. TOP-53 contains a fundamental aminoalkyl bunch that may incline it to cooperate explicitly with phospholipids, thusly prompting an expansion of drug.accumulation in the tissues. Thusly, we have

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examined its connection with phospholipids in vitro utilizing a natural dissolvable water segment framework. TOP-53 seemed to have the most powerful restricting fondness (Ka = 563 x 10(- 2) microM) to phosphatidylserine (PhS), though VP-16 indicated no association with any phospholipid tried. PhS content decided after HPLC detachment changed among tried tissues; be that as it may, huge amounts were found in typical lung and lung malignant growth tissues far surpassing those present in the liver and kidney. The anticipated tissue-to-plasma parcel coefficient esteems, assessed dependent on PhS substance and its coupling proclivity, took after those tentatively decided. We inferred that tissue dispersion of TOP-53 is controlled by PhS content in the tissues and bybinding affinity.

Uses: Because of explicit amassing in the lung, TOP-53 seemed to show a solid antitumor action (increment of life expectancy = 171%) against malignant growth metastasizing to the lung, while VP-16 was less compelling (increment of life expectancy = 78%). These outcomes propose that TOP-53 may have a favorable position over VP-16 in the treatment of lung malignancies in patients. Disappointment of top-53: Despite the preclinical accomplishment of TOP-53, a few inquiries remain with respect to its cytotoxic instrument. It caused lethality in certain number of patients.

Alchemix:

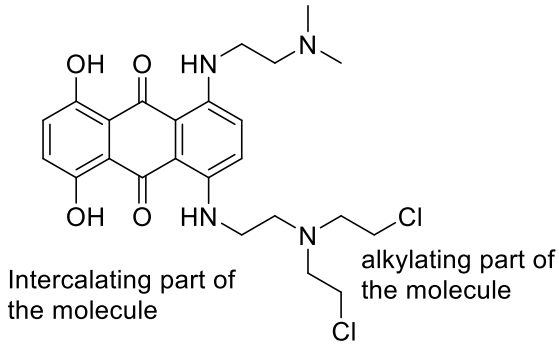
Alchemix has recently been accounted for to be the most strong of these mixes, with a capacity to have hostile to malignant growth movement against both standard drugs for safe tumor xenografts in mice.

Mechanism: The medication is equipped for instigating a DDR at nanomolar fixations and this is because of actuation of ATR-and DNA-PK-subordinate pathways. Both the alkylating and Top 2 inhibitory exercises of Alchemix add to this. In perspective on topoisomerase II's association in DNA loosening up preceding anaphase it is not out of the ordinary that Alchemix would detrimentally affect cell burn movement through S stage.

Uses: Alchemix is effective against engrafted human ovarian cell lines which had developed resistance to cisplatin or doxorubicin.

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ICT2901 (propyl), ICT2902 (butyl) andICT2903 (pentyl), are the alternatives for alchemix: causes a higher number of DNA alkylation destinations, progressively intense topoisomerase II hindrance and produced more apoptotic and necrotic cells when broke down in p53-capable HCT116 cells.

GL-331:

GL331 is a novel podophyllotoxin-inferred compound and is more effective than its congener VP-16 in murdering a few sorts of malignant growth cells, that has advanced significant enthusiasm for its probability of clinical use.

Instrument: GL331-actuated cell cycle annoyance happened upon beginning 8-h presentation, and pretreatment of NPC-TW01 cells with GL331 for 8 h essentially meddled with the cytotoxicities of VP-16, cisplatin, 5-fluorouracil and adriamycin. At the point when the timetable of medication organization was switched, high-lethal convergences of these operators uncovered an adversarial impact on GL331; be that as it may, their low-dangerous portions had the added substance or considerably more-than-added substance impact on the cytotoxicity initiated by GL331 at 0.1 microM or less, yet for GL331 centralizations of more noteworthy than 1 microM, the impact turned out to be not exactly added substance

Use: GL331 used in nasopharyngeal carcinoma

Disappointment of GL-331: It flopped in preclinical examinations results showed neutropenic sepsis one patient didn't get the full portion for reasons irrelevant to GL331, nine patients had dynamic infection with a middle endurance of 80 days.

4: Conclusions

Malignant growth is characterized as Abnormal and controlled expansion (development) of cells, emerging from cells. Disease cell have lost their capacity to separate. There is increment in number of cells, with the positional to attack to different parts of body. Disease

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cells can make their own blood supply, split away from organ of beginning and spread to different parts of body. Topoisomerase is a protein that controls the overwinding or underwinding of DNA. An uncommon accentuation was given to topoisomerase 2 inhibitors. A total audit on drugs named amsacrine, mitoxantrone, geneistein, top-53, alchemix and GL-331 was finished. Their viability as topo 2 inhibitors was assessed and purposes behind the disappointment of different medications in preclinical investigations were evaluated.

Conflict of interest

The authors declare that they have no conflict of interests.

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